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Prefrontal Transcranial Direct Current Stimulation for Treatment of Schizophrenia With Predominant Negative Symptoms: A Double-Blind, Sham-Controlled Proof-of-Concept Study

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Negative symptoms are highly relevant in the long-term course of schizophrenia and are an important target domain for the development of novel interventions. Recently, transcranial direct current stimulation (tDCS) of the prefrontal cortex has been investigated as a treatment option in schizophrenia. In this proof-of-concept study, 20 schizophrenia patients with predominantly negative symptoms were randomized to either 10 sessions of add-on active (2 mA, 20 min) or sham tDCS (anode: left DLPFC/F3; cathode: right supraorbital/F4). Primary outcome measure was the change in the Scale for the Assessment of Negative Symptoms (SANS) sum score; secondary outcomes included reduction in Positive and Negative Syndrome Scale (PANSS) scores and improvement of depressive symptoms, cognitive processing speed, and executive functioning. Sixteen patients underwent 4 functional connectivity magnetic resonance imaging (fcMRI) scans (pre and post 1st and pre and post 10th tDCS) to investigate changes in resting state network connectivity after tDCS. Per-protocol analysis showed a significantly greater decrease in SANS score after active (−36.1%) than after sham tDCS (−0.7%). PANSS sum scores decreased significantly more with active (−23.4%) than with sham stimulation (−2.2%). Explorative analysis of fcMRI data indicated changes in subgenual cortex and dorsolateral prefrontal cortex (DLPFC) connectivity within frontal-thalamic-temporo-parietal networks. The results of this first proof-of-concept study indicate that prefrontal tDCS may be a promising intervention for treatment of schizophrenia with predominant negative symptoms. Large-scale randomized controlled studies are needed to further establish prefrontal tDCS as novel treatment for negative symptoms in schizophrenia.

Key words: transcranial direct current stimulation—tDCS/schizophrenia/negative symptoms/resting-state networks/functional connectivity MRI—fcMRI

Introduction

Negative symptoms of schizophrenia comprise affective flattening, alogia, avolition-apathy, anhedonia-asociality, and attention problems,[1] are associated with neurocognitive deficits,[2] typically increase over time,[3,4] show modest response to antipsychotic medication[5] and are related to poor functional outcome.[6] They are conceptualized as unitary or partial constructs that include overlapping concepts of deficit schizophrenia (DS), persistent negative symptoms (PNS) or depression in schizophrenia.[7] Although findings from neuroimaging studies are not consistent across these constructs, dysfunctional connectivity between hub regions may play a major role in the pathophysiology of the negative symptom spectrum: eg, dysfunction of fronto-thalamic-parietal or frontal-striatal networks.[7–9] The dorsolateral prefrontal cortex (DLPFC) represents an important hub involved in these circuits and shows functional changes in schizophrenia with negative symptoms and cognitive dysfunction.[7,10,11] The connectivity between the left DLPFC and fronto-parietal, as well as cingulo-opercular networks has recently been reported to be associated with an accelerated age-related decline in schizophrenia as compared to healthy controls.[12]

Because of its putative role in the pathophysiology of schizophrenia,[9] the left DLPFC has been a target for studies investigating noninvasive brain stimulation (NIBS) for the treatment of negative symptoms, eg, repetitive transcranial magnetic stimulation (rTMS). Although several clinical trials investigating rTMS in schizophrenia showed a significant treatment effect over sham stimulation, the largest randomized controlled trial (RCT) to date recently failed to demonstrate its therapeutic efficacy.[13] Thus, the jury is still out regarding the role of NIBS for treatment of negative symptoms in schizophrenia.

Transcranial direct current stimulation (tDCS) is another NIBS technique that leads to long-lasting excitability changes toward facilitation (anodal tDCS [atDCS]) or inhibition (cathodal tDCS [ctDCS]), and tDCS of the prefrontal cortex has been shown to modulate resting state functional connectivity magnetic resonance imaging (fcMRI).[14] In schizophrenia, there is first evidence that atDCS of the left DLPFC and ctDCS of the left temporo-parietal junction improve positive (primary endpoint) and negative symptoms (secondary endpoint).[15] The effect of tDCS on positive symptoms in schizophrenia was investigated in 3 monocentric RCTs[15–17]: atDCS of the left DLPFC and ctDCS of the left temporoparietal junction improved both positive and negative symptoms compared to sham tDCS in 2 of these studies,[15,16] but the study showed no superiority of atDCS.[17] For the treatment of negative symptoms, an RCT in 15 patients showed a significant decrease in the Positive and Negative Syndrome Scale (PANSS) total score and negative subscale after atDCS of the left DLPFC compared to sham stimulation.[18] An open-label study[19] in 9 patients with negative symptoms found a 24% improvement in the PANSS negative subscale after atDCS of the left DLPFC. Our proof-of-concept study presents findings on the efficacy of left prefrontal atDCS as an add-on therapy to improve negative symptoms as a primary outcome in schizophrenia patients. Moreover, it provides first preliminary fcMRI data for this stimulation condition, which has been previously characterized in healthy subjects.[14]

