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Transcranial direct-current stimulation in ultra-treatment-resistant schizophrenia

J.P. Lindenmayer [a, b, c, *], Mila Kirstie C. Kulsa [a, b, d], Tania Sultana [a, b], Amandeep Kaur [a, b], Ran Yang [a, b, d], Isidora Ljuri [a, b], Benedicto Parker [a, b], Anzalee Khan [b, e]

[a] Manhattan Psychiatric Center, 600 East 125th Street Wards Island, New York, NY, 10035, USA
[b] Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Orangeburg, NY, 10962, USA
[c] New York University School of Medicine, 550 First Avenue, New York, NY, 10016, USA
[d] Teachers College Columbia University, 525 West 120th Street, New York, NY, 10027, USA
[e] NeuroCog Trials, 3211 Shannon Road #300, Durham, NC, 27707, USA

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ABSTRACT

Background: Transcranial direct-current stimulation (tDCS), a non-invasive neurostimulation treatment, has been reported in a number of sham-controlled studies to show significant improvements in treatment-resistant auditory hallucinations in schizophrenia patients, primarily in ambulatory and higher-functioning patients, but little is known of the effects of tDCS on hospitalized, low-functioning inpatients.

Objective/Hypothesis: The purpose of this study was to examine the efficacy and safety of tDCS for auditory hallucinations in hospitalized ultra-treatment-resistant schizophrenia (TRS) and to evaluate the effects of tDCS on cognitive functions. We hypothesized that treatment non-response reported in previous tDCS studies may have been due to the insufficient duration of direct-current stimulation.

Methods: Inpatient participants with DSM-V schizophrenia, long-standing treatment-resistance, and auditory verbal hallucinations (AVH) participated in this 4-week sham-controlled, randomized trial. Assessments included the Positive and Negative Syndrome Scale (PANSS) and MATRICS Consensus Cognitive Battery (MCCB) at baseline and endpoint (at the end of Week 4), and the Auditory Hallucinations Rating Scale (AHRS) administered at baseline, endpoint, and weekly throughout the study. Participants were randomized to receive active vs. sham tDCS treatments twice daily for 4 weeks.

Results: Twenty-eight participants were enrolled (tDCS, $n = 15$; control, $n = 13$) and 21 participants completed all 4 weeks of the trial. Results showed a significant reduction for the auditory hallucination total score ($p \le 0.05$). We found a 21.9% decrease in AHRS Total Score for the tDCS group and a 12.6% decrease in AHRS Total Score for the control group. Significant reductions in frequency, number of voices over time, length of auditory hallucinations, and overall psychopathology were also observed for the tDCS group. When assessing cognitive functioning, only Working Memory showed improvement for the tDCS group.

Conclusion: Although there was only a small improvement noted in auditory hallucination scores for the tDCS group, this improvement was meaningful when compared to no standard treatment of the control group. While this makes the interpretation of clinical significance debatable, it does confirm that tDCS combined with pharmacological intervention can provide clinical gains over pharmacological intervention alone. Therefore, tDCS treatment appears to be effective not only for ambulatory, higher-functioning patients, but also for patients with ultra-treatment-resistant schizophrenia.

* Corresponding author. Manhattan Psychiatric Center Wards Island Complex, New York, NY, 10035, USA.
E-mail addresses: jean-pierre.lindenmayer@nki.rfmh.org (J.P. Lindenmayer), mck2177@tc.columbia.edu (M.K.C. Kulsa), tania.sultana@omh.ny.gov (T. Sultana), amandeep.kaur@omh.ny.gov (A. Kaur), ran.yang@omh.ny.gov (R. Yang), isidora.ljuri@omh.ny.gov (I. Ljuri), benedicto.parker@nki.rfmh.org (B. Parker), anzalee.khan@nki.rfmh.org (A. Khan).

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Introduction

Although antipsychotic (AP) medications have been the conventional therapeutic intervention for chronic schizophrenia [1], 10%–30% of individuals with schizophrenia have no response to these treatments, and up to an additional 30% have only partial responses [2,3]. Adjunctive interventions for treatment-resistant schizophrenia (TRS) have been developed to target both positive and negative symptoms. Among these augmentation treatments is transcranial direct-current stimulation (tDCS), a non-pharmacological, non-invasive neurostimulation consisting of a weak, electrical direct-current delivered over the scalp that has been increasingly and successfully utilized for neurologic and psychiatric symptoms [4–6]. Transcranial brain stimulation was initially implemented as a treatment for psychosis in the 1870s and 1880s for individuals with severe depression and schizophrenia with debilitating symptoms [7]. German psychiatrists Arndt and Tigges were the first to conduct studies involving tDCS as an intervention for pervasive symptoms of severe affective disorders and psychoses, and their methodology is still implemented in current tDCS clinical trials [7]. More recently, tDCS has been found to have beneficial effects on the clinical symptoms of a variety of conditions, such as post-stroke rehabilitation [8], Parkinson's disease [9], and depression [10], with no adverse sequelae noted [5]. There also has been a resurgence of the application of tDCS specifically for individuals with treatment-refractory auditory hallucinations in schizophrenia [11].

