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Original article

Exploratory study of once-daily transcranial direct current stimulation (tDCS) as a treatment for auditory hallucinations in schizophrenia

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ABSTRACT

Background: Auditory hallucinations are resistant to pharmacotherapy in about 25% of adults with schizophrenia. Treatment with noninvasive brain stimulation would provide a welcomed additional tool for the clinical management of auditory hallucinations. A recent study found a significant reduction in auditory hallucinations in people with schizophrenia after five days of twice-daily transcranial direct current stimulation (tDCS) that simultaneously targeted left dorsolateral prefrontal cortex and left temporo-parietal cortex.
Hypothesis: We hypothesized that once-daily tDCS with stimulation electrodes over left frontal and temporo-parietal areas reduces auditory hallucinations in patients with schizophrenia.
Methods: We performed a randomized, double-blind, sham-controlled study that evaluated five days of daily tDCS of the same cortical targets in 26 outpatients with schizophrenia and schizoaffective disorder with auditory hallucinations.
Results: We found a significant reduction in auditory hallucinations measured by the Auditory Hallucination Rating Scale ($F_{2,50} = 12.22$, $P < 0.0001$) that was not specific to the treatment group ($F_{2,48} = 0.43$, $P = 0.65$). No significant change of overall schizophrenia symptom severity measured by the Positive and Negative Syndrome Scale was observed.
Conclusions: The lack of efficacy of tDCS for treatment of auditory hallucinations and the pronounced response in the sham-treated group in this study contrasts with the previous finding and demonstrates the need for further optimization and evaluation of noninvasive brain stimulation strategies. In particular, higher cumulative doses and higher treatment frequencies of tDCS together with strategies to reduce placebo responses should be investigated. Additionally, consideration of more targeted stimulation to engage specific deficits in temporal organization of brain activity in patients with auditory hallucinations may be warranted.

1. Introduction

Medication-refractory hallucinations occur in about 25% of all people with schizophrenia and represent a significant cause of impaired quality of life in affected individuals [1]. Noninvasive brain stimulation that targets pathological network dynamics, in particular repetitive transcranial magnetic stimulation (rTMS), has been evaluated with mixed success for the treatment of auditory hallucinations [2–4]. Transcranial direct current stimulation (tDCS) has emerged as a complementary noninvasive brain stimulation modality that modulates cortical activity by applying a weak, constant electric current to the scalp [5]. The resulting weak electric field alters neuronal activity levels in a polarity-specific way and appears to recruit brain-derived neurotrophic factor (BDNF)-dependent plasticity [6]. A recent study successfully employed twice-daily tDCS to treat medication-refractory auditory hallucinations by simultaneously

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targeting hypoactivity in left dorsolateral prefrontal cortex (dl-PFC) and hyperactivity in left temporo-parietal junction [7].

The rationale for this spatial targeting strategy was based on imaging and electrophysiological studies. Specifically, auditory cortical areas in the left temporo-parietal region have been shown to be hyperactive during auditory hallucinations in functional magnetic resonance imaging (fMRI) studies [8,9]. In addition, a diverse set of changes in cortical oscillation patterns and functional connectivity during auditory verbal hallucinations measured by magnetoencephalography (MEG) and electroencephalography (EEG), in particular but not limited to left auditory areas, have been reported [10–14]. Further motivation for simultaneously targeting both dl-PFC and temporo-parietal junction is provided by findings of impaired functional fronto-temporal connectivity that scaled with severity of auditory hallucinations [15].

We performed a double-blind, sham-controlled exploratory clinical trial to examine if once-daily tDCS of the same targets reduce auditory hallucinations in people with schizophrenia as determined by the auditory hallucination rating scale (AHRS).

2. Methods

The study was performed at University of North Carolina - Chapel Hill (Clinical Trials.gov, NCT01963676) and approved by the UNC - Chapel Hill Institutional Review Board. Participants were recruited through referral by mental health care providers in local university clinics. All 26 participants met DSM-IV criteria for schizophrenia or schizoaffective disorder, confirmed by the Structured Clinical Interview for DSM-IV (SCID-IV). The inclusion criteria required that patients had at least three auditory hallucinations per week and were clinically stable (defined by no hospitalization or change in level of care) for a minimum of 12 weeks with no change in antipsychotic medication dose for at least 4 weeks prior to study entry. All participants were verified by chart review and/or discussion with the treating clinician to have treatment-persistent auditory hallucinations, defined as having ongoing auditory hallucinations during trials of at least 2 antipsychotic agents of adequate dose and duration. All participants or their legally authorized representatives provided written informed consent. Exclusion criteria required that subjects did not meet DSM-IV alcohol or substance abuse criteria within the past month or alcohol or substance dependence criteria within the past 6 months (other than nicotine or caffeine), had no history of significant head trauma, and had no comorbid neurological conditions (e.g. seizure disorder) or unstable medical illness.

The study design was double-blind, randomized, and sham-controlled. Blinding of the participants and all study personnel was achieved by using the "study mode" of the Neuroconn DC Plus stimulators (NeuroConn Ltd., Ilmenau, Germany) used in this study. Every participant received a numeric code by randomization performed by a third party with no knowledge or interest in the outcome of the study. Participants were assigned to a code based on entry date into the study. There were no restrictions on randomization such as blocking or stratification. All authors of the study and all other personnel involved therefore did not know which patients received verum and which patients received sham stimulation until completion of the entire study. TDCS was performed with two Neuroconn DC Plus stimulators that were synchronized by an external trigger device (Fig. 1). The montage in this study is functionally equivalent to the one used in [7,16]. However, two stimulators were used since we are preparing a follow-up study that will contrast tDCS with tACS and we did not want the study personnel or the patients to be able to discriminate between these two arms of these planned future studies by the number of devices used. A consistent electrode montage across studies will facilitate future comparisons. Three saline-soaked (0.9% sodium chloride, irrigation, USP) electrodes (7 × 5 cm) were placed between F3/FP1 (anodal, left dorsolateral prefrontal cortex), T3/P3 (cathodal left temporo-parietal junction) and a return electrode placed over Cz (posterior midline). For the tDCS used here, the return electrode has a nominally zero current flow and therefore the montage is equivalent to the ones used on previous studies. However, if theoretically the output of the two stimulators were not matched due to technical imperfections, a small stimulation current could be passed through Cz. We performed electric field simulations for a worst-case scenario of a 10% mismatch between the current output of the two stimulators using the option to simulate standard tDCS electrode pads in the HDExplore software (Soterix, New York, New York). We compared the resulting electric field distribution to the one from the original Brunelin montage and found only minimal differences that are unlikely to drive any of the effects observed in this study (Fig. 2). The location of the stimulation electrodes on the patients was found using the 10–20 placement system. Stimulation was set at +2 mA (at frontal site, anodal) and −2 mA (at temporo-parietal site, cathodal) for 20 minutes for the treatment group. The active sham group only received an initial 40 s of stimulation (same amplitudes as in treatment group) to mimic the skin sensation of tDCS. Stimulation was administered at approximately the same time of day (± 2 hours) for 5 consecutive days (Monday through Friday).

The primary outcome measure was change in auditory hallucinations severity after the 5 days of stimulation assessed

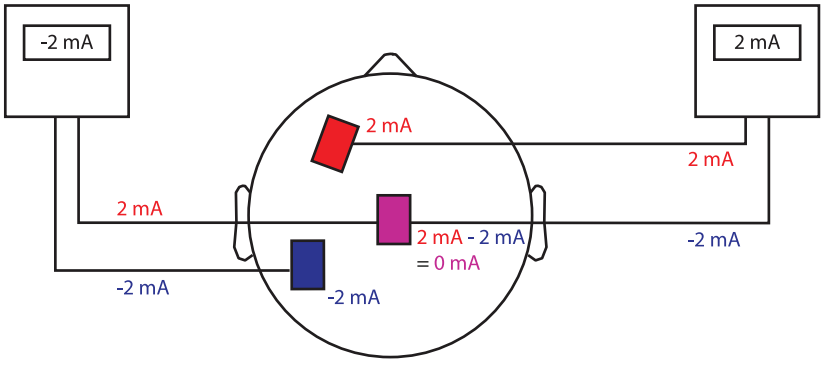

Fig. 1. Symbolic representation of stimulator and electrode configuration. Using two stimulators in the arrangement shown is functionally equivalent to using one stimulator as done in the Brunelin et al.'s study. We used this more complex setup in preparation of a study that requires two devices such that blinding to study condition can be maintained in the future.

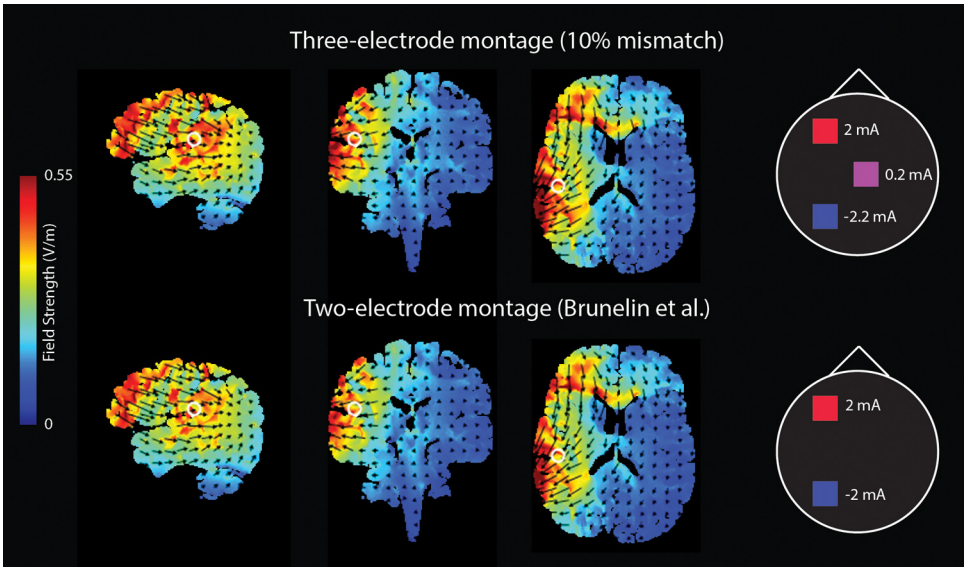

Fig. 2. Comparison of electric field applied through our three-electrode montage (top) and the Brunelin electrode montage (bottom) under a worst-case scenario for a 10% mismatch in stimulation amplitude between the two devices used in our study. Qualitatively, the targeting of macroscopic brain structures by the two electric fields is very similar. Parasagittal, coronal, and horizontal views of areas with high field strength are shown (white circle references MNI coordinates -46, -22, 22). Cartoons indicate montages (top view of symbolized head). Images created with HDExplore using the conventional pad electrode option (Soterix, New York, NY).

by the Auditory Hallucination Rating Scale (AHRS) that was administered immediately before application of the first stimulation and immediately after the last stimulation on the fifth day. As a secondary outcome, AHRS scores at 1 month (30–45 days window) after completion of stimulation sessions were used to assess maintenance of stimulation effects. The Positive and Negative Syndrome Scale (PANSS) was used at baseline, after 5 days of treatment, and at 1 month follow-up to assess changes in schizophrenia symptom severity. An adverse effects stimulation questionnaire was administered at completion of the final stimulation session (Likert Scales for headache, neck pain, scalp pain, tingling, itching, burning, sleepiness, trouble concentrating, acute mood change, and flickering lights, all scales ranged from 1 - absent to 4 - severe) and all participants were asked about whether they believe they had received active treatment or not. Demographic information and handedness information [17] was collected from the participants and medication status was obtained from the medical record and the treatment providers. All assessments were administered by a researcher blind to the group assignment; none of the investigators or study personnel was aware of group assignment prior to the data lock after the last participant had completed participation.

Custom-written scripts in R (R Foundation for Statistical Computing, Vienna, Austria) and SPSS software version 21.0 (IBM, Armonk, NY) were used for the analysis. Libraries used in R included lme4 [18] and pbkrtest [19]. Differences in demographics and characteristics of the two study arms (Tables 1–3) and in severity of adverse effects were assessed with Student's *t*-test. For the primary and the secondary outcome, effects of tDCS on AHRS scores (baseline, immediately after stimulation, and 1 month follow-up) were assessed with a linear mixed model with fixed factors "session" and "treatment" and with random factor "participant" to account for repeat measures within participants. We used the Kenward-Roger approximation to perform F-tests and to estimate *P*-values for each factor and their interaction in the mixed model [19]. Kenward-Roger approximation yields the exact F-statistic for balanced mixed classification and is better suited than the classical Chi^2 approximation for small and moderate sample sizes [19]. Post-hoc paired *t*-tests were applied to compare the three sessions (primary and secondary outcome) and Bonferroni correction was applied to

Table 1
Baseline demographic and clinical characteristics of participants.

Characteristic	Active tDCS ($n=13$)		Sham tDCS ($n=13$)		*P*-value
	Mean	SD	Mean	SD	
Age (years)	43.38	12.64	40.00	10.74	0.47
Years since symptom onset (years)	15.38	9.26	16.62	11.10	0.76
Auditory Hallucination Rating Scale score	27.00	6.90	26.69	6.30	0.91
Positive and Negative Syndrome Scale					
Total score	73.15	12.90	66.92	17.17	0.31
Positive symptoms	20.54	4.77	20.08	6.03	0.83
Negative symptoms	19.00	7.56	16.00	6.65	0.29
General psychopathology	33.62	6.61	30.85	7.49	0.33
Hallucinations	4.54	0.78	4.62	0.87	0.81

tDCS: transcranial direct current stimulation.

Table 2
Medication use by participants.

Characteristic	Active tDCS Number of participants	Sham tDCS Number of participants
Antipsychotic drugs[a]	11	13
Aripiprazole	1	1
Chlorpromazine	1	0
Clozapine	4	4
Fluphenazine	1	0
Haloperidol	2	5
Lurasidone	0	1
Olanzapine	1	2
Paliperidone	1	0
Quetiapine	1	1
Risperidone	4	2
Ziprasidone	1	0
Benzodiazepines[b]	4	0
Anticonvulsant drugs[b]	3	1

Bold corresponds to medication classes, whereas regular font corresponds to specific medications. tDCS: transcranial direct current stimulation.

[a] Nine participants were receiving 2 antipsychotic drugs (active tDCS: 6, sham tDCS: 3).

[b] In the active tDCS group, 2 participants were receiving both 1 benzodiazepine and 1 anticonvulsant.

Table 3
AHRS and PANSS scores after tDCS/sham stimulation and 1 month follow-up.

Measure	Active tDCS ($n=13$)		Sham tDCS ($n=13$)		*P*-value
	Mean	SD	Mean	SD	
After tDCS/sham stimulation					
Auditory Hallucination Rating Scale score Positive and Negative Syndrome Scale	20.62	8.13	18.15	10.77	0.52
Total score	73.38	14.24	63.85	14.25	0.25
Positive symptoms	21.31	4.87	18.15	5.71	0.14
Negative symptoms	19.23	6.82	16.31	6.20	0.26
General psychopathology	32.85	7.45	29.38	5.71	0.20
Hallucinations	4.46	0.88	3.85	1.41	0.19
1 month follow-up					
Auditory Hallucination Rating Scale score Positive and Negative Syndrome Scale	21.62	11.17	21.92	8.25	0.75
Total score	72.92	13.34	66.23	14.04	0.85
Positive symptoms	20.77	4.87	18.54	5.75	0.30
Negative symptoms	19.08	7.15	16.15	6.03	0.27
General psychopathology	33.08	6.75	31.54	6.57	0.56
Hallucinations	4.23	1.36	4.08	1.19	0.76

AHRS: Auditory Hallucination Rating Scale; PANSS: Positive and Negative Syndrome Scale; tDCS: transcranial direct current stimulation.

account for multiple comparisons. For further exploratory analyses, Wilcoxon signed-rank tests were separately applied to each subscale of the AHRS for each of the two treatment arms. Chi^2 test was used to assess if the number of patients who believed they received stimulation was significantly different between the tDCS and the sham groups. Given that this was designed as an exploratory study, outcomes were not corrected for multiple comparisons except where indicated.

3. Results

Twenty-six participants with schizophrenia and schizoaffective disorder were included in this study (schizophrenia: 19, schizoaffective disorder: 7; 22 men, 4 women). One additional participant gave written consent but immediately withdrew from the study before any assessment or stimulation was performed. No reason for withdrawal was provided. All other 26 participants completed the trial with no assessment or stimulation session missed. The 26 participants were randomized to the active treatment (tDCS) or sham treatment groups (13 patients per group). At baseline, there were no statistical differences between groups in terms of age, years since disease onset, AHRS score, and PANSS scores (Table 1). Most participants were male (11 in sham group, 9 in tDCS group) and right-handed (11 in sham group, 10 in tDCS group). Both tDCS and sham stimulation were well tolerated. Participants reported mild tingling, itching, and burning (stimulation questionnaire items with average scores of 1.5 or above in at least one of the two groups). No group-averaged score exceeded a value of 2 (moderate) and no differences between the tDCS and sham groups were found for any of the queried side-effects ($P > 0.1$). Blinding to treatment assignment was successful (11 in the sham and 7 in the tDCS group believed they received tDCS, $P = 0.20$, Chi^2 test). Medication use is documented in Table 2.

3.1. Auditory hallucinations (AHRS)

Factor "session" was significant in the analysis of the AHRS (mixed linear model with levels "baseline", "after tDCS", and "1 month follow-up" for "session", $F_{2,50} = 12.22$, $P < 0.0001$). Post-hoc testing with Bonferroni correction for multiple comparisons confirmed a difference between "baseline" and "after tDCS" ($P = 0.0001$) and between "baseline" and "1 month follow-up" ($P = 0.016$). The tDCS group showed a mean improvement of 24% (mean: −6.38 points, SD 6.38) and the sham group showed a mean improvement of 34% (mean: −8.54 points, SD 8.68) after 5 consecutive days of daily stimulation of sessions (Table 3, Fig. 3). No difference was found for the effect of tDCS on auditory hallucinations between tDCS and sham groups (interaction "treatment":"session", $F_{2,48} = 0.43$, $P = 0.65$). Since treatment effect was absent, no post-hoc testing was performed for the interaction and both primary and secondary outcomes were negative.

3.2. Schizophrenia symptoms (PANSS)

We found no significant effects for factors "session" ($F_{2,50} = 0.72$, $P = 0.49$), "treatment" ($F_{1,24} = 1.87$, $P = 0.18$), and the interaction "treatment":"session" ($F_{2,48} = 1.11$, $P = 0.34$) for the PANSS scores. We found no significant effects for factors "session" ($F_{2,50} = 0.54$, $P = 0.59$), "treatment" ($F_{1,24} = 1.00$, $P = 0.33$), and the interaction "treatment":"session" ($F_{2,48} = 2.05$, $P = 0.14$) for the positive symptoms subscore. We found no significant effects for factors "session" ($F_{2,50} = 0.16$, $P = 0.85$), "treatment" ($F_{1,24} = 1.30$, $P = 0.27$), and the interaction "treatment":"session" ($F_{2,48} = 0.00$, $P = 1.0$) for the negative symptoms subscore. We found no significant effects for factors "session" ($F_{2,50} = 2.00$, $P = 0.15$), "treatment" ($F_{1,24} = 1.03$, $P = 0.32$), and the interaction "treatment":"session" ($F_{2,48} = 1.07$, $P = 0.35$) for the general psychopathology subscore.

3.3. Exploratory analysis of AHRS subscales

Exploratory analysis of the 11 subscales of the AHRS revealed that the "loudness" score exhibited a different modulation pattern than the other subscales (Table 4). Specifically, "loudness" was not affected by sham stimulation, neither immediately after stimulation ($P = 0.74$) nor at the 1-month follow-up ($P = 0.74$). In contrast, the tDCS group exhibited a significant reduction in "loudness" after tDCS ($P = 0.039$) and at the 1-month follow-up at trend level ($P = 0.068$). At baseline, there was no difference in loudness between the two groups ($P = 0.69$). The reduction in the loudness

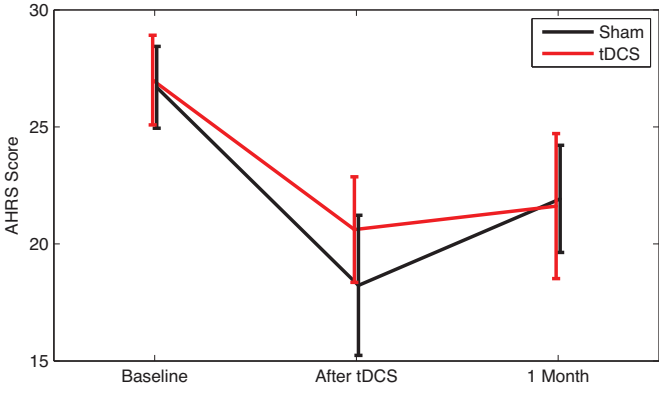

Fig. 3. Auditory Hallucination Rating Scale (AHRS) scores for transcranial direct current stimulation (tDCS) and sham groups at baseline (before first stimulation), after tDCS (after the last stimulation), and at the 1-month follow-up.

Table 4
Exploratory analysis of AHRS subscales (difference of absolute scores).

AHRS score	Active tDCS ($n = 13$)		Sham tDCS ($n = 13$)		*P*-value
	Mean	SD	Mean	SD	
After tDCS/sham stimulation					
Frequency	−0.69	1.03	−0.69	0.63	0.61
Duration	−0.38	0.87	−0.92	0.95	0.11
Location	−0.15	1.46	−1.00	1.47	0.08
Loudness	−0.77	1.30	−0.08	0.86	0.14
Beliefs re: origin of voices	−0.38	1.26	−0.69	1.25	0.31
Amount of negative content	−0.77	1.09	−0.92	1.66	0.98
Degree of negative content	−0.69	1.18	−0.77	1.36	0.93
Amount of distress	−1.00	1.68	−1.08	1.85	0.94
Intensity of distress	−1.10	1.32	−0.92	1.32	0.63
Disruption	−0.23	0.73	−0.46	0.78	0.47
Control	−0.23	1.17	−0.92	1.50	0.07
1 month follow-up					
Frequency	−0.92	1.38	−0.62	0.87	0.67
Duration	0.00	0.91	−0.46	1.13	0.31
Location	−0.38	1.19	−0.85	1.21	0.18
Loudness	−0.77	1.36	0.08	0.86	0.16
Beliefs re: origin of voices	−0.69	1.75	0.23	1.59	0.39
Amount of negative content	−0.31	1.60	−0.31	1.93	0.55
Degree of negative content	0.00	1.41	−0.54	1.27	0.47
Amount of distress	−0.77	1.17	−0.69	1.97	0.89
Intensity of distress	−0.54	1.05	−0.62	1.26	0.77
Disruption	−0.38	0.77	−0.31	0.95	0.71
Control	−0.62	1.56	−0.69	1.32	0.59

AHRS: Auditory Hallucination Rating Scale; tDCS: transcranial direct current stimulation.

scale was −0.77 in the verum group both immediately after stimulation treatment and at the 1-month follow-up. This subscale can assume values from zero to four, and a change in less than one point is of unclear clinical relevance.

4. Discussion

We performed an exploratory trial to evaluate the efficacy of once-daily combined anodal and cathodal stimulation for the treatment of auditory hallucinations in patients with clinically stable schizophrenia and schizoaffective disorder. Both primary and secondary outcomes were negative. Our study was motivated by a previous study by Brunelin et al. that found a pronounced decrease in auditory hallucination severity using twice-daily tDCS [7]. Importantly, our study had several differences in design to this positive study that are discussed below. In principle, these differences in design could explain the differences in outcome. Importantly, a pilot study that also used once-daily tDCS failed to find an effect on auditory hallucinations assessed by the auditory hallucination item of the PANSS [16]. A recent study with no sham stimulation arm [20] and several case reports describing the application of tDCS for the treatment of auditory hallucinations provide limited additional insight into the utility of tDCS given the lack of a randomized, double-blind study design [21]. Together with our results presented here, several important points of consideration for the further development of transcranial current stimulation for the treatment of auditory hallucinations arise.

4.1. TDCS dosage

We have chosen to perform stimulation once a day instead of twice a day because of the clinical usefulness. Getting patients in for two treatments a day is more difficult and would likely reduce compliance. However, a parsimonious explanation for the lack of efficacy in two of the three randomized, sham-controlled studies of tDCS is the choice of one instead of two stimulation sessions per day. Since there currently is no objective biomarker for changes of excitability in prefrontal cortex, determining optimal dosage (and spacing) of administration remains a challenge. Stimulation of motor cortex with tDCS, where changes in excitability can be objectively measured with TMS, indeed suggests complex dependence of stimulation-induced outlasting effects as a function of the time elapsed between two sessions [22]. However, it remains unclear if these effects translate to the cortical areas targeted for the treatment of auditory hallucinations. In addition, the five-day duration of the treatment studied here may be too short. For example, early TMS studies for depression used short treatments of up to two weeks [23]; today treatment durations are typically four to six weeks [24]. Further studies at a higher cumulative dose and higher treatment frequency (such as twice daily or greater) are needed as a next step.

4.2. Symptom improvement in sham group

We found substantial improvement in the auditory hallucination symptoms as measured by the AHRS in the sham-stimulated group. Pronounced placebo responses are a well-known issue in clinical trials of interventions for psychiatric illnesses. Of note, no statistically significant overall changes in the PANSS were found for either group. This is a further contrast to the study by Brunelin at al. [7]. The limitation of the placebo effect to auditory hallucinations can be explained by the fact that patients were aware of the fact that the study investigated a potential novel treatment for auditory hallucinations. Furthermore, no difference between the groups was found when the patients with fewer than daily hallucinations were excluded from the analysis, suggesting that the placebo effect was not driven by the patients who likely had more fluctuating symptoms due to the reduced frequency of their hallucinations. Interestingly, Brunelin et al. [7] found a reduction in AHRS scores of only 8% immediately after sham treatment with a reduction of 3% at the 1-month follow-up. This strongly contrasts with our finding of a 34% reduction after treatment and a continued 16% reduction at the 1-month follow-up for the sham group. A direct comparison with the study by Fitzgerald et al. [16] is more difficult since the authors used a single item from the PANSS for assessing auditory hallucinations and not the more comprehensive AHRS. This difference in placebo response to sham stimulation raises interesting questions for future studies of tDCS in schizophrenia. Many factors have been identified that could contribute to a placebo response, including the emergence of a therapeutic relationship with the study personnel, desire of study participants to please the study personnel, increased quality of care due to enrollment in study, and selection bias towards healthier patients that are more likely to exhibit spontaneous improvement or remission. Our data does not allow identification of the cause of the sham response but clearly identifies the placebo response as a concern for tDCS studies in patients with schizophrenia, in line with what is typically seen in clinical trials of antipsychotic medication (and most other medical interventions, in general). Development and adoption of strategies for reduction of the placebo responses in such tDCS trials for psychiatric indications appears to be crucial for future study designs [25]. For example, repeat assays of auditory hallucinations (spaced by few weeks) before onset of the treatment week may identify patients who experience an improvement in their symptoms due to non-specific

activities associated with enrollment in the study and not due to treatment itself. In addition, it may be worth considering a sham stimulation lead-in where all enrolled patients first receive sham stimulation and only the ones who do not exhibit a pronounced placebo effect are continued in the randomized part of the study.

4.3. Dimensions of auditory hallucinations

Our study results point towards a possible positive effect of tDCS on loudness of hallucinations. This is interesting since a previous study that used transcranial magnetic stimulation (TMS) also found no overall effect but a significant effect for loudness [26]. The interpretation of this finding in our study is limited by the exploratory nature of the analysis of AHRS subscales. However, it appears reasonable to assume that tDCS that targets auditory and language cortical structures may predominantly modulate the sensory processing aspect of hallucinations less so than the subjective negative valence that is also extensively queried as part of the AHRS assessment and substantially contributes to the overall score. Our study therefore proposes that a more refined and targeted assessment of the auditory processing aspects of auditory hallucinations should be considered as outcome measures for future studies.

4.4. Limitations

Several limitations of the current trial need to be considered. First, the sample size of this exploratory trial was small and statistical power was therefore limited to identifying changes with large effect sizes. While the data from Brunelin et al.'s study suggested a large effect size, future studies may need larger sample sizes to reliably establish the effects of tDCS on auditory hallucinations. Other limitations include the potential confounding effects of a broad background of different antipsychotic medications with different receptor affinities as well as other classes of concomitant medications that subjects were taking while in this trial (see Table 2). In particular, more subjects in the active tDCS arm were receiving benzodiazepines and/or anticonvulsants than in the sham arm, which could have limited tDCS response [27,28]. Exploratory analysis of the subset of participants who were prescribed neither benzodiazepines nor anticonvulsants revealed no difference after 5 days of tDCS (27% versus 28% percent reduction in AHRS for active tDCS versus sham tDCS) but a greater reduction at the 1-month follow-up (17% versus 9%). No statistical testing was performed due to the very small sample size in this particular analysis. In addition, blocking dopaminergic D2 receptors almost completely suppressed enhancement of motor cortex excitability in healthy human participants [29]. Therefore, it is conceivable that medications, which target the dopaminergic system in patients with schizophrenia, also modulate the response to tDCS. The heterogeneity of antidopaminergic medication in our patient sample makes further analysis of this covariate infeasible. The substantial placebo response on auditory hallucination in the current trial was somewhat unexpected, especially given the relative absence of placebo response in the study by Brunelin et al. [7].

5. Conclusions

Despite similarities in study design, our study is not a replication of the work by Brunelin et al. [7], since we tested once-daily stimulation. Nevertheless, we would have expected at least a partial effect for our dosage. Furthermore, the pronounced difference in magnitude of the placebo effect opens important questions about identifying key factors that distinguished the patient populations in the two studies. Clearly, future studies are needed to identify the most promising approach for the continued development of noninvasive brain stimulation for treatment-persistent hallucinations.

Note added to proof: a second clinical trial by the Brunelin group with a sample that overlaps with the previous study discussed here has become available online [30].

Disclosure of interest

The authors declare that they have no competing interest.

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