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Significant improvement in treatment resistant auditory verbal hallucinations after 5 days of double-blind, randomized, sham controlled, fronto-temporal, transcranial direct current stimulation (tDCS): A replication/extension study

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a potentially novel treatment for antipsychotic-resistant auditory verbal hallucinations (AVH) in schizophrenia. Nevertheless, results have been mixed across studies.
Methods: 89 schizophrenia/schizoaffective subjects (active: 47; Sham: 42) were randomized to five days of twice-daily 20-min active tDCS vs. sham treatments across two recruitment sites. AVH severity was assessed using the Auditory Hallucination Rating Scale (AHRS) total score. To assess target engagement, MRI was obtained in a sub sample.
Results: We observed a statistically significant, moderate effect-size change in AHRS total score across one-week and one-month favoring active treatment following covariation for baseline symptoms and antipsychotic dose ($p = 0.036$; $d = 0.48$). Greatest change was observed on the AHRS loudness item ($p = 0.003$; $d = 0.69$). In exploratory analyses, greatest effects on AHRS were observed in patients with lower cognitive symptoms ($d = 0.61$). In target engagement analysis, suprathreshold mean field-strength (>0.2 V/m) was seen within language-sensitive regions. However, off-target field-strength, which correlated significantly with less robust clinical response, was observed in anterior regions.
Conclusions: This is the largest study of tDCS for persistent AVH conducted to date. We replicate previous reports of significant therapeutic benefit, but only if medication dosage is considered, with patients receiving lowest medication dosage showing greatest effect. Response was also greatest in patients with lowest levels of cognitive symptoms. Overall, these findings support continued development of tDCS for persistent AVH, but also suggest that response may be influenced by specific patient and treatment characteristics.
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Introduction

Auditory verbal hallucinations (AVH) are amongst the most consistent hallmarks of schizophrenia. Approximately 70–80% of schizophrenia patients have AVH at initial presentation [1,2], and AVH persist in approximately 30% of schizophrenia patients overall [2–4]. Persistent AVH lead to significant emotional distress, poor societal integration and, in the case of "command" AVH, potentially violent acts directed against oneself or others [5–7].

Starting in the 1990s [8–10], increasing attention was paid to the relationship between AVH and structural/functional abnormalities of the receptive language areas of the brain. In particular,

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the left temporo-parietal-occipital junction (TPOJ) [11], a region encompassing the posterior left superior temporal gyrus (STG: Wernicke's area), appears important in AVH pathophysiology, along with parts of the supramarginal gyrus and the angular gyrus in the inferior parietal lobule.

Similarly, in functional connectivity analyses, a consistent finding in patients with AVH has been abnormal functional connectivity between auditory regions in STG and anterior language regions [12]. Most recently, AVH have been attributed to attaching undue salience to perceptual experience, which is associated with hyperactivation of critical regions located in anterior insula cortex, inferior frontal gyrus (IFG), anterior cingulate cortex, and auditory association regions within posterior superior temporal sulcus [13–15]. These findings encourage use of noninvasive neuromodulatory approaches such as transcranial Direct Current Stimulation (tDCS), transcranial magnetic (TMS) or electrical (TES) stimulation to target critical nodes to modulate connectivity within the dysfunctional networks, as previously reviewed [16]. Since, regions associated with AVH have primarily been cortical language regions [12,13,17,18], this suggests that these may be effective targets for neuromodulation-based intervention.

tDCS modulates brain function using low (<2 mA) currents applied to the scalp. Because direct currents (DC) are used, the polarity of stimulation significantly determines the effect. In general, cathodal stimulation is considered to reduce excitability in underlying brain regions, while anodal stimulation is considered to increase excitability [19,20], although network-level effects may be critical as well [21].

Unlike other brain stimulation approaches such as electroconvulsive therapy, deep brain stimulation or TMS, tDCS does not induce *de novo* brain activity at doses presently employed in human studies ($\leq$2 mA), which are associated with local field strengths within brain of <1 V/m [22]. However, significant effects on oscillatory coupling may be observed even with field strengths as low as 0.2 V/m [22], suggesting local physiological effect and a minimum threshold for response.

An initial double-blind study of tDCS [23] showed highly significant, 31% reduction in AVH severity in a group of 15 schizophrenia subjects with antipsychotic treatment resistant AVH who received active tDCS stimulation vs. 15 treated with sham ($p < 0.001$, Cohen's $d = 1.58$). This study used a twice daily 20 min treatment for 5 days with a montage in which the cathodal electrode was placed over the left TPOJ, producing radially outward field strength, and the anodal electrode was placed over left dorsolateral prefrontal cortex (DLPFC), producing radially inward field strength. Highly significant improvement ($p = 0.01$, $d = 0.98$) was also observed on total score on the Positive and Negative Symptom Scale (PANSS) [24], as well as the negative symptom subscale score ($p = 0.01$, $d = 1.07$). In the active treatment group, improvements persisted throughout a 3 month follow up period. Moreover, this effect was subsequently shown to correlate with resting state connectivity reductions between left TPOJ and insula [25].

In follow-up studies using the same tDCS montage, both positive [25–28] and negative [29,30] results have been obtained (reviewed in Refs. [31–33]). Negative results have also been observed when alterative montages are used [34–36]. The most recent meta-analysis [37] included 242 subjects, and found no significant overall benefit of tDCS (standardized mean differences (SMD) = 0.50, $p = 0.10$), although subgroup analysis supported significant effects with twice daily treatments (SMD = 1.04, $p = 0.02$) or >10 sessions (SMD = 0.86, $p = 0.009$). Thus, differences in electrode placement, treatment frequency, cumulative dose or patient characteristics may all potentially impact efficacy of tDCS.

Here, we used the same montage and treatment dosage as in the initial study [23] in a larger, multicenter study. As opposed to the initial investigation, we studied both in- and outpatients, and individuals with schizoaffective disorder as well as schizophrenia in order to assess generalizability of the effect. We also explored potential effects of both antipsychotic medication dose and target engagement - based upon across-subject variations in tDCS-induced field strength - to help identify and potentially treatment responsive subgroups and allow more precise targeting in future, definitive investigations.