The study by Brunelin et al. [12] was the first robust randomized controlled trial (RCT) using tDCS to show evidence for a significant reduction of antipsychotic-refractory auditory hallucinations in schizophrenia in 30 ambulatory participants with schizophrenia. Although there were no full remissions from auditory hallucinations, Brunelin et al. [12] reported significant, albeit small, effects in reductions of hallucinations from tDCS treatment compared to sham tDCS (31% reduction at the end of treatment, 36% after 1 month, and 38% after 3 months). More recent studies of tDCS have also shown efficacy in decreasing visual hallucinations [13], improving auditory hallucinations [12–14] while concurrently enhancing insight [15], and reducing overall symptom severity [12,16–18] with good tolerability [16,17]. In addition, research has shown tDCS to be a useful, non-pharmacological modality for improving cognition in schizophrenia [19–22]. Mondino et al. [23] reported positive effects after tDCS on patients' learning, working memory, attention, and source-monitoring. There has also been evidence supporting the lasting attenuation of auditory hallucinations from even a very limited number of tDCS sessions from twice daily for 5 consecutive days [12,15] to once daily for 5 days over 4 weeks [13]. One open-label study to date has shown the beneficial effects of long-term tDCS [24]. More recently, Lee et al. [25] reported positive effects from conducting a meta-analysis of existing studies on the efficacy of tDCS on hallucinations in individuals with schizophrenia. Further, another recent meta-analysis [26] of tDCS effects on psychosis symptom dimensions reported significant effects on negative symptoms and auditory hallucinations, but not on positive symptoms. However, there have also been negative, controlled studies with tDCS, which reported no significant effects on reducing hallucinations [27,28]. Fitzgerald et al. [27] conducted two small, randomized double-blind controlled trials comparing bimodal tDCS to sham stimulation applied once daily for 3 weeks and did not find any change in neither the Positive and Negative Syndrome Scale (PANSS) Hallucinatory Behavior Item nor negative symptoms. These authors recommended to investigate higher doses of stimulation or more frequently applied treatment schedules. Similarly, Frohlich et al. [28] did not find any effect of tDCS on auditory hallucinations in a well-conducted controlled trial administering tDCS once daily for 5 days. They concluded again that higher cumulative doses and higher treatment frequencies of tDCS together with strategies to reduce placebo responses should be investigated.

There remain questions on whether tDCS improves treatment-refractory auditory hallucinations [27,28]. While there are RCTs that investigated the efficacy of tDCS in other mental illness like treatment-resistant major depression [29], there is very little research involving randomized controlled studies on treatment-refractory schizophrenia patients. Most schizophrenia patients in the reported trials are outpatients with higher levels of functioning, allowing them to live in more independent, residential settings. Furthermore, there is minimal literature to date on ultra-treatment-refractory schizophrenia patients with auditory hallucinations and significant low functioning. Another important question of clinical relevance is whether tDCS can ameliorate other symptom dimensions besides auditory hallucinations in patients with treatment-resistant schizophrenia, such as cognitive functions.

The aim of the present study was to examine the efficacy and safety of tDCS treatment for both auditory hallucinations as measured by the Auditory Hallucinations Rating Scale (AHRS) Total Score and cognitive functions as measured by the MATRICS Consensus Cognitive Battery (MCCB) Composite Score in hospitalized patients with long-term treatment non-response. TRS is typically defined as the persistence of positive symptoms despite ≥2 trials of antipsychotic medications at an adequate dose and duration with documented adherence. Our patients did not only satisfy this definition, but most were also clozapine-resistant, hence the term "ultra-treatment-resistant schizophrenia" [30]. Since it has been reported that 70% of hospitalized chronic schizophrenia patients relapse within two years following optimal treatment as inpatients [31], clarifying that the effectiveness of tDCS as an intervention for patients with high levels of treatment-resistance has important clinical implications. This randomized, double-blind trial aimed to provide insight as to whether the extended use of tDCS treatment for low-functioning, ultra-treatment-resistant schizophrenia inpatients results in the significant abatement of persistent auditory hallucinations.

Material and methods

Design

This is a randomized, sham-controlled double-blind trial with blinded raters in inpatients treated in a long-term tertiary care setting (Manhattan Psychiatric Center, New York). After screening and baseline assessments, participants were randomized to one of two conditions: active tDCS treatment or a control condition (sham tDCS). Both treatments were administered twice daily for 4 weeks.

Participants

Twenty-eight inpatients with DSM-V schizophrenia or schizoaffective disorder, long-standing treatment-resistance, and persistent auditory verbal hallucinations (AVH) were recruited. Participants had to display treatment-resistant schizophrenia — defined by at least two failed antipsychotic trials at adequate dosages and of two different pharmacological families for ≥6 weeks — and treatment-refractory auditory verbal hallucinations for the past 5 years — defined by the persistence of daily auditory hallucinations without remission despite antipsychotic medications as documented in the medical records and by being placed on clozapine, unless medically contraindicated. Participants were maintained on their current antipsychotic treatment throughout the study period and were not allowed to have medication or dosing changes except for safety reasons. While the electrode montage was followed as described by Brunelin et al. [12], a longer treatment exposure was implemented in this study, as compared to previous negative studies [27,28]. The rationale was that participants with marked TRS may need a more extended period of stimulation (i.e., 4 weeks). The study was approved by the Institutional Review Board and all participants provided written informed consent (ClinicalTrials.gov # NCT 03485131).

