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Letter to the Editors

Prefrontal transcranial direct current stimulation (tDCS) changes negative symptoms and functional connectivity MRI (fcMRI) in a single case of treatment-resistant schizophrenia

Dear Editors,

Transcranial direct current stimulation (tDCS) is a neuromodulatory, non-invasive brain stimulation technique that has been investigated in various neuropsychiatric disorders (Nitsche and Paulus, 2011). tDCS studies in patients with schizophrenia revealed an improvement of positive symptoms in single cases (Brunelin et al., 2012b; Rakesh et al., 2013; Shiozawa et al., 2013) as well as in groups of patients compared to controls (Brunelin et al., 2012a). Moreover, imaging techniques have been introduced to investigate effects of tDCS on brain function of neuropsychiatric patients (Halko et al., 2011; Homan et al., 2011; Volpato et al., 2013). To our knowledge, this is the first case study of functional connectivity MRI (fcMRI) after tDCS in a subject diagnosed with schizophrenia with predominantly negative symptoms.

A 19-year old right handed patient participated in this case study after giving his written informed consent. The study was approved by our institutional ethics committee. The patient was diagnosed with paranoid schizophrenia (DSM-IV: 295.30). Prodromal symptoms emerged at the age of 14 years and two years later the patient suffered from auditory hallucinations, paranoia, sleep disturbances and rapid mood changes. He was admitted to our hospital following an intervention of the youth welfare office; at that time symptoms had been present for five years with a nearly symptom-free interval of 1.5 years. Treatment with olanzapine 20 mg/day for 8 weeks showed no relevant psychopathological change and the patient remained bedridden, predominantly showing avolition, lack of impetus, social withdrawal, flattened affect and depressed mood. The antipsychotic medication was continued at stable dose during the subsequent tDCS treatment. The patient underwent tDCS (2 mA, 20 min/day, anode over the left dorsolateral prefrontal cortex [DLPFC], cathode over the contralateral supraorbital region) on 10 weekdays within 2 weeks. At baseline and after 5 and 10 tDCS sessions, clinical symptoms and cognitive performance were assessed (Fig. 1A).

For fcMRI a 3.0 Tesla Achieva system was used (Achieva TX, Philips Healthcare, Hamburg, Germany). The baseline scan was recorded prior to the first tDCS session (t0), the second scan immediately after the first tDCS session (t1) and the third scan after the completion of 10 tDCS sessions (t2). For fcMRI data acquisition at rest, the patient was instructed to keep his eyes closed without falling asleep, and try to think of nothing in particular. Measurements were acquired on exactly the same time of day to ensure equal inter-day testing conditions. For functional MR imaging, an echo-planar imaging (EPI) sequence with the following parameters was used: Repetition time (TR): 2500 ms, echo time (TE): 25 ms, flip angle (FA): 90 deg., spatial resolution: $3 \times 3 \times 3$ mm^3, imaging matrix: 76×77, field-of-view (FoV): $230 \times 230 \times 132$ mm, number of slices: 44, number of volumes: 180 and SENSE: 1.8 (p reduction, AP). Data processing and statistical analyses were carried out using FSL version 4.17 and AFNI. Preprocessing and post-analyses were performed as previously described (Keeser et al., 2011b). Different scan sessions were compared by a paired sample t-test.

After two weeks of tDCS, there was a considerable improvement in psychopathology. Both positive and negative symptoms decreased, disorganization, flattened affect, lack of concentration and impetus improved. The patient, formerly bedridden most of the day began to ask spontaneously for help and therapeutic assistance. Scores of clinical scales and cognitive tests are shown in Fig. 1A; fMRI data are shown in Fig. 1B.

The reduction of positive symptoms by 37% and of negative symptoms by 25% in our case are in line with the findings of a recent study of tDCS for the treatment of hallucinations in schizophrenia (Brunelin et al., 2012a) with a reduction of 16% in the positive and 12% in the negative dimension of the PANSS after active tDCS.

The reduced functional connectivity in the anterior part of the DMN of our patient may underlie this reduction of depressive and negative symptoms. Recently, it has been shown that prefrontal tDCS with the same electrode configuration used here reduced DMN activity (Pena-Gomez et al., 2012), but increased frontal–parietal functional connectivity (Keeser et al., 2011a; Pena-Gomez et al., 2012). The additional reduction of positive symptoms, however, was surprising as neither anodal tDCS of the left DLPFC nor cathodal tDCS over the right orbitofrontal cortex are supposed to have an impact on symptoms in schizophrenia.