A limitation for designing precise target engagement brain stimulation studies for AVH treatment is that the stereotactic (e.g. MNI) coordinates used to define potential target regions (e.g. STG) have differed substantially across mapping studies, and may also differ across individuals [38]. Thus, for the present study, we used a recently developed multimodal parcellation scheme to assess target engagement and communicate results [38].

For our target engagement analysis, we focused on language sensitive regions, including the posterior language regions ("core Wernicke's area"), which is localized primarily to the Peri-Sylvian Language area (PSL) of TPOJ, as well as language sensitive regions in both posterior (e.g. Glasser region 129: Area STSd posterior—STSdp) and anterior (e.g. Glasser region 123: Area STG anterior: STGa) auditory association cortex, and early auditory regions (e.g. Primary Auditory Cortex: A1). In insula, language sensitive regions are centered in the Anterior Ventral Insular Area (AVI) and the Frontal Opercular Areas 4 and 5 (FOP4-5), and extend into IFG, which encompasses traditionally defined Broca's area [38].

Materials and methods

Subjects: This study was conducted across two sites: Columbia University Medical Center/New York State Psychiatric Institute (CUMC/NYSPI) and the Nathan Kline Institute for Psychiatric Research (NKI). 53 subjects, all outpatients, were recruited from CUMC/NYSPI and 36 subjects, including 19 chronically hospitalized inpatients were recruited from NKI. Across sites, 17 subjects had schizoaffective disorder. Written informed consent for participation was obtained from all subjects across two sites. Clinical trials registration: ClinicalTrials.gov—NCT01898299. Prespecified "n" was 90 subjects, with an interim analysis previously presented though 82 subjects [39].

Enrollment criteria and sample size were modeled after the prior positive study [23], and powered by estimating a 10% drop-out rate and a AHRS test/retest ICC of 0.8, which provided 80% power to detect a clinically relevant, moderate-large effect-size ($d = 0.65$).

Subjects were aged 18–55 with DSM-IV diagnosis of schizophrenia or schizoaffective disorder [40], were right handed, and had antipsychotic treatment resistant AVH, defined as an Auditory Hallucination Rating Scale (AHRS) [41] score >18 (moderate) at screening and baseline despite a stable dose of antipsychotic medication for at least 1 month prior to screening. Changes to baseline antipsychotics were not permitted until after the one week ratings. Exclusion criteria were: current treatment with seizure lowering medications (Lithium, Theophylline, Tricyclic antidepressants, Buproprion >450 mg/day, Clozapine >600 mg/day, methylphenidate/mixed amphetamine salts), alcohol or substance abuse/dependence within 30 days before the study, neurological disorders (e.g., epilepsy, loss of consciousness), metallic implants, frequent and persistent migraines, skin disease or history of prior adverse response to brain stimulation protocols. An initial restriction on serotonergic antidepressants (noted on clinicatrials.gov) was removed prior to study initiation.

Design/intervention: This was a randomized, double-blind, parallel group study. Raters, experimenters, and patients were blind to treatment assignment. Subjects were randomly assigned to the active or sham condition in a 1:1 ratio in blocks of 4 in a sequence generated by an unblinded investigator (Pejman Sehatpour) not involved with study ratings/analysis.

Previously described methods were used [23]. Briefly, subjects were randomized within 30 days of screening, participated in two daily tDCS/sham sessions of 20 min each for 5 consecutive weekdays (Monday-Friday), separated by at least 3 h, with missed sessions made up the following week ($n = 9$). Stimulation was performed using a battery-driven BrainStim SYS (Brainvision LLC, Germany), and transferred through two 6.75×5.75 cm sponge electrodes soaked in a saline solution (0.9% NaCl). As previously [23], placement was guided by the international 10–20 electrode placement system, with the cathode over the left TPOJ (midway between T3 and P3) and the anode was over left DLPFC (midway between F3 and FP1).

For the active group, the stimulation level was set at 2 mA, including a 40 s ramp up/ramp down for 20 min total stimulation. In sham stimulation, electrodes were placed in the same positions as in active stimulation and the same 40 s ramp up/down was used, but without any current for the bulk of the 20 min treatment. During the treatment sessions, subjects were allowed to read material of their choice, although only 2 subjects read during sessions.

Outcomes: Both the AHRS, including the total and individual items, and the PANSS, including the PANSS hallucination item (P3), total and subscales were assessed at baseline, one week following the final treatment, and at 1- and 3-month follow-up time-points. Safety was monitored by the Wong-Baker Faces Pain Rating Scale (0–5 scale) [42] and the Brunoni tDCS Adverse Effects Questionnaire [43]. In *exploratory* analyses, effects of patient characteristics were assessed based upon a recent study [44] which found the summed score of 3 specific PANSS cognitive-symptoms (N5, G10, G11) potentially indexed etiologically discrete patient subgroups. In this study, a mean score of <9 served as the optimal cutoff for between-group differentiation.

Field strength mapping: To assess local field strength relative to intended targets, we evaluated all available structural MR scans in the active group ($n = 21$). Subjects in the sham group who received MRIs were not used for this analysis. MRIs were obtained on a 3T GE MR750 3T system at Columbia/NYSPI ($n = 18$) or Siemens 3T TiM Trio at the NKI Center for Advanced Brain Imaging ($n = 3$). For Columbia, structural images were comprised of two T1-weighted images (3D sagittal, 0.8 mm isotropic, matrix size $= 300 \times 300$, slices $= 220$, TR $= 7.856$ ms, TE $= 3.108$ ms, flip angle $= 12°$, TI $= 450$ ms) and two T2-weighted images (3D sagittal, 0.8 mm isotropic, matrix size $= 320 \times 320$, slices $= 220$, TR $= 2500$ ms, TE $= 95.708$, flip angle $= 90°$). For NKI, structural images of the entire brain were acquired from each subject using a standard MPRAGE sequence (TR $= 2500$ ms, TE $= 3.5$ ms, TI $= 1200$ ms, matrix $= 256 \times 256$, FOV $= 256$, slice thickness $= 1$ mm, 192 slices, no gap). Prior to modeling, all images were resliced at 1 mm SPM8 and Human Connectome Project [45] pipelines were used for preprocessing.