Inclusion criteria

Participants were included who were: 1) inpatients (age 18–65 years) who met diagnostic criteria for schizophrenia or schizoaffective disorder [using the Structured Clinical Interview for DSM-V (SCID-5)]; 2) auditory hallucinations without remission over 5 years (remission was defined as a period of 4 weeks without auditory hallucinations) as documented in the patients' medical records; 3) met TRS criteria as defined by failure to respond to two previous adequate antipsychotic trials with adequate duration and dosage; 4) PANSS total rating ≥ 70 at screening; 5) PANSS Hallucinatory Behavior Item score ≥ 4; 6) able to understand and sign informed consent; 7) on a stable antipsychotic regimen 4 weeks prior to screening which was expected to be maintained for the duration of the trial; 8) normal hearing.

Exclusion criteria

Participants were excluded who had a: 1) prior history of seizure, other than that induced by electroconvulsive therapy (ECT); 2) family history of seizures; 3) significant, unstable medical condition; 4) inability to provide informed consent; 5) actively suicidal and/or showing violent behavior as assessed by each participant's treating psychiatrist; 6) significant organic brain pathology by history and neurological examination, inclusive of history of head trauma, loss of consciousness >5 min, intracranial metal implants, known structural brain lesion, devices that may be affected by tDCS (i.e., pacemaker, medication pump, cochlear implant, implanted brain stimulator); 7) active substance abuse; 8) increased intracranial pressure, unstable cardiovascular disease, or sleep apnea; 9) individuals with a clinically-defined neurological disorder; 10) frequent and persistent migraines; 11) history of adverse reaction to neurostimulation or open skin wounds that would preclude the safe placement of tDCS electrodes; 12) current use of medications known to lower seizure threshold (serotonergic or tricyclic antidepressants); 13) pregnancy; 14) if pregnant or breast-feeding at the time of screening.

tDCS treatment

The Chattanooga, dual channel CHA-1335 stimulator with two 7×5 cm (35 cm^2) sponge electrodes soaked in a saline solution (0.9% NaCl) was used for the delivery of the 2 mAmp current. Electrodes were placed based on the International 10/20 electrode positioning system [32]. For active tDCS treatment, participants had the inhibitory (cathodal) tDCS electrode placed over the left auditory cortex ["over a point midway between T3 and P3 (left temporal-parietal junction, assumed to correspond to a region including BA 22, 39, 40, 41, and 42, depending on the patient)" [12]] relative to an excitatory (anodal) electrode placed over the frontal cortex on the left side ["over a point midway between F3 and FP1 (left prefrontal cortex: dorsolateral prefrontal cortex, assumed to correspond to a region including Brodmann's areas [BA] 8, 9, 10, and 46, depending on the patient)" [12]].

Two mAmp tDCS treatments took place twice daily for 20 min each per day for 4 weeks on consecutive weekdays. Twice-daily sessions were separated by at least 3 h (one before midday and the other in the afternoon). The duration of treatment followed the proposal of Andrade [24] that patients with severe treatment-resistant hallucinations, as in the present participants, need more than the 2 weeks as used in the Brunelin et al. study [12].

For participants assigned to the placebo stimulation (sham tDCS), the stimulation parameters were displayed, but after 40 s of real stimulation of 2 mAmp to simulate the tDCS-induced skin sensation, only a small current pulse was delivered every 550 msec (110 mu Amp over 15 msec) through the remainder of the 20-min period. During the delivery of the tDCS treatment, participants were given the opportunity to read magazines or to watch National Geographic® photographs on a computer.

Assessments

Efficacy assessments

The primary efficacy outcome is the total score on the 7-item Auditory Hallucinations Rating Scale (AHRS) developed by Hoffman et al. [33] which was administered by three blinded raters, who were unaware of the participants' assigned treatment groups. Interrater reliability and internal consistency have been reported in the acceptable range for the AHRS [33] and interrater reliability [Intraclass Correlation (ICC)] of the three raters was 0.80. The AHRS was administered one week before the start of treatment, at baseline (the day before treatment began), and after each week of tDCS or sham treatment. The PANSS, Clinical Global Impression - Severity (CGI-S), and MCCB were administered at baseline and endpoint (at the end of Week 4). No change of antipsychotic medication was allowed during the trial, except for safety reasons.

Safety assessments

Each participant was evaluated for medical clearance for tDCS prior to the procedure. Vital signs (VS) were assessed by a registered nurse (RN) in the morning of each day prior to tDCS treatment. Participants were also monitored for side effects by research staff who completed Side Effects Questionnaires, which assessed the presence of symptoms (tingling, numbness, pain, burning sensation, hearing change) and signs (redness, tenderness, physical burn), after each tDCS session and by attending medical physicians' physical examinations before and after the course of tDCS treatment. Each participant was also tested with an online auditory acuity test [34] before and after the completion of the tDCS treatment period.