In conclusion, anodal tDCS of the left DLPFC seems to be a promising tool for the treatment of negative symptoms in schizophrenia and may even alter positive symptoms. However, randomized controlled trials are needed for investigating the specific action of tDCS on the symptom spectrum in schizophrenia, using different electrode placements and stimulation protocols.

Conflict of interest

F.P. has received grant/research support from Brainsway Inc., Israel and neuroConn GmbH, Ilmenau, Germany.

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A

	Baseline	Week 1	Week 2	Total changes in %
PANSS				
- positive	19	15	12	-37
- negative	29	25	22	-25
- grandiosity/	16	10	10	-17
- disorganisation/	30	26	25	-17
- depression/ anxiety	26	17	17	-35
- total	***120***	***93***	***86***	***-29***
SANS				
- affective blunting	25	21	20	-20
- alogia	16	14	13	-19
- avolition	16	12	12	-25
- anhedonia	12	9	8	-33
- attention	10	4	4	-60
- total	***79***	***60***	***57***	***-28***
CDSS	7	3	2	-82
TMT				
- Version A (sec.)	0:39	0:24	0:22	
- Version B (sec.)	1:49	1:32	1:10	
SOPT				
- errors	4	2	1	

B

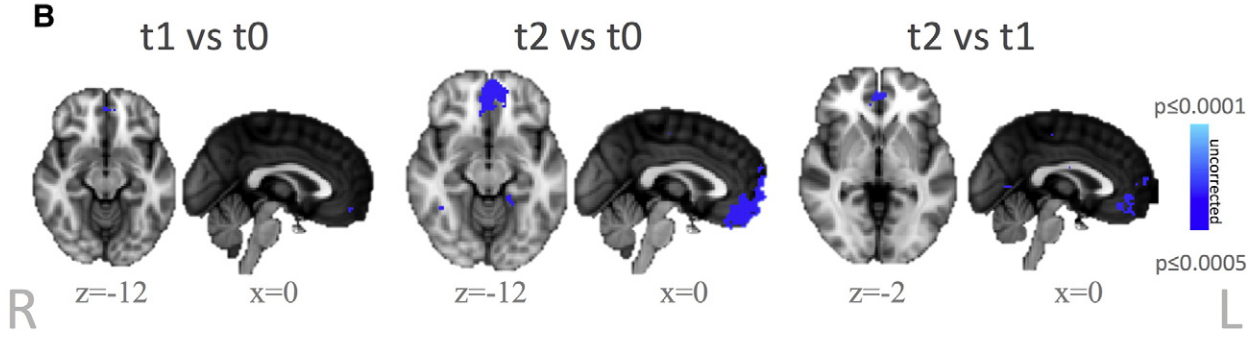

Fig. 1. A) Clinical and neuropsychological measures at baseline, after 1 and 2 weeks of tDCS treatment: Positive and Negative Symptom Scale (PANSS), Scale for the Assessment of Negative Symptoms (SANS), Calgary Depression Rating Scale in Schizophrenia (CDSS), Self-Ordered Pointing Task (SOPT), and Trail Making Test (TMT) versions A and B. B) Resting state fMRI: The dual regression analysis produced z-score maps representing connectivity within the selected Resting State Networks. Randomize 2.6 (permutation-based nonparametric inference) was used to determine the voxel-wise nonparametric statistical contrasts (with 5000 permutations) between the conditions for the selected networks. Due to the exploratory character and the single case of the analysis, effects were considered significant at a level of $p_{uncorrected} < 0.0005$ with a cluster extent of more than 20 voxels. The following contrasts are shown: immediately after the first tDCS (t1) vs. baseline (t0), after 10 days of tDCS (t2) vs. (t0) and (t2) vs. (t1). A significant change of connectivity was found in the anterior part of the Default Mode Network (DMN) for the comparison of t0 vs. t1 (reduced fcMRI in the cluster: subgenual cortex; cluster peak coordinates: $x = -2$, $y = 48$, $z = -14$, 30 voxels, $p \leq 0.0005$, uncorrected). This effect was even more pronounced for t0 vs. t2 (reduced fcMRI in the cluster: subgenual cortex, anterior cingulate, medial frontal gyrus, superior frontal gyrus; cluster peak coordinates: $x = -4$, $y = 50$, $z = -14$, 1626 voxels, $p \leq 0.0005$).

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