Finite-element modeling of electric field strength was performed on each subject using the "Realistic vOlumetric-Approach to Simulate Transcranial Electric Stimulation" (ROAST) [46]. Each subject's native space structural MRI coupled with electrode sizes, positions, and current strength was inputted, yielding the field strength in V/m at each voxel.

A co-registration matrix from native space to the standard 6th gen MNI-152 head was then constructed in FSL (Analysis Group, FMRIB, Oxford, UK) and used to morph each subject's electric field strength map into MNI space. Connectome Workbench (https://www.humanconnectome.org) was then used to convert volumetric files into surface files and to parcellate according to the Glasser multimodal parcellation scheme [38].

***Statistical analysis*:** The prespecified primary behavioral endpoint was percent change across AHRS items after the five-day treatment conducted using a repeated-measures MANCOVA (rmMANCOVA) with group status as a between-subjects factor and time following randomization (one week and one month) and item (7 individual items) included as within-subject factors. In prespecified analyses, only baseline AHRS score was used as a covariate. However, higher chlorpromazine equivalents (CPZE) [47] correlated significantly with higher baseline AHRS total ($r = 0.22$, $p = 0.04$) and PANSS P3 ($r = 0.30$, $p = 0.005$) scores, justifying its inclusion as an additional covariate for all analysis. Neither baseline AHRS or CPZE differed significantly between groups (Table 1), supporting our statistical analysis plan [48,49], and results were similar without controlling for CPZE.

Secondary endpoints were PANSS P3 (hallucination item), AHRS individual item scores, PANSS negative, total and subscales, three month results and *post hoc* subgroups (in-vs. outpatients, cognitive-symptoms, made-up sessions, antipsychotic changes and schizoaffective), and analyzed using a similar rmMANCOVA as in the primary, co-varying for baseline and CPZE, but without a within-subject factor for item. Three month analysis did not use the time factor.

Remission and response (>30% improvement) rates were compared using a Fisher exact test. Mean side effects across treatment days and within active/sham group comparisons were compared with a *t*-test. In target engagement analysis, Glasser parcels with mean suprathreshold mean electric field strength were identified, defined as a field strength >0.2 V/m [22]. Pearson correlations between field strength in auditory/language network-related parcels and percent change in AHRS total was calculated.

Results were unchanged if gender was included as a covariate. Between-group effect-sizes were calculated using Cohen's d expressed in SD units. Values in the text are Mean ± SD unless otherwise specified.

Results

Sample description

89 subjects were randomized (Fig. 1; active: 47; sham: 42). Baseline characteristics were similar between the groups (Table 1). 86.5% of subjects were on other psychotropic medications, including antidepressants (34.8%), anticholinergic/extrapyramidal symptoms treatments (34.8%), mood stabilizers (30.3%), anti-anxiety (29.2%), sleep aids (18.0%) and stimulants (2.2%).

Primary AVH outcomes: Post treatment AHRS raw and percent-change scores are found in Tables 2A–C and Supplemental 2A-C, respectively. When the AHRS rmMANCOVA was calculated using only baseline AHRS score as a covariate, tDCS-induced change in the primary endpoint did not reach statistical significance ($F_{1,79} = 3.2$, $p = 0.07$). However, when analyses were repeated using CPZE as an additional covariate, a significant treatment effect emerged ($F_{1,78} = 4.6$, $p = 0.036$, $d = 0.48$, Fig. 2) such that subjects receiving active tDCS showed significant larger reduction in AVH across the 1 week and 1 month observations. The group X time interaction ($F_{1,78} = 0.3$, $p = 0.58$) was non-significant, suggesting similar trajectory of symptoms from 1 week to 1 month across the groups.

Secondary outcomes: Significant improvement was also seen in PANSS-rated hallucinations (P3) across 1 week and 1 month in a secondary analysis, as reflected in a significant main effect of

Table 1
Study demographics and baseline.[a]

	Outpatient (n = 70)[b]		Inpatient (n = 19)[b]		Total (n = 89)	
	Active (n = 37)	Sham (n = 33)	Active (n = 10)	Sham (n = 9)	Active (n = 47)	Sham (n = 42)
Age	39.6 ± 10.1	40.3 ± 8.7	33.2 ± 7.1	39.6 ± 9.0	38.2 ± 9.9	40.1 ± 8.6
Male (%)	73%	82%	50%	89%	68%	83%
Education (yrs)	13.3 ± 3.5	13.6 ± 3.6	11.1 ± 2.6	12.5 ± 1.2	12.8 ± 3.4	13.4 ± 3.3
Antipsychotic dose[c]	709 ± 784	574 ± 445	1161 ± 610	825 ± 515	806 ± 768	628 ± 466
Schizoaffective (n)	9	3	3	2	12	5
AHRS Total	23.6 ± 5.0	24.5 ± 6.0	29.2 ± 6.2	27.7 ± 4.2	24.8 ± 5.7	25.2 ± 5.7
AHRS Frequency	3.4 ± 3.0	3.7 ± 3.0	5.6 ± 2.7	5.7 ± 3.4	3.9 ± 3.1	4.1 ± 3.1
AHRS Reality	4.1 ± 1.4	4.4 ± 0.9	4.3 ± 0.8	4.7 ± 0.7	4.2 ± 1.3	4.5 ± 0.9
AHRS Loudness	2.8 ± 1.0	2.8 ± 1.1	2.8 ± 0.9	2.4 ± 0.7	2.8 ± 1.0	2.7 ± 1.1
AHRS Number	2.7 ± 1.9	3.6 ± 1.9	4.9 ± 1.9	4.0 ± 2.1	3.2 ± 2.1	3.7 ± 1.9
AHRS Length	2.7 ± 1.0	2.8 ± 0.9	2.6 ± 0.7	2.7 ± 0.7	2.7 ± 0.9	2.8 ± 0.9
AHRS Salience	4.2 ± 1.4	4.1 ± 1.2	5.5 ± 1.0	4.8 ± 1	4.5 ± 1.4	4.3 ± 1.1
AHRS Distress	3.4 ± 1.2	3.1 ± 1.1	3.4 ± 1.0	3.4 ± 0.7	3.4 ± 1.2	3.2 ± 1.1
PANSS Hallucinations (P3)	4.5 ± 0.8	4.3 ± 1.0	5.2 ± 0.4	5.0 ± 0.5	4.7 ± 0.8	4.4 ± 0.9
PANSS positive	19.2 ± 3.6	18.2 ± 5.4	24.5 ± 2.9	22.3 ± 2.8	20.3 ± 4.1	19.1 ± 5.2
PANSS negative	17.7 ± 5.2	16.9 ± 4.7	15.8 ± 3.8	18.8 ± 5.7	17.3 ± 5.0	17.3 ± 5.0
PANSS Total	73.6 ± 13.4	70.4 ± 14.3	81.8 ± 9.0	83.1 ± 11.6	75.3 ± 12.9	73.2 ± 14.4