Statistical analysis

Intention-to-treat (ITT) analysis was used, and all participants were included who completed baseline and at least one subsequent week of treatment. Participants who refused treatment after baseline evaluations were censored. The values for mean and standard deviation (SD) are provided for the following variables: age, duration of illness, antipsychotic dose (transformed into chlorpromazine equivalents), weekly AHRS total scores, AHRS item scores, PANSS subscale scores, and CGI-S scores. The demographic and clinical characteristics of the two groups (tDCS and sham) were compared at baseline using one-way analysis of variance (ANOVA) or Chi-square test for categorical variables. The primary outcome measure was the change over time in the AHRS Total Score. To compare the overall effect of treatment on auditory verbal hallucinations (AHRS Total Score) over time in the two groups, data from the full ITT efficacy sample were analyzed with treatment (tDCS and sham) as between-subject factor and time as within-subject repeated measures analysis of covariance (RM ANCOVA) and change scores with baseline AHRS Total Score as a covariate for the interaction effect (time x group). Using at least 30% of baseline minus endpoint score as the definition of response, responder analysis was conducted using the reduction in total AHRS score. Furthermore, a regression analysis was performed to assess any interactions between changes in the scores of AHRS, PANSS, MCCB, and demographic variables. Additional exploratory outcomes were the changes in each item of the AHRS, auditory hallucinations as measured by the PANSS Hallucinatory Behavior Item, the PANSS Total Score, PANSS Positive Symptoms Item score, CGI-S score change, and change in cognitive function as measured by the MCCB Total Score and its seven component scores. Bonferroni adjustments to account for multiple comparisons were not applied for the exploratory outcome measures. SPSS software version 23.0 (IBM, SPSS, 2015) was used for all analyses.

Results

A total of 28 participants were enrolled (tDCS, n = 15; control, n = 13); 21 participants completed the trial and 7 participants did not complete the study (see Fig. 1). The mean age of the enrolled participants was 40.2 years (SD = 10.69). Most participants were male (tDCS, n = 13; 86.7%; control, n = 11; 84.6%; see Table 1). Additionally, most participants were diagnosed with schizophrenia (tDCS, n = 11; 73.3%; control, n = 8; 53.3%). Length of present psychiatric admission ranged from 1 to 25 months, with a mode of 2 months and an average of 2.9 months (SD = 4.47). Hallucinatory behavior as assessed by PANSS Item P3: Hallucinatory Behavior and the AHRS Total Score did not show any significant differences between the tDCS and control groups at baseline (see Table 2). Participants were on clozapine (n = 20), haloperidol (n = 2), paliperidone (n = 5), and fluphenazine decanoate (n = 1) as primary antipsychotic medications. The mean chlorpromazine equivalence (CPZE) for

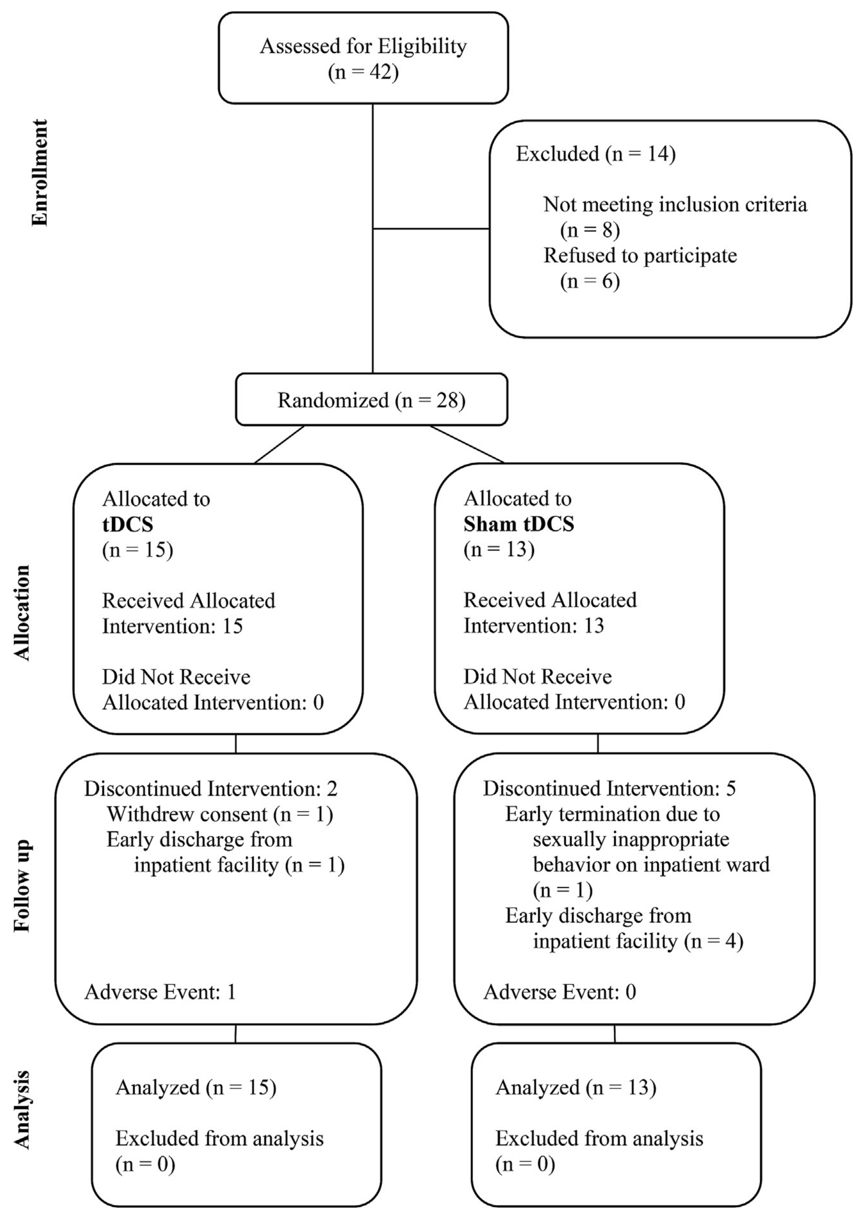

Fig. 1. Consort diagram.

Table 1
Demographic characteristics.

	tDCS (n = 15)	Control (n = 13)	Chi Square
	N (%)	N (%)	
Gender			Chi Square (1) = 0.045, *p* = 0.812
Male	13 (86.7%)	11 (84.6%)	
Race			Chi Square (3) = 2.553, *p* = 0.309
African American	8 (53.3%)	7 (46.7%)	
Asian	2 (13.3%)	2 (15.4%)	
Hispanic	5 (33.3%)	2 (15.4%)	
White (Non-Hispanic)	0 (0.0%)	2 (15.4%)	
Education			Chi Square (3) = 5.156, *p* = 0.545
7–11th Grade	7 (46.7%)	8 (53.3%)	
High School	6 (40.0%)	3 (20.0%)	
College or Higher	2 (13.3%)	2 (15.4%)	
Diagnosis			Chi Square (2) = 1.422, *p* = 0.444
Schizophrenia	11 (73.3%)	8 (53.3%)	
Schizoaffective	4 (26.7%)	5 (38.5%)	

Table 2
Clinical characteristics for hallucinatory behavior at baseline.

	tDCS (n = 15)	Control (n = 13)	ANOVA
	Mean (SD)	Mean (SD)	
PANSS Total Score	81.53 (7.539)	82.85 (9.406)	F(1,27) = 0.168, *p* = 0.685
AHRS Total Score	25.00 (3.546)	24.38 (4.426)	F(1,27) = 0.167, *p* = 0.686
PANSS Hallucinatory Behavior	4.20 (0.561)	4.15 (0.376)	F(1,27) = 0.063, *p* = 0.803

SD = Standard Deviation; PANSS = Positive and Negative Syndrome Scale; AHRS = Auditory Hallucinations Rating Scale; ANOVA = Analysis of Variance.

all participants' primary antipsychotic medications was 891.81 mg CPZE/participant.

Although screening AHRS total scores were unchanged statistically compared to baseline AHRS total scores, we observed a gradual and continuous improvement in mean AHRS total scores in the tDCS treatment group when we compared the AHRS total scores over the four weeks of treatment (see Table 3). Whereas the mean AHRS total scores of the control group remained relatively the same, the mean AHRS total scores for participants in the tDCS group decreased significantly from 25.77 (Baseline) to 22.91 (Week 2) and then to 20.17 at endpoint (Week 4). We found a 21.9% decrease in AHRS Total Score for the tDCS group and a 12.6% decrease in AHRS Total Score for the control group. A significant difference was observed for the primary efficacy outcome: AHRS Total Score [F = 3.88 ($p = 0.025$; partial $\eta^2 = 0.27$)]. Therefore, the progression of the AHRS Total Scores demonstrates that participants in the tDCS group improved throughout the study's treatment in this primary outcome measure.

The regression analysis that was performed to examine any interactions between the scores of AHRS, PANSS, MCCB, and demographic variables found results that were similar to those reported from the ANOVA (see Table 2), with no interactions observed. Furthermore, no interactions were observed between the Working Memory domain of the MCCB and AHRS scores ($p = 0.342$) and no interaction was observed between the decrease in AHRS total scores and PANSS scores ($p = 0.220$).

The exploratory outcome measures, including the AHRS Items of Frequency, Number of Voices over time, and the Length of Auditory Hallucinations, as well as the PANSS Total Score, were significant at $p \leq 0.05$, with greater reduction in scores observed for the tDCS group (see Table 4). There was no significant change over time observed for neither the PANSS subscales nor the PANSS Hallucinatory Behavior Item score (see Table 4). Participants who were classified as improvers (i.e., 30% reduction in AHRS score) were 30.7% for the tDCS group (n = 4) and 20.0% for the control group (n = 3). Chi-square analysis showed no significant difference between the two groups in terms of improver status [X^2 (2) = 3.182, $p = 0.204$]. When assessing cognitive functioning, only the Working Memory domain of the MCCB showed a significant change ($p = 0.048$; partial $\eta^2 = 0.0211$) in the tDCS group. The tDCS group showed an increase in *T*-score as compared to the control group, which showed a reduction in *T*-score (see Table 5).

Discussion

The present study provides further insight into the efficacy and safety of tDCS for treatment-refractory auditory hallucinations in ultra-treatment-refractory schizophrenia patients. Our results indicate that tDCS treatment can lead to a significant reduction in the auditory hallucination total scores for persistent auditory verbal hallucinations. Additionally, reduction in scores corresponding to the frequency, number of voices perceived, and length of

Table 3
Progression of auditory hallucinations rating scale (AHRS) total scores.

	tDCS (n = 15)						Control (n = 13)					
	AHRS Screening	AHRS Baseline	AHRS Week 1	AHRS Week 2	AHRS Week 3	AHRS Week 4 Endpoint	AHRS Screening	AHRS Baseline	AHRS Week 1	AHRS Week 2	AHRS Week 3	AHRS Week 4 Endpoint
Mean	25.85 (n = 15)	25.77 (n = 14)	23.75 (n = 12)	22.91 (n = 11)	20.11 (n = 9)	20.17 (n = 12)	23.07 (n = 13)	23.14 (n = 13)	20.17 (n = 12)	20.08 (n = 12)	20.30 (n = 10)	20.15 (n = 13)
SD	2.940	3.086	3.545	4.085	4.372	7.095	4.464	4.400	7.107	7.657	4.458	7.278

AHRS = Auditory Hallucinations Rating Scale; SD = Standard Deviation.

Table 4
Change in exploratory outcome measures across groups.

	tDCS (n = 15)		Control (n = 13)		RM ANCOVA (group x time)
	Baseline Mean (SD)	Endpoint Mean (SD)	Baseline Mean (SD)	Endpoint Mean (SD)	
AHRS Items					
Frequency of Auditory Hallucinations	4.40 (0.90)	2.08 (1.37)	3.69 (1.81)	2.98 (1.13)	$F(1,20) = 3.001$, $p = 0.044$* Partial $\eta^2 = 0.069$
Reality of Auditory Hallucinations	3.80 (0.94)	4.08 (1.36)	3.69 (1.11)	3.92 (1.22)	$F(1,20) = 0.126$, $p = 0.724$ Partial $\eta^2 = 0.010$
Distress Level from Auditory Hallucinations	2.40 (0.99)	2.00 (0.95)	2.31 (1.12)	2.17 (1.07)	$F(1,20) = 0.155$, $p = 0.720$ Partial $\eta^2 = 0.006$
Loudness of Auditory Hallucinations	3.87 (1.41)	2.58 (1.24)	2.62 (1.01)	2.33 (0.98)	$F(1,20) = 0.231$, $p = 0.711$ Partial $\eta^2 = 0.013$
Number of Voices of Auditory Hallucinations	3.93 (1.10)	2.01 (1.80)	2.92 (1.16)	2.25 (1.06)	$F(1,20) = 5.532$, $p = 0.030$* Partial $\eta^2 = 0.264$
Length of Auditory Hallucinations	3.60 (1.06)	2.03 (1.40)	3.62 (1.22)	3.67 (0.98)	$F(1,20) = 3.845$, $p = 0.033$* Partial $\eta^2 = 0.064$
Attentional Salience of Auditory Hallucinations	3.07 (1.34)	3.42 (1.51)	2.77 (0.62)	3.50 (1.11)	$F(1,20) = 0.169$, $p = 0.712$, Partial $\eta^2 = 0.020$
PANSS Items					
PANSS Positive Symptoms	21.87 (2.36)	20.56 (3.40)	21.08 (3.64)	20.55 (3.21)	$F(1,23) = 0.789$, $p = 0.423$ Partial $\eta^2 = 0.041$
PANSS Negative Symptoms	19.10 (1.11)	18.23 (2.12)	19.01 (1.36)	18.69 (3.01)	$F(1,23) = 0.779$, $p = 0.424$ Partial $\eta^2 = 0.041$
PANSS General Psychopathology Symptoms	38.65 (4.36)	37.56 (4.33)	37.55 (3.69)	36.45 (4.02)	$F(1,23) = 0.709$, $p = 0.420$ Partial $\eta^2 = 0.040$
PANSS Total Score	81.53 (7.34)	73.34 (11.11)	82.85 (9.41)	80.53 (9.56)	$F(1,23) = 4.169$, $p = 0.040$* Partial $\eta^2 = 0.172$
PANSS Hallucinatory Behavior Score	4.20 (0.56)	3.23 (1.022)	4.15 (0.38)	3.20 (1.12)	$F(1,23) = 0.796$, $p = 0.569$ Partial $\eta^2 = 0.008$
CGI-S Items					
CGI-S – Severity	4.07 (2.15)	N/A	3.69 (1.65)	N/A	$F(1, 27) = 0.260$ $p = 0.615$ Partial $\eta^2 = 0.008$
CGI-S – Improvement	N/A	3.91 (0.54)	N/A	4.00 (0.01)	$F(1,23) = 0.28$ $p = 0.605$ Partial $\eta^2 = 0.007$

*Significant at $p = 0.05$; SD = Standard Deviation; AHRS = Auditory Hallucinations Rating Scale; PANSS = Positive and Negative Syndrome Scale; CGI-S = Clinical Global Impression Scale - Severity; RM ANCOVA = Repeated Measures Analysis of Covariance.

auditory hallucinations were also observed for participants receiving the active tDCS intervention. Moreover, we found that tDCS treatment produced a reduction of the total severity of psychosis symptoms in our treatment-refractory participants. While there was no statistically significant pattern regarding the driver for the reduction in the PANSS Total Score, the largest reduction was seen in the PANSS General Psychopathology subscale (see Table 4). We also found a significant improvement in working memory after tDCS; however, we must be cautious to place too much weight on improvement in a single domain as the MCCB Composite Score did not improve in the active tDCS group. In fact, the Working Memory domain showed an actual worsening in the control group.

Equally as important is our finding that tDCS can be effective not only for ambulatory, higher-functioning patients as shown in previous reports [12,15,17,24], but can also be effective for much lower-functioning schizophrenia patients with established TRS and medication-refractory auditory verbal hallucinations. Our participants included in the current study were comparatively very impaired, not reaching the average MATRICS *T*-score composite of 37 found in other published samples of schizophrenia participants [35]. Interestingly, our response rate of 30% was very close to the one reported by Brunelin et al. [12] of 31% in ambulatory patients.

Throughout the study, there was only 1 participant among the 28 enrolled who reported an adverse event (AE). One participant in the active tDCS group reported slight redness and minimal burning sensation on the left temporal area where the electrode was placed during tDCS treatment. The redness and mild burning sensation persisted approximately 30 min after the treatment session ended, and both symptoms were reported to have resolved after 48 h. Although this participant refused the following session of tDCS treatment because of the reported symptoms, this participant continued on to complete the study. In contrast to the absence of any serious adverse events in our study, Poreisz et al. [36] reported that participants experienced headache (11.8%), nausea (2.9%), and insomnia (0.98%) after tDCS treatment. The reported AE in our study corroborates the reports of transient redness [37] and tingling or burning sensation [38], which are common following tDCS treatment.

The present results may also contribute to better clarify the question of effective dosing of tDCS. Positive studies with tDCS show that administering tDCS for the limited duration of twice daily for 5 consecutive days [12,15] to once daily for 5 days over 4 weeks [13] resulted in the reduction of auditory hallucinations. Andrade [24] reported that an extensive maintenance of 1- to 3-mAmp of tDCS for 20–30 min once to twice daily over a duration of 3 years produced benefits and no adverse side effects. Negative studies with tDCS appear to have used a limited dose [27,28] of tDCS sessions. Fitzgerald et al. [27] delivered 20 min of 2 mAmp once per day for 3 weeks, while Frohlich et al. [28] administered stimulation set at +2 mAmp (anodal) and −2 mAmp (cathodal) for 20 min on 5 consecutive days. Based on the negative studies with tDCS, we decided to evaluate the efficacy of tDCS using more frequently applied treatments on an extended treatment schedule. While the shorter duration of tDCS treatment is an advantage from a practical point of view, we did not attempt to assess a dose-response relationship between number of sessions and response in AHRS scores; therefore, we cannot draw any conclusions about this issue. However, we expanded the duration of stimulation to 4 weeks of treatment with twice-daily, 2-mAmp tDCS sessions, which may have contributed to the observed significant effect in

Table 5
Change in cognition.

	tDCS (n = 8)		Control (n = 8)		
	Baseline Mean (SD)	Endpoint Mean (SD)	Baseline Mean (SD)	Endpoint Mean (SD)	RM ANCOVA
MCCB Domain *T*-Score					
MCCB Composite	18.29 (10.58)	22.14 (21.02)	12.56 (8.86)	14.89 (8.61)	F(1,16) = 1.931, $p = 0.186$ Partial $\eta^2 = 0.121$
Speed of Processing	15.63 (21.09)	19.75 (17.31)	20.70 (10.54)	26.30 (9.45)	F(1,16) = 0.066, $p = 0.800$ Partial $\eta^2 = 0.004$
Attention/Vigilance	22.50 (8.59)	23.38 (11.73)	22.78 (15.84)	22.44 (14.64)	F(1,16) = 0.002, $p = 0.967$ Partial $\eta^2 < 0.001$
Working Memory	29.25 (10.47)	31.75 (8.84)	22.20 (9.13)	19.60 (10.28)	F(1,16) = 4.278, $p = 0.046$* Partial $\eta^2 = 0.0211$
Verbal Learning	27.13 (5.72)	28.75 (5.39)	26.80 (5.14)	28.40 (3.78)	F(1,16) = 0.027, $p = 0.872$ Partial $\eta^2 = 0.002$
Visual Learning	35.00 (16.02)	41.25 (9.63)	28.90 (13.32)	35.20 (12.64)	F(1,16) = 1.179, $p = 0.294$ Partial $\eta^2 = 0.069$
Reasoning and Problem-Solving	38.38 (9.72)	44.50 (14.77)	37.00 (4.71)	39.40 (5.62)	F(1,16) = 1.057, $p = 0.319$ Partial $\eta^2 = 0.062$
Social Cognition	32.38 (8.35)	31.75 (15.91)	26.90 (5.11)	24.80 (5.41)	F(1,16) = 2.539, $p = 0.131$ Partial $\eta^2 = 0.137$

*Significant at $p = 0.05$; SD = Standard Deviation; MCCB = MATRICS Consensus Cognitive Battery; RM ANCOVA = Repeated Measures Analysis of Covariance.

reducing AVH. This would be an indirect confirmation of the hypothesis that non-response in previous studies may have been due to insufficient duration of direct-current stimulation.

Our study also found an improvement in overall psychosis, which confirms the findings of a recent meta-analysis by Kennedy et al. [26], who found that tDCS improved all symptom dimensions compared to sham, but the effect reached significance only for negative symptoms and was associated with modest, non-significant worsening of positive symptoms. We did not find an effect on negative symptoms, which may have been due to the long-standing presence of negative symptoms and the TRS status of our participants.

There have been several hypotheses regarding the possible mechanism of action of tDCS underlying the improvement of auditory hallucinations. In our fronto-temporal tDCS administration with the cathode targeting the left temporo-parietal junction (TPJ) and the anode targeting the left dorsolateral prefrontal cortex (dlPFC), we attempted to accurately follow the original method as described by Brunelin et al. [12]. tDCS may affect cortical excitability and may shift neuronal membrane polarization (subthreshold depolarization or hyperpolarization of resting membrane potential [12]) as well as modify N-methyl-D-aspartate (NMDA) receptor efficacy [39], which results in prolonged synaptic efficacy changes [38]. The cathodal placement may have served to inhibit neurotransmission in underlying brain regions. Jardri et al. [40] reported an association between AVH and aberrant activation involving the left TPJ and the left inferior frontal cortex, as well as their right homologues. The tDCS-induced cathodal inhibition of electrical activity may have contributed to the reduction of AVH. On the other hand, the anodal placement may have served to stimulate NMDA-receptor-mediated neurotransmission in the underlying brain regions of the left dlPFC. This region subserves neurobiologically-relevant modulations of brain networks mediating cognitive functions, such as working memory [41].

We acknowledge that this study has several limitations. First, our participants are from an ultra-treatment-resistant population with auditory hallucinations and, thus, these results may not be generalizable to other populations with schizophrenia. However, our findings can be extended to a significant group of patients who are hospitalized in long-term settings and are largely unresponsive to antipsychotic polypharmacy or even to clozapine. Another limitation is that our limited sample size can lead to type-2 error and neither allowed us to draw any conclusions from delineating age categories nor allowed us to examine predictors of response, which would be helpful since tDCS treatment is a very labor-intensive intervention in an inpatient setting. This study also does not assess the durability of tDCS: whether the effects of tDCS on reducing auditory hallucinations persist following the discontinuation of tDCS treatment and, if so, how long these effects may persist. Since the first report of tDCS sessions resulting in substantial decrease in the severity of antipsychotic-refractory auditory hallucinations [18], there has been further evidence supporting the lasting attenuation of auditory hallucinations from a limited number of tDCS sessions [13,15] and the efficacy of decreasing auditory hallucinations even after administering tDCS as monotherapy [14]. Additionally, despite statistical significance, there was only a small improvement noted in auditory hallucination scores (21.9% decrease in AHRS Total Score for the tDCS group), yet this improvement was meaningful when compared to no tDCS treatment (12.6% decrease in AHRS Total Score for the control group), which makes the interpretation of clinical significance debatable, yet confirming that tDCS combined with pharmacological intervention can provide clinical gains over pharmacological intervention alone.

Conclusions

In contrast to previous studies, this sham-controlled, randomized study was conducted on a notably low-functioning and ultra-treatment-resistant inpatient population with treatment-resistant auditory verbal hallucinations. In addition, this trial expands our understanding of the efficacy and safety of tDCS since we implemented more frequently applied treatments during an extended treatment period and observed the absence of any serious adverse events. Despite the typical low-responsivity of schizophrenia patients with prolonged, severe symptoms to new treatments, our results indicate that participants who are ultra-resistant to antipsychotic treatments and who received prolonged tDCS treatment presented with significant diminution of their auditory hallucinations and total psychopathology. The efficacy of tDCS in this population can be attributed to the subtle tDCS effects, as they stimulate small changes in the membrane potential; therefore, greater effects may be achieved from extending stimulation exposure, which may be more feasible in such inpatient settings. We conclude that tDCS can be effective not only for ambulatory, higher-functioning patients, but can also be adapted and used for much lower-functioning, chronic schizophrenia patients with medication-refractory auditory verbal hallucinations.

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Conflicts of interest

We confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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