Methods and Materials

Participants

Twenty patients with paranoid schizophrenia or disorganized schizophrenia according to DSM-IV criteria[20] were recruited at the Department of Psychiatry, Ludwig Maximilian University, Munich, Germany, and randomized to 10 sessions of active or sham tDCS (supplementary figure 1: CONSORT Flowchart). Patients between 18 and 65 years with a clinical presentation of predominant negative symptoms (according to the clinical judgement of 2 experienced psychiatrists), PANSS score[21] > 70, and stable antipsychotic drug regimen >4 weeks were included. Exclusion criteria were relevant comorbid psychiatric disorders (substance abuse disorders, acute suicidality), neurological disorders (epilepsy, stroke or cerebrovascular diseases, neurodegenerative disorders), and somatic disorders (malignant and infectious diseases, cardiac insufficiency); pregnancy; and metal implants or skin diseases affecting the scalp. Antipsychotic medication was continued at stable doses during the study.

The study was approved by the local ethics committee and performed according to the Declaration of Helsinki. Before enrolment, the study was registered at www.clinicaltrials.gov (NCT01378078). Written and oral informed consent was obtained from all participants.

Randomization and Blinding

Randomization to the active or sham group was carried out 1:1 by the principal investigator (U.P.) without any restrictions (such as blocking and stratification) and according to a computer-generated randomization list. U.P. had continuous access to the randomization list and unblinded the study after the final visit of the last patient. Patients, tDCS operators, and clinical raters were kept blind to treatment conditions until this unblinding; patients were not asked to guess the condition, and raters were not involved in tDCS application. However, skin reddening may occur after active tDCS and might endanger blinding.[22,23] Therefore, participants were seated in a room without a mirror during tDCS and a brief post-stimulation period lasting 10 to 20 minutes.

Intervention

tDCS was delivered at 2 mA intensity for 20 minutes per day (+15 s fade-in and fade-out); sessions were performed on 10 days within 2 weeks but not at weekends. An Eldith DC-stimulator PLUS (neuroConn) with numerical code-dependent activation of the active and sham mode was used with the anode placed over the left DLPFC (F3) and the cathode over the right orbitofrontal region (Fp2); electrodes (35 cm^2) were covered by saline-soaked sponges and fixed with rubber bands. The dual-mode tDCS device, which includes a novel sham mode that mimics sensory artefacts of tDCS, has been previously evaluated in healthy controls.[22]

Outcome Measures

Time points for assessment were 1 week before 1st tDCS (t-7), 1 day before 1st tDCS (t0), after 5th tDCS (t1), after 10th tDCS (t2), and 4 weeks after 1st tDCS (ie, 2 wk after 10th tDCS, t3).

Primary Outcome Measure. Change in the Scale for the Assessment of Negative Symptoms (SANS)[24] after tDCS

(t3) compared to baseline (t0). SANS was assessed twice before 1st tDCS to measure baseline stability (t-7 and t0), at t1, t2, and t3.

Secondary Outcome Measures. PANSS[21] at t-7, t0, t1, t2, and t3 and Calgary Depression Scale for Schizophrenia (CDSS)[25] and Subjective Well-being under Neuroleptic Treatment Scale (SWN)[26] at t0, t1, t2, and t3. Cognitive performance was tested at t0, t1, and t2 with the Self-Ordered Pointing Task (SOPT)[27] for working memory, the Trail-Making Test (TMT-A)[28] for processing speed, and TMT version B for executive functioning. Cognitive tests were conducted within 6 hours after tDCS. To assess safety, adverse events were documented at their occurrence and by the Comfort Rating Questionnaire (CRQ) during each tDCS session. The CRQ assesses the level of pain, tingling, burning, fatigue, nervousness, disturbed concentration, disturbed visual perception, and headache.[29]

fcMRI—Acquisition and Analysis

To provide a first insight into the effects of repetitive tDCS on brain activation patterns in schizophrenia patients, a subgroup of 16 patients underwent 4 fcMRI scans immediately before and after the 1st and 10th tDCS (figure 1A). Full description of this exploratory fcMRI acquisition and analysis is given in detail in the supplementary material—Functional MRI Connectivity Analysis.

Statistical Analysis

Statistical analyses were performed with SPSS version 20.0 (IBM Corp). Normal distribution of primary outcome data was established with the Kolmogorov-Smirnov

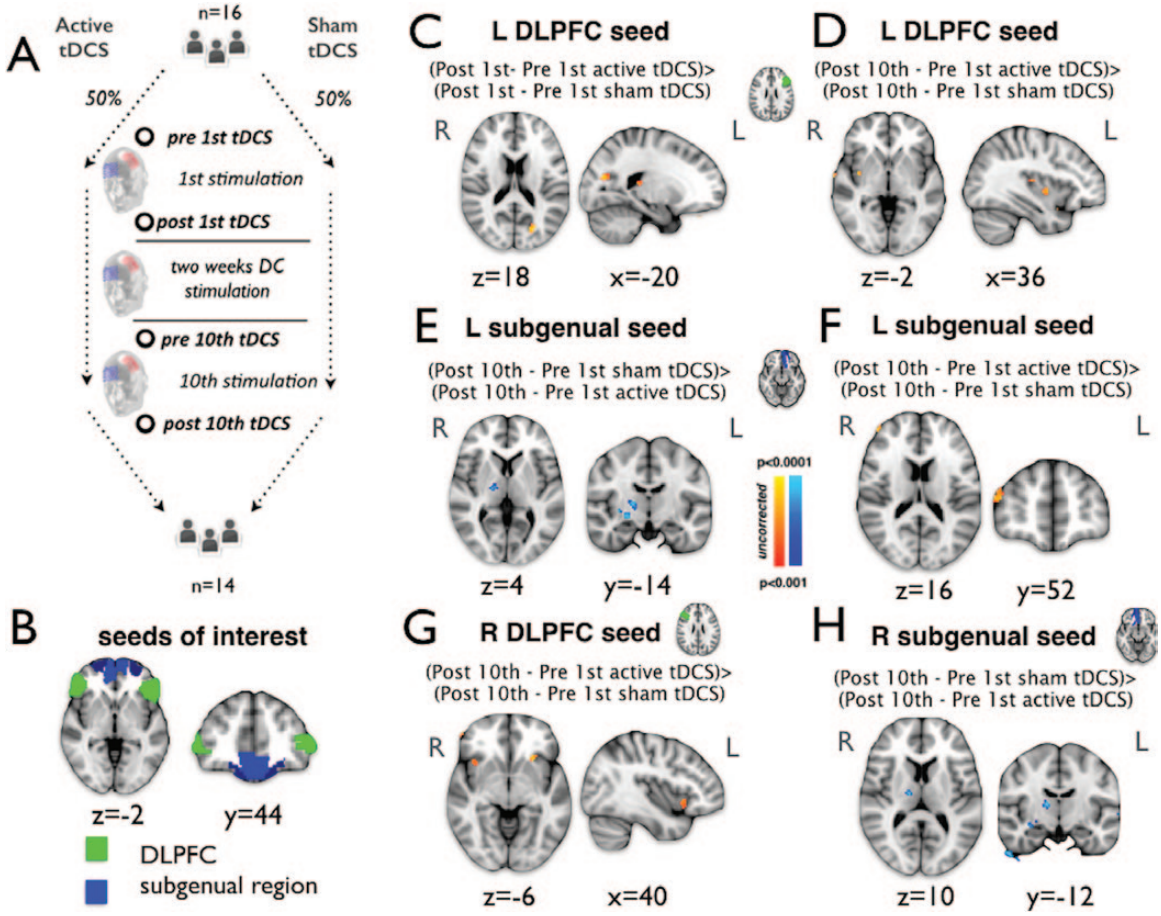

Fig. 1. **A.** Functional connectivity Magnetic Resonance Imaging (fcMRI) acquisition and analysis. **B.** Seeds of interest used for the seed-based analysis (SBA) of fcMRI data; green = left and right dorsolateral prefrontal cortex (DLPFC), blue = subgenual area; **C.** Connectivity changes (post 1st − pre 1st active transcranial direct current stimulation [tDCS]) > (post 1st − pre 1st sham tDCS) of the left DLPFC seed; **D.** Connectivity changes (post 10th − pre 1st active tDCS) > (post 10th − pre 1st sham tDCS) of the left DLPFC seed; **E.** Connectivity changes (post 10th − pre 1st sham tDCS) > (post 1st − pre 1st active tDCS) of left subgenual seed region; **F.** Connectivity changes (post 10th − pre 1st active tDCS) > (post 10th − pre 1st sham tDCS) of left subgenual seed region; **G.** Connectivity changes (post 10th − pre 1st active tDCS) > (post 10th − pre 1st sham tDCS) of the left DLPFC seed; **H.** Connectivity changes (post 10th − pre 1st active tDCS) > (post 10th − pre 1st sham tDCS) of the right subgenual seed region. $P < .001$ (cluster size > 20 voxels). Radiological convention, xyz-coordinates in Montreal Neurological Institute (MNI) space.

test. Qualitative variables of demographic and clinical parameters were compared by the Pearson chi-square test for contingency tables (handedness) or by Fisher's exact test (gender distribution), and quantitative variables were compared by a *t* test for independent samples (age, age at onset, duration of psychosis, number of hospitalizations, duration of hospitalizations, duration of actual hospitalization, number of episodes, duration of episodes, and chlorpromazine equivalents).

SANS, PANSS, and CDSS sum scores were compared between treatment groups with a mixed factorial analysis of variance for repeated measures (rmANOVA) with time points (t-7, t0, t1, t2, and t3) as the within-subject factor and group (active, sham) as the between-subject factor. These 5 time levels were used for PANSS and SANS sum scores and 4 time levels (t0, t1, t2, t3) were used for CDSS sum scores; 2 group levels (active, sham) were used for all 3 scales. In addition, mixed factorial rmANOVAs were performed to compare the influence of active and sham treatment on cognitive performance parameters (SOPT, TMT-A, TMT-B), with time (t0, t1, t2) and group (active, sham) as the within-subject and between-subject factors, respectively. Three time levels (t0, t1, t2) and 2 group levels (active, sham) were used for SOPT, TMT-A, and TMT-B. PANSS and SANS subscale scores were compared between groups by mixed factorial rmANOVAs, with 5 time levels (t-7, t0, t1, t2, t3) of SANS and PANSS as within-subject factor and group (active, sham) as between-subject factor. If a significant group factor was found, post hoc *t* tests were performed to compare single time points. F-value correction was applied by means of adjusting the degrees of freedom (*df*) by a factor Epsilon (ε) if the sphericity test (Mauchly W test) was significant, indicating heterogeneity of covariances (Greenhouse-Geisser correction). For our main findings, we computed the 95% CI with lower and upper endpoints for SANS and PANSS and calculated partial eta-squared (PES) as the effect size of treatment.

One-way ANOVAs were performed to detect head motion differences between fcMRI measurements in the sham and active groups separately.

The CRQ was compared between treatment groups by a mixed factorial rmANOVA. Time levels (CRQ scores after each stimulation) were used as the within-subject factor and group (active, sham) was used as the between-subject factor.

Mean scores are reported ± SD; the level of significance was set at $P = .05$.

Results

Demographic and Clinical Characteristics at Baseline

Twenty patients (15 male, 5 female; mean age 36.1 ± 11.4 y, age range 22–57) completed the study; 19 patients underwent all tDCS sessions and only 1 patient (active tDCS) missed 1 tDCS session (analyzed per-protocol sample: $N = 20$) (CONSORT, supplementary figure 1). Significant group differences were found for gender ($P < .001$), handedness ($P < .001$), and age of onset ($P = .008$), but for no other demographic or clinical characteristic (table 1).

SANS, PANSS, CDSS, SOPT, and TMT-A/B scores did not differ significantly between t-7 and t0 in either group and at t0 between both groups ($P > .05$; table 1).

Primary Outcome Measures

Scale for the Assessment of Negative Symptoms. A mixed factorial rmANCOVA (within-subject effect: SANS sum score t-7, t0, t1, t2, t3; between-subject factor: active vs sham group; covariates: gender, handedness, and age of onset) revealed a significant time × group interaction effect (Greenhouse-Geisser correction time × group: $F = 5.312$, $df = 1.675$, $\varepsilon = 0.419$, $P = .016$; PES = 0.262; active group: CI = 34.902 – 63.572; sham group t-7: CI = 51.988 – 80.658). No significant effects were detected for handedness ($F = 0.076$, $df = 1$, $P = .786$), gender ($F = 0.039$, $df = 1$, $P = .847$), or age of onset ($F = 0.111$, $df = 1$, $P = .743$). Mean SANS sum scores decreased by −36.1% from baseline (t0: 59.6 ± 23.0) to follow-up (t3: 38.1 ± 21.7). In the sham tDCS group, mean SANS sum scores decreased by −0.7% (t0: 64.4 ± 13.1, t1: 66.4 ± 12.1; t2: 65.2 ± 10.3; t3: 63.9 ± 16.4). Significant differences in the SANS sum score between the active and sham groups could be observed after week 2 (t2; $P = .005$), and at follow-up 4 weeks after the 1st tDCS (t3; $P = .008$; figure 2A).

Secondary Outcome Measures

SANS Dimensions. A significant effect of active tDCS treatment compared to sham treatment over time (t0; t3) was observed for the reduction of the SANS dimension alogia (40.9% vs 6.7%; $P = .033$; PES = 0.229; active group: CI = 6.75 – 12.65; sham group: CI = 11.34 – 17.26), whereas the other subscales did not show statistically significant differences between both groups (supplementary table 1).

Positive and Negative Syndrome Scale. The mixed factorial rmANOVA regarding PANSS sum scores (within-subject-factors: PANSS sum score at t-7, t0, t1, t2, t3; between-subject factors: active vs sham group) showed a significant time effect (Greenhouse-Geisser correction time: $F = 5.608$, $df = 1.607$, $\varepsilon = 0.402$, $P = .013$; PES = 0.238; active group: CI = 63.579 – 81.741; sham group t-7: CI = 76.179 – 94.341), and a significant time × group interaction (Greenhouse-Geisser correction time × group: $F = 4.748$, $df = 1.607$, $\varepsilon = 0.402$, $P = .022$; PES = 0.209). Mean sum scores decreased by 23.4% after active tDCS (t0: 79.5 ± 20.0; t3: 60.9 ± 22.1) and by −2.2% after sham tDCS (t0: 85.6 ± 6.8; t3: 83.7 ± 8.7). Post hoc analyses of PANSS (1-way mixed factorial rmANOVAs with PANSS sum scores at t-7, t0, t1, t2, and

Table 1. Demographic and Clinical Characteristics of Schizophrenia Patients Treated With Active (n = 8) Transcranial Direct Current Stimulation (tDCS) or Sham tDCS (n = 8)

	Active tDCS (n = 10)	Sham tDCS (n = 10)	Total (N = 20)	Active vs Sham		
				P Value	χ^2	*df*
Gender, m/f	5/5	10/0	15/5	**.000**[a]	5.000	1
Handedness, r/l	10/0	9/1	19/1	**.000**[b]	16.200	1
				P value	*F*	*df*
Age, y	38.4 (12.9)	34.1 (10.7)	36.1 (11.4)	.426[c]	0.420	18
Age at onset, y	31.3 (11.0)	20.4 (3.3)	28.5 (10.6)	**.008**[c]	9.827	18
Duration of psychosis, y	7.1 (6.1)	13.8 (12.1)	10.5 (9.9)	.134[c]	3.026	18
Number of hospitalizations, *n*	3.6 (2.6)	6.0 (6.4)	4.8 (4.9)	.289[c]	5.970	18
Duration of hospitalizations, mo	12.2 (7.8)	21.0 (21.9)	16.6 (16.6)	.244[c]	19.284	18
Duration of actual hospitalization, wk	8.5 (5.2)	8.8 (6.1)	8.6 (5.5)	.953[c]	0.008	18
Number of episodes, *n*	3.9 (2.6)	7.7 (8.2)	5.5 (5.9)	.207[c]	3.944	14
Duration of episodes, mo	4.8 (1.6)	5.4 (1.5)	5.1 (1.5)	.416[c]	0.793	14
CPZ, mg/d	558.8 (304.5)	481.5 (226.2)	520.1 (264.1)	.528[c]	0.938	18
Primary and secondary outcome measures						
SANS at t0	59.6 (23.0)	64.4 (13.1)	62.0 (18.4)	.574[c]	4.352	18
SANS at t3	38.1 (21.7)	63.9 (16.4)	51.0 (22.9)	**.008**[c]	1.358	18
PANSS total at t0	79.5 (20.0)	85.6 (6.8)	82.6 (14.9)	.374[c]	4.570	11.028
PANSS total at t3	60.9 (22.1)	83.7 (8.7)	72.3 (20.1)	**.011**[c]	13.590	11.735
PANSS negative at t0	24.0 (5.4)	25.1 (4.1)	24.6 (4.7)	.612[c]	0.262	18
PANSS negative at t3	16.6 (6.9)	26.6 (4.2)	21.6 (7.6)	**.001**[c]	3.364	18
PANSS positive at t0	10.0 (3.9)	10.7 (4.1)	10.4 (3.9)	.697[c]	0.009	18
PANSS positive at t3	7.5 (2.8)	9.7 (4.5)	8.6 (3.8)	.202[c]	0.746	18
CDSS at t0	6.0 (4.9)	8.6 (3.6)	7.3 (4.4)	.195[c]	1.208	18
CDSS at t3	2.6 (2.4)	5.7 (3.8)	4.2 (3.5)	**.042**[c]	1.876	18
SWN at t0	83.1 (10.8)	72.7 (16.3)	77.9 (14.4)	.184[c]	1.993	12
SWN at t3	94.6 (14.4)	73.0 (18.9)	83.8 (19.7)	**.033**[c]	0.372	12
SOPT at t0	4.7 (4.8)	5.6 (3.8)	5.2 (4.2)	.648[c]	0.048	18
SOPT at t2	3.4 (3.7)	5.3 (3.7)	4.4 (3.7)	.260[c]	0.022	18
TMT A at t0	45.7 (26.2)	34.4 (10.3)	40.1 (20.2)	.220[c]	1.387	18
TMT A at t2	37.9 (27.8)	29.9 (9.1)	33.9 (20.5)	.398[c]	2.860	18
TMT B at t0	122.8 (96.1)	88.1 (40.4)	104.5 (72.3)	.310[c]	2.095	17
TMT B at t2	91.7 (82.9)	79.5 (45.0)	85.3 (64.1)	.697[c]	0.332	17

Note: t0, baseline (1 day before the first tDCS session); t2, after 2 weeks (10 sessions) of tDCS; t3, follow-up 4 weeks after first tDCS session; CPZ, Antipsychotic dose in chlorpromazine equivalents; SANS, Scale for the Assessment of Negative Symptoms; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; SWN, Subjective Well-being under Neuroleptic Treatment Scale; SOPT, Self-Ordered Pointing Task; TMT A, Trail-Making Test, Version A; TMT B, Trail-Making Test, Version B; *df*, degrees of freedom. Data presented as mean (SD). Significant results are in bold type.
[a]Fisher's exact test.
[b]Chi-square test.
[c]*t* test.

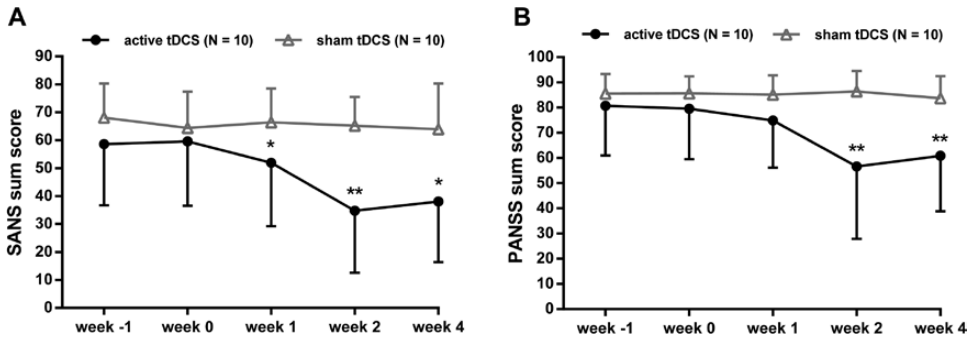

Fig. 2. A. Scale for the Assessment of Negative Symptoms (SANS) sum score and **B.** Positive and Negative Syndrome Scale (PANSS) sum score in schizophrenia patients treated with active transcranial direct current stimulation (tDCS) or sham tDCS. Figure shows mean and standard error of the mean (SEM). Significant differences between active and sham group are indicated by **P* < .05, ***P* < .01.

t3 as within-subject factors and active and sham group as between-subject factors) showed a significant trend toward a more pronounced PANSS symptom reduction in the active group from t2 onwards (t-7: $F = 0.511$, $df = 1$, $P = .484$; t0: $F = 0.832$, $df = 1$, $P = .374$; t1: $F = 1.418$, $df = 1$, $P = .249$; t2: $F = 7.962$, $df = 1$, $P = .011$, t3: $F = 9.183$, $df = 1$, $P = .007$; figure 2B). Post hoc analyses of PANSS negative subscales showed a significantly greater reduction after active tDCS than after sham tDCS at t2 ($F = 7.38$, $df = 1$, $P = .014$) and t3 ($F = 15.34$, $df = 1$, $P = .001$). Significant effects of active tDCS compared to sham tDCS were observed in the PANSS negative (−30.8% vs +5.9%) and depression/anxiety (−19.3% vs −7.5%) dimensions (supplementary table 1).

Depression and Well-Being. Results are reported in the supplementary material—Secondary Outcome Parameters.

Working Memory, Cognitive Processing Speed, and Executive Functioning. Results are reported in the supplementary material—Secondary Outcome Parameters.

Medication

Medication was kept stable during the study. Patients received various antipsychotics, antidepressants, and mood stabilizers. Three patients of the active group continuously received benzodiazepines up to 1.5 mg lorazepam equivalents (supplementary table 2).

Safety and Blinding Integrity

tDCS was well tolerated, and patients spontaneously reported only mild tingling and transient headache. There were no significant differences between active and sham tDCS in any of the symptom categories measured by the CRQ (detailed results are reported in the supplementary material—Secondary Outcome Parameters). Patients and raters were not asked to guess the tDCS conditions.

Neuroimaging Results

Results of Dual Regression, Seed-based analysis (SBA) of the Insula, and correlative analyses are reported in the supplementary material—Functional MRI Connectivity Analysis.

Seed-Based Analysis. The binarized masks (seeds) were defined on the basis of regions showing changes in fcMRI ICA and are shown on an MNI standard template in figure 1B. Significant effects were found for the left and right DLPFC and left and right subgenual seeds (inter-group comparison, $P < .001$, cluster size >20 voxels, figures 1C–H, table 2). SBA of "acute effects" of the comparison (post 1st – pre 1st active tDCS) > (post 1st – pre 1st sham tDCS) showed changes of fcMRI connectivity of the left DLPFC

Table 2. Seed-Based Analysis (SBA)

Seed of Interest	Contrast/Uncorrected *P*	Cluster/Brain Area	Brodman's Area	Number of Voxels	MNI Coordinates		
					x	y	z
L DLPFC	(Post 1st – Pre 1st active tDCS) > (Post 1st – Pre 1st sham tDCS), $P < .001$	1) L Posterior Cingulate/ L Precuneus	30, 31	57	−18	−76	18
			—	28	−20	−34	12
		2) L Thalamus	37	37	68	40	12
	(Post 10th – Pre 1st active tDCS) > (Post 10th – Pre 1st sham tDCS), $P < .001$	1) L Inferior/Middle Temporal Gyrus					
L subgenual	(Post 10th – Pre 1st sham tDCS) > (Post 10th – Pre 1st active tDCS), $P < .001$	1) R Thalamus (Nuclei: posterior medial, posterior lateral, medial dorsal, ventral lateral, lateral posterior)	—	71	18	−14	4
			—	38	26	−14	−8
			9, 10, 46	40	46	46	16
	(Post 10th – Pre 1st active tDCS) > (Post 10th – Pre 1st sham tDCS), $P < .001$	2) R Putamen, R Pallidus					
		1) R Middle/Superior Frontal Gyrus					
R DLPFC	(Post 10th – Pre 1st active tDCS) > (Post 10th – Pre 1st sham tDCS), $P < .001$	1) R Insula, R Inferior Frontal Gyrus	13, 47	35	38	18	−10
			—	27	−26	22	−6
		2) L Claustrum					
R subgenual	(Post 10th – Pre 1st sham tDCS) > (Post 10th – Pre 1st active tDCS), $P < .001$	1) R Thalamus (Nuclei: medial dorsal, ventral lateral)	—	29	14	−14	10

Note: R, right hemisphere; L, left hemisphere; DLPFC, dorsolateral prefrontal cortex; tDCS, transcranial direct current stimulation. Brain regions showing significant tDCS-induced inter-group connectivity changes for the left DLPFC seed region, left subgenual seed region, right DLPFC seed region, and right subgenual seed region to the whole brain, cluster size > 20 voxels, $P < .001$.

seed with the left posterior cingulate/left precuneus and the left thalamus (figure 1C, table 2). An analysis of the "overall treatment effect" of tDCS treatment (figures 1D–H, table 2) that compared (post 10th – pre 1st active tDCS) > (post 10th – pre 1st sham tDCS) showed significant effects for all 4 seeds, $P < .001$, cluster size > 20 voxels, ie, (1) left DLPFC to left inferior/middle temporal gyrus (figure 1C); (2) right DLPFC: Right insula, right inferior frontal gyrus, left claustrum gyrus (figure 1D); and (3) right subgenual gyrus: right thalamus gyrus (figure 1F). We found a significant group effect for the comparison (post 10th – pre 1st sham tDCS) > (post 10th – pre 1st active tDCS) as well: (4) left subgenual gyrus: right thalamus, right putamen, right pallidus, right middle/superior frontal gyrus (figure 1E); and (5) right subgenual gyrus: right thalamus (nuclei: medial dorsal, ventral lateral; figure 1H).

Discussion

The results of this proof-of-concept study show that prefrontal tDCS added to stable antipsychotic medication can improve negative symptoms of schizophrenia in severely affected patients. We found a significant improvement of the SANS sum score (primary outcome) and PANSS negative sum score (secondary outcome) after active tDCS compared to sham stimulation.

To date, 2 alternative tDCS electrode montages representing different cortical targets have been investigated in treatment studies for positive and negative symptoms of schizophrenia. The first approach was a combined stimulation with atDCS of the DLPFC (midway between F3 and FP1 or F3) and ctDCS of the temporoparietal junction (midway between T3 and P3 or TP3 or TP4). This approach was based on the assumption that focusing tDCS on these 2 regions, particularly with ctDCS on the left temporoparietal junction (TPJ), may reduce the severity of auditory hallucinations in schizophrenia.[15] The second approach focused on atDCS of the left DLPFC (F3) either with an extracephalic cathode position over the contralateral deltoid area[19] or with ctDCS over the right DLPFC (F4).[18] This approach has been considered to be of interest for the treatment of negative symptoms in schizophrenia.[18,19]

Here, we investigated the second tDCS approach by focusing on schizophrenia with predominant negative symptoms and using 2 mA atDCS for 20 minutes over the left DLPFC (F3) and ctDCS over the right orbit (Fp2). These electrode positions and parameters were previously characterized in healthy subjects in terms of their putative action on working memory[30] and resting state fcMRI[14] and found to improve working memory performance and modulate resting state fcMRI networks.[14,30]

Two previous clinical studies have investigated the DLPFC-focused montages in schizophrenia, ie, a small open trial ($n = 9$)[19] and a small RCT ($n = 15$).[18] Both trials showed an improvement of negative symptoms. In the latter trial, Gomes et al[18] observed a superior effect of daily active tDCS over 10 days on PANSS negative, general, and total scores compared to sham stimulation. In contrast to our study, neither trial included patients with predominant negative symptoms, and no neuroimaging data are available.

For the TPJ-focused approach, data from 3 placebo-controlled pilot trials are available.[15–17] In an RCT, Brunelin et al[15] applied tDCS twice daily in 30 patients with schizophrenia over 5 days and showed a significant effect of active tDCS on auditory hallucinations and negative symptoms compared to sham stimulation. Very recently, the same group published fcMRI data from a second RCT ($N = 22$) with a patient sample that partially overlapped with that of the prior study; these data confirmed the clinical results and demonstrated changes in fcMRI seed-based TPJ connectivity.[16] In contrast, Fitzgerald et al[17] found negative results in a very small pilot trial that compared unilateral tDCS ($N = 13$, F3/TP3) and bilateral tDCS ($N = 11$, F3/TP3 and F4/TP4) with sham tDCS. The main methodological difference compared to Brunelin et al[15] were the exact electrode positions and treatment frequency with 15 daily sessions over 3 consecutive weeks.[17] Although the current study adds to the body of positive data suggesting tDCS to be a novel intervention in schizophrenia, optimal electrode montages need to be further identified because they are hypothesized to play a key role for directing tDCS toward relevant dysfunctional regions.[31] Bifrontal montage has shown to be efficacious for the treatment of major depressive disorder,[32] and computational models suggest a more focal current flow in the DLPFC than in TPJ regions.[31] This may be linked to the marked improvement of negative symptoms in our active group compared to the study by Brunelin et al,[15] ie, a reduction in the PANSS negative subscale by 36.1% (vs 11.9%). Such comparisons, however, are hampered by differences between clinical groups, eg, higher PANSS negative scores at baseline in our study compared to those of Brunelin et al[15] and Mondino et al.[16] Positive symptoms, a secondary outcome in our study, also showed a clinically relevant change in the active group (−25.0%), suggesting a potential role of the prefrontal cortex in cognitive control over delusional thoughts or hallucinations.

Whereas the primary outcome (SANS) improved after active tDCS in our study, secondary outcomes showed mixed results: CDSS scores improved in both groups, which could be interpreted as a placebo effect in the sham group resulting from the study procedure itself, but cognitive performance measured by SOPT and TMT-A/B did not significantly change after active treatment compared to sham. The explorative analysis of fcMRI data showed effects in key regions (DLPFC, subgenual cortex) also identified in our previous study in healthy subjects.[30] However, the domains of negative symptoms, depressive symptoms, and cognitive deficits in schizophrenia overlap,[33] and the functional contribution of the DLPFC to different symptom clusters is not fully elucidated.[8,9]

One may argue that atDCS of the left DLPFC may have restored DLPFC function in its connectivity, but one must also be aware that most tDCS studies—including ours—use 2 active electrodes, ie, a cathode over the contralateral orbitofrontal region.[14] Although there is no direct evidence from our data, we cannot exclude that ctDCS also contributed to the therapeutic effects observed here.

To explore the fcMRI data, we compared active and sham tDCS in a subgroup of 16 patients and did not detect a whole-brain effect of active tDCS on resting state fcMRI networks robust for multiple comparison; however, changes in SRN, FPN, and DMN networks were found at an uncorrected level of $P_{\text{uncorrected}} < .001$. Thus, we decided to define the respective voxels post hoc (left and right DLPFC, left and right subgenual regions, and the left insula) as seed regions for further exploratory analysis, according to the approach in the study by Mondino et al.[16] Similar to this group, we observed changes in seed-based connectivity after the 1st and the 10th tDCS compared to baseline for active compared to sham tDCS; however, there was no correlation with the primary clinical outcome measure.

We are aware that this proof-of-concept study has several limitations, including the sample size; the imbalance for gender, handedness, and medication (clozapine) despite proper randomization; the definition of negative symptoms on the basis of clinical judgement instead of applying standardized criteria[3] (although this approach was chosen to obtain a similar sample to another study that used operationalized criteria for predominant negative symptoms[13]); no control of blinding integrity in patients, operators, and raters; a possible bias from concomitant medication; and the limited duration of assessment of stability of effects, ie, a follow-up period of only 2 weeks after tDCS. Moreover, inter-individual fcMRI, especially in studies with limited sample-sizes, is highly variable,[34] whereas intra-individual functional connectivity is very stable.[35] Recent research has found that individual fcMRI fronto-parietal and medial frontal networks could be identified with a high accuracy of up to 99% on 2 repeated measurements in the resting state.[35] This raises the question whether future studies should investigate the individual variability and results of prefrontal tDCS in healthy subjects and neuropsychiatric patients. The strengths of our study were the pre-evaluated tDCS conditions,[14,30] and the sham tDCS mode with a dual mode stimulator. Future studies investigating the efficacy and safety of prefrontal atDCS should address the critical issues and limiting factors in our study, and larger RCTs should be developed from these findings.

In conclusion, this proof-of-concept study showed that negative symptoms in schizophrenia can be treated with prefrontal tDCS with the F3-Fp2 electrode montage. Further preclinical and clinical studies are needed to develop tDCS towards a disorder-tailored and personalized NIBS approach for the effective treatment of schizophrenia and its entities.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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