[a] No significant between group differences overall, mean ± SD.
[b] For outpatients 53 subjects from Columbia and 17 from NKI. All 19 inpatients were from NKI.
[c] Antipsychotic dose is listed as Chlorpromazine equivalents [26].

treatment group ($F_{1,77} = 4.2$, $p = 0.044$, $d = 0.46$, Fig. 3A), again without any significant interaction effects.

Across AHRS items, improvement was independently significant for the loudness item ($F_{1,78} = 9.5$, $p = 0.003$, $d = 0.69$, Fig. 3B). No significant treatment effect was seen for other AHRS items considered independently, nor for PANSS total, negative or cognitive symptom factors (all $p > 0.09$, (Supplemental Table D).

Symptom remission: Six of 44 subjects assigned to active treatment, all outpatients, reported complete remission (AHRS = 0) at 1-month, as opposed to 0 of 38 subjects assigned to sham ($p = 0.028$). There was a significantly greater proportion of outpatients with a >30% improvement ($p < 0.05$) to active (n = 13) vs. sham (n = 4) treatment, but no differential response rate for the full sample ($p = 0.19$).

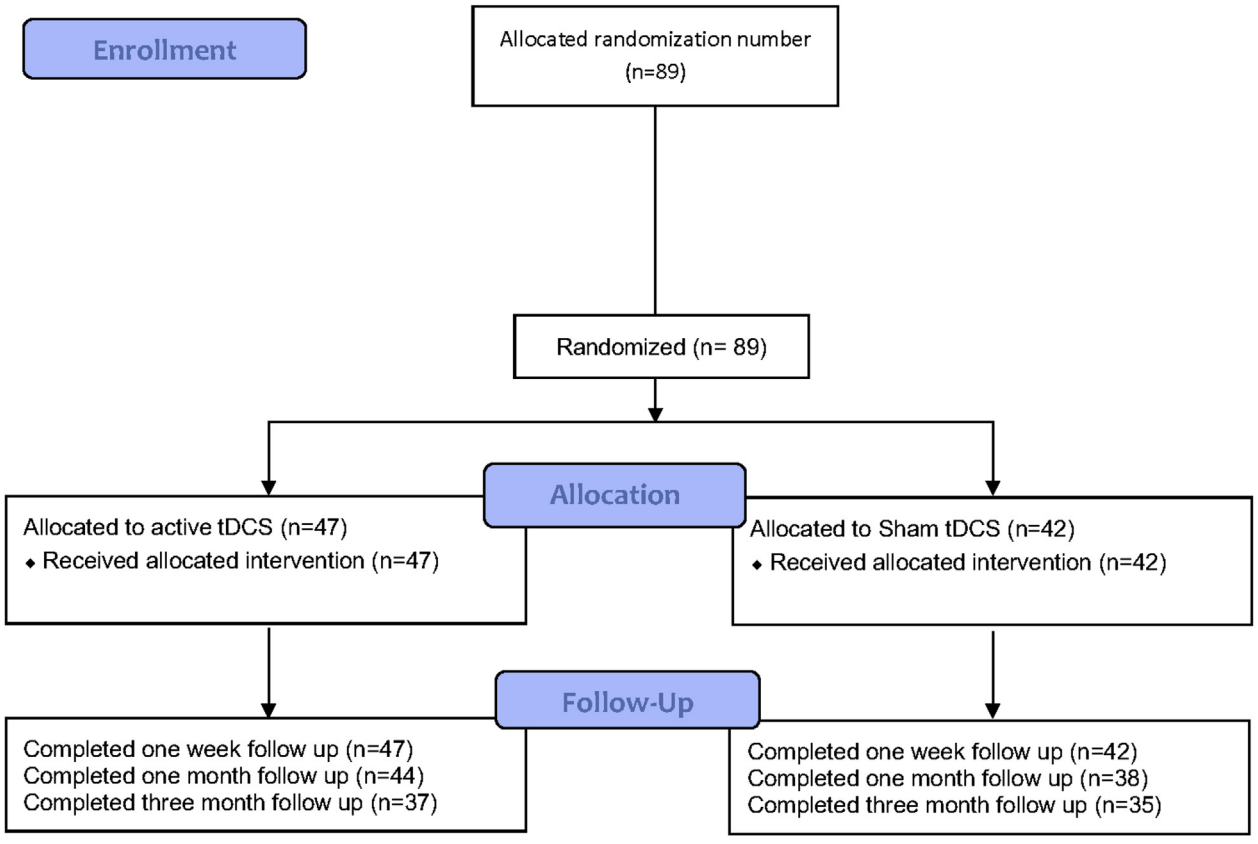

Fig. 1. Consort chart.

Table 2A
Post treatment AHRS Total: One week.[a]

	Outpatient (n=70)		Inpatient (n=19)		Total (n=89)	
	Active (n=37)	Sham (n=33)	Active (n=10)	Sham (n=9)	Active (n=47)	Sham (n=42)
AHRS Total	17.3±10.4	20.1±10.2	27.6±6.4	23.2±9.7	19.5±10.6	20.7±10.1
AHRS Frequency	2.6±2.8	2.9±2.9	5±3.3	3.6±3	3.1±3.1	3.1±2.9
AHRS Reality	3.1±2.1	3.7±1.9	3.9±1.4	4.2±1.6	3.3±2	3.8±1.8
AHRS Loudness	1.9±1.3	2.4±1.5	3±1.6	2.6±1.1	2.1±1.4	2.4±1.4
AHRS Number	2.3±2.2	2.7±1.9	4.2±2.1	3.3±2.3	2.7±2.3	2.8±2
AHRS Length	2±1.4	2.2±1.4	2.7±1.3	2.3±1.2	2.2±1.4	2.2±1.4
AHRS Salience	2.9±2	3.4±1.9	5.3±1.2	4.4±1.9	3.4±2.1	3.6±1.9
AHRS Distress	2.4±1.9	2.7±1.5	3.5±1	2.8±1.3	2.6±1.8	2.7±1.4

[a] Mean ± SD.

Effect persistence: In three-month analysis (n = 72), there was no significant between group effect of tDCS for the AHRS total ($F_{1,71} = 0.1$, $p = 0.7$, $d = 0.09$), and no differential remission rate (7 out of 37 assigned to active treatment and 4 out of 35 assigned to sham, $p = 0.52$), including 6 and 3 outpatients assigned to active and sham treatment, respectively.

Post hoc subgroup analysis

Recruitment setting

No significant differential response was observed by implementation site (CUMC/NYSPI vs. NKI). By contrast, apparent differential response was observed for patients recruited from outpatient (n = 70) vs. inpatient (n = 19) treatment settings across sites.

Among outpatients, a significant beneficial tDCS treatment effect was seen on AHRS total ($F_{1,60} = 5.2$, $p = 0.026$, $d = 0.58$), PANSS P3 ($F_{1,58} = 4.9$, $p = 0.032$, $d = 0.57$, Fig. 3C) and the AHRS loudness item ($F_{1,60} = 10.6$, $p = 0.002$, $d = 0.83$, Fig. 3D). By contrast, among active-group inpatients, significantly less improvement for the AHRS was seen compared both with the active-group outpatients ($t_{36.2} = 2.7$, $p = 0.01$) and with the inpatient sham group ($F_{1,14} = 4.8$, $p = 0.045$, $d = -1.1$). Similarly, a nonsignificant moderate effect size favoring the sham group was seen for the PANSS P3 ($F_{1,15} = 1.3$, $p = 0.27$, $d = -0.56$, Supplemental Tables).

Symptom profile: To further explore the differences between outpatients and inpatients, we evaluated the degree to which this could be accounted for by differential pretreatment symptom profiles. We have previously observed that outpatients and inpatients differ in terms of specific cognitive symptoms as measured by the PANSS [44]. Groups were therefore divided into a low cognitive-symptom group (n = 60, including 50 outpatients and 10 inpatients and 32 active and 28 sham subjects) and a high cognitive-symptom group (n = 29, including 15 active and 14 sham subjects) subgroups using this proxy [44].

In the low cognitive-symptom subgroup, a significant, moderate to large, between treatment group difference was seen for AHRS total ($F_{1,53} = 5.1$, $p = 0.028$, $d = 0.61$, Fig. 4A) and the AHRS Loudness ($F_{1,53} = 10.6$, $p = 0.002$, $d = 0.88$) and Reality ($F_{1,53} = 9.0$, $p = 0.004$, $d = 0.81$, Fig. 4B) items. Trend level differences were seen for PANSS P3 ($F_{1,53} = 3.8$, $p = 0.056$, $d = 0.53$). By contrast, no significant differences were seen in the high cognitive-symptom subgroup (all $p > 0.6$).

Neither the schizoaffective ($F_{1,11} = 0.8$, $p = 0.4$, $d = 0.52$) nor the schizophrenia ($F_{1,63} = 1.7$, $p = 0.2$, $d = 0.35$) subgroups were individually significant. Finally, AHRS total score results were similar following the removal of subjects that had post-treatment antipsychotic changes (7 active and 6 sham; $F_{1,63} = 5.0$, $p = 0.029$, $d = 0.56$) or needed >5d to complete (4 active and 5 sham; $F_{1,70} = 3.9$, $p = 0.05$, $d = 0.47$).

Target engagement: Structural MRI was analyzed on a subset of active group subjects (n = 21) with available MRIs. For these subjects, local field strength was modeled computationally based upon individual anatomy (Fig. 5A).

As intended, significant suprathreshold field strength was obtained in auditory association regions and TPOJ under the cathode (Table 3). However, field strength was heterogeneously distributed within these regions, with greatest achieved strength in areas STV and PSL of TPOJ, and areas A4 and A5 of auditory association cortex (Fig. 5B). Conversely, suprathreshold field strength under the anode was observed in multiple frontal regions, including language regions of left insula and IFG, consistent with placement of the anodal electrode over left frontal regions.

We did not observe significant correlations between field strength in posterior regions and clinical response. However, we did observe significant inverse correlation between field strength and parcels in insula, IFG and premotor cortex (Fig. 5C), such that greater achieved field strength under the anode in these regions was associated with less robust clinical response.

Safety: 98.7% of subjects completed the 5-day treatment, with one active group subject withdrawn for moderate insomnia after 3

Table 2B
Post treatment AHRS Total: One month.[a]

	Outpatient (n = 63)		Inpatient (n = 19)		Total (n = 82)	
	Active (n = 34)	Sham (n = 29)	Active (n = 10)	Sham (n = 9)	Active (n = 44)	Sham (n = 38)
AHRS Total	17.9 ± 9.7	22.9 ± 7.1	28.7 ± 4.7	23.7 ± 6	20.1 ± 9.9	23.1 ± 6.8
AHRS Frequency	2.5 ± 2.8	3.1 ± 2.9	6.1 ± 2.6	3.7 ± 2.7	3.2 ± 3.1	3.3 ± 2.8
AHRS Reality	3.2 ± 2.0	4 ± 1.4	4.3 ± 1	4.3 ± 1.1	3.5 ± 1.9	4.1 ± 1.3
AHRS Loudness	2.1 ± 1.3	2.7 ± 1.2	2.8 ± 1.2	2.6 ± 0.9	2.3 ± 1.3	2.7 ± 1.1
AHRS Number	2.4 ± 2.1	3.6 ± 1.7	5.0 ± 2.0	3.4 ± 2.1	2.9 ± 2.3	3.6 ± 1.8
AHRS Length	2.1 ± 1.2	2.7 ± 1.0	2.2 ± 0.8	2.4 ± 0.7	2.1 ± 1.1	2.7 ± 0.9
AHRS Salience	3.1 ± 1.8	3.7 ± 1.6	5.3 ± 1	4.4 ± 1.4	3.6 ± 1.9	3.9 ± 1.6
AHRS Distress	2.5 ± 1.7	3.0 ± 1.2	2.9 ± 1.2	2.8 ± 1.2	2.6 ± 1.6	2.9 ± 1.2

[a] Mean ± SD.

Table 2C
Post treatment AHRS Total: Three months.[a]

	Outpatient (n = 54)		Inpatient (n = 18)		Total (n = 70)	
	Active (n = 28)	Sham (n = 26)	Active (n = 9)	Sham (n = 9)	Active (n = 38)	Sham (n = 32)
AHRS Total	18.0 ± 10.2	19.9 ± 9.9	25.6 ± 10.8	20.4 ± 9.1	19.7 ± 10.7	20 ± 9.6
AHRS Frequency	3.1 ± 3.3	2.9 ± 2.5	5.7 ± 2.2	3.6 ± 2.4	3.6 ± 3.2	3.1 ± 2.5
AHRS Reality	3.3 ± 2.2	3.3 ± 1.9	4.4 ± 1.0	3.3 ± 1.8	3.5 ± 2	3.3 ± 1.9
AHRS Loudness	2.3 ± 1.5	2.4 ± 1.5	3 ± 1.2	2.4 ± 1.2	2.5 ± 1.4	2.4 ± 1.4
AHRS Number	1.9 ± 1.9	3.1 ± 1.9	4.9 ± 1.9	2.9 ± 1.8	2.5 ± 2.2	3.1 ± 1.9
AHRS Length	2.1 ± 1.5	2.5 ± 1.3	2.9 ± 1.1	2.0 ± 1.1	2.3 ± 1.4	2.4 ± 1.3
AHRS Salience	2.9 ± 2.0	3.3 ± 1.7	5.6 ± 0.8	3.8 ± 2.1	3.5 ± 2.1	3.4 ± 1.8
AHRS Distress	2.4 ± 1.7	3 ± 1.3	3 ± 1.4	2.5 ± 1.3	2.5 ± 1.7	2.9 ± 1.3

[a] Mean ± SD.

days. 92% completed the 1-month follow-up and 81% the 3-month follow-up. There were no significant differences in mean safety ratings including tDCS specific pain and side effects rating (Table 4), supporting both the tolerability of the treatment and the integrity of the blind.

Discussion

Non-invasive brain stimulation methods, including tDCS, represent a potential new treatment approach for medication-resistant symptoms of schizophrenia and other major mental disorders. However, ideal approaches to operationalizing these treatments are still under development. Several small scale studies using the same tDCS parameters used in the present study have shown significant beneficial effects [23,25–27], although negative results have been reported using similar, or only slightly different methods [29,30,34–36].

To our knowledge, this is the largest study to date of tDCS for persistent AVH. Our cumulative exposure was 2 mA for 200min over 1 week (400 mA-min total). tDCS produced a moderate (d = 0.48) improvement in symptoms that persisted for 1 month following the end of treatment, along with secondary, parallel improvement in the hallucination (P3) item of the PANSS (d = 0.46). In addition, in *post hoc* analyses, we identified both patient characteristics and target engagement measures that may help refine future studies.

As in the initial study using this paradigm [23], tDCS was well tolerated in both groups, with no significant differential side effect profile that would lead to unblinding (Table 4). Moreover, the effect size reported in the present study was similar to the most recent meta-analysis [37], which found an overall SMD of 0.5. As compared to these previous reports, the present report found both a smaller percent improvement in the active group and a greater sham effect. Prior studies have also differed in the degree to which negative symptoms improved along with AVH. Consistent with [27], we did not replicate improvement in negative symptoms or overall symptom change.

In a secondary finding, we observed that the largest reduction on the AHRS was on the loudness item (d = 0.69, p < 0.003), whereas no significant effects were observed on other AHRS individual items in the full sample. Other than [28], which found the largest improvement in number of voices, previous studies did not report the AHRS response to tDCS by category, limiting our ability to compare differential improvement across studies. However, a previous factor analysis suggests that loudness of AVH may load separately from other aspects of AVH [50], including distress, frequency and location. In addition, fMRI studies suggest that the loudness perception of AVH may be primarily localized to left sided cortex [51], as opposed to other components that were less clearly localized.

Role of CPZE: Between-group, tDCS-induced change in the primary endpoint required co-varying for both CPZE and baseline

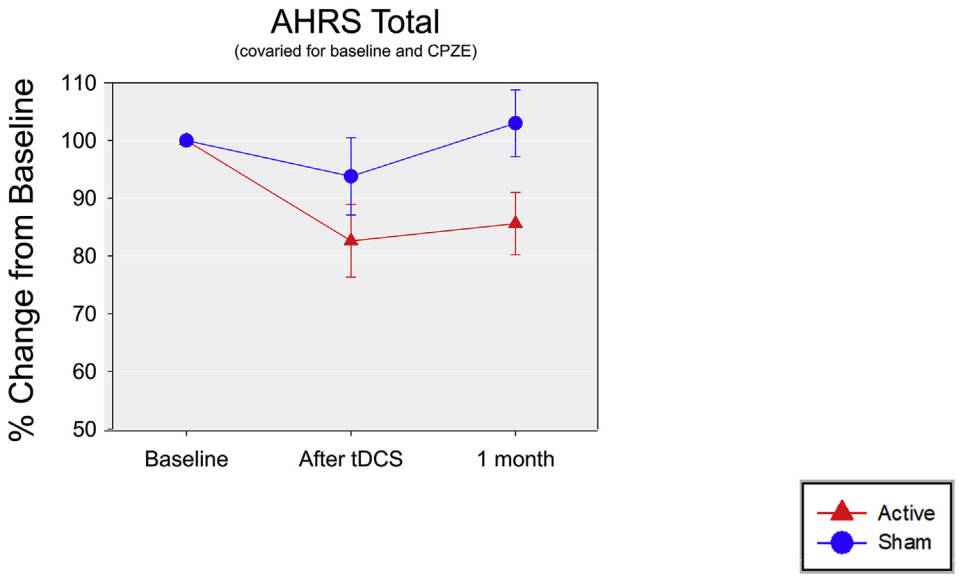

Fig. 2. Line graph showing marginal means, co-varied for Baseline scores and CPZE, for percent (±SEM) improvement from baseline (100%) in the Auditory Hallucination Rating Scale (AHRS) total score for subjects with available data through one month.

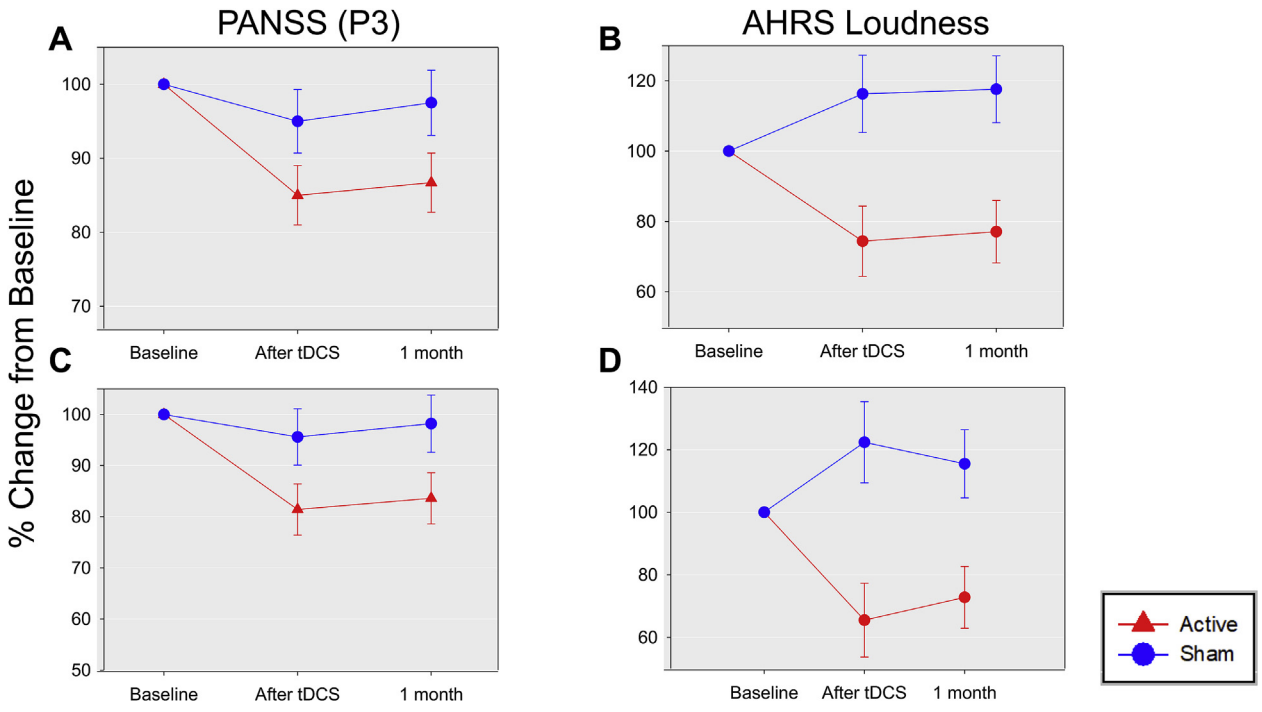

Fig. 3. Line graph showing marginal means, co-varied for Baseline scores and CPZE, for percent (±SEM) improvement from baseline (100%) in (A) the Positive and Negative Symptom Scale Hallucination item (PANSS P3) and (B) the Auditory Hallucination Rating Scale (AHRS) loudness item for subjects with available data through one month. (C–D) Line graphs showing marginal means, co-varied for Baseline scores and CPZE, for percent improvement in PANSS P3 (C) and AHRS loudness (D) for subjects recruited from outpatient settings.

AHRS scores. In general, use of MANCOVA approaches to control for clinical variables potentially related to the variable of interest increases the statistical power to detect a treatment effect [48,49]. In the present case, antipsychotic dose (CPZE) showed a paradoxical relationship to AHRS, such that higher doses were predictive of significantly higher scores on both the AHRS total ($p = 0.04$) and PANSS P3 ($p = 0.005$).

Since antipsychotics, in general, are thought to decrease severity of AVH, the fact that AVH severity correlated positively with CPZE appears paradoxical. We note that the mean CPZE in this study (721 ± 646 mg) were already higher that generally recommended [52], and thus well above commonly efficacious doses for AVH [53]. Moreover, several independent reports suggest that individuals receiving high dose treatment may be more likely to have high levels of positive symptoms in general [54,55], or AVH in particular [54], suggesting that high CPZE may be an attempt to treat antipsychotic resistant symptoms. Finally, tDCS may be less efficacious with higher CPZE, as proposed previously [56]. Thus, use of CPZE as a covariate along with AHRS score may therefore help equate baseline characteristics across individuals, thereby increasing statistical power to detect change [48,49]. Based upon present results, we suggest that covariation for baseline medication dose be used in prespecified analyses of future AVH treatment studies.

Patient selection: In terms of patient characteristics, the present study was implemented across two recruitment sites that differ in terms of outpatient/inpatient status. In a *post hoc* analysis, significant beneficial tDCS effects were observed only in the outpatient group, whereas significantly less between group improvement was observed in chronically hospitalized inpatients. This was not a factor of recruitment site, since outpatients at CUMC and NKI

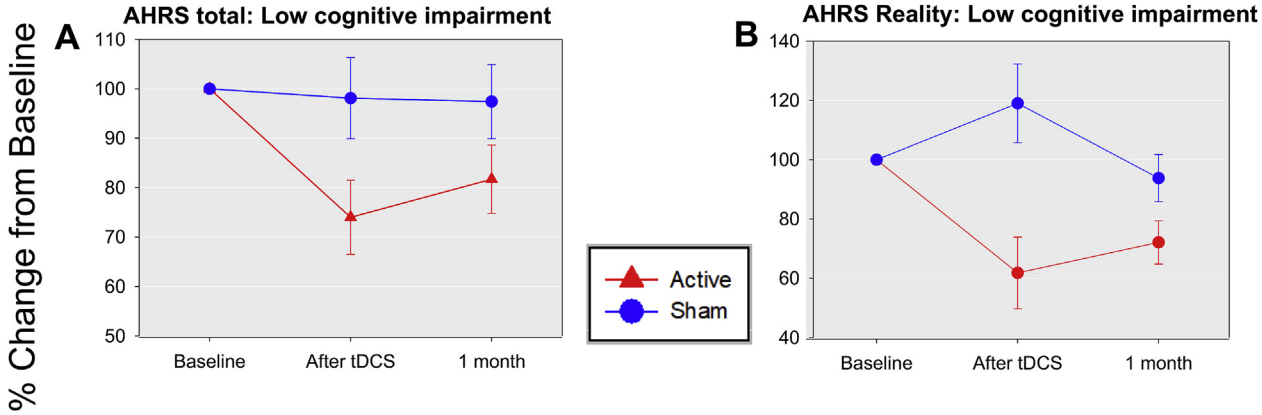

Fig. 4. Line graphs showing percent (±SEM) marginal means, co-varied for Baseline scores and CPZE, for percent improvement from baseline (100%) [47] in Auditory Hallucination Rating Scale (AHRS) total (A) or Reality (B) subjects meeting proxy criteria for intact low cognitive-symptom (early auditory processing) ($n = 60$).

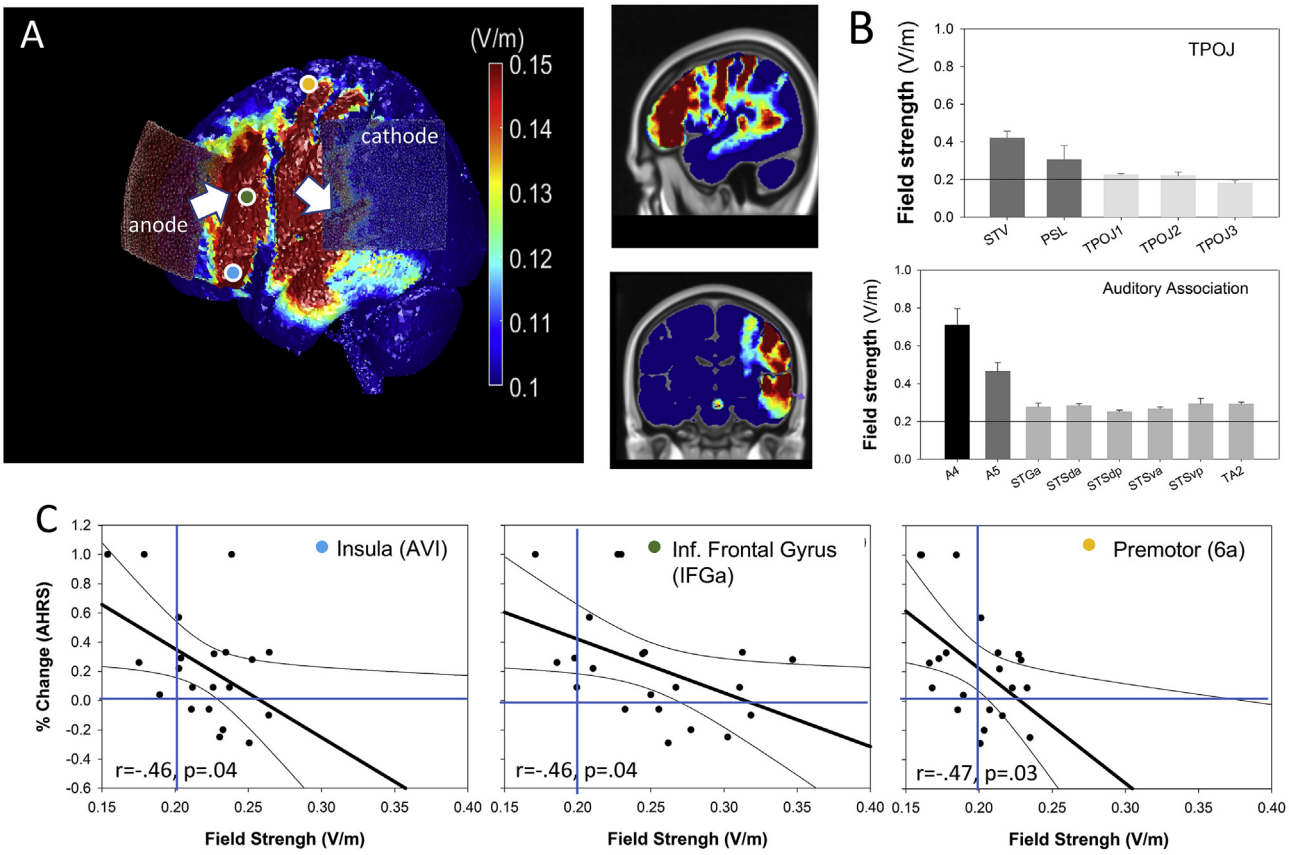

Fig. 5. Local tDCS field strength relative to clinical response. A. Field strength map calculated using Realistic vOlumetric-Approach to Simulate Transcranial Electric Stimulation" (ROAST) [46]. Cathodal and anodal electrodes are as indicated. Direction of current flow is indicated by arrows. Circles represent regions where field strength is inversely correlated with treatment response. Right panels represent sagittal and coronal views at the level of auditory cortex. B. Field strength by parcel within TPOJ and auditory association regions. Reference line represents threshold-level current flow. C. Scatterplots of field strength vs. clinical response for indicated parcels. Reference lines represent 0% change (horizontal) and threshold-level field strength (vertical).

showed similar response patterns. Thus, it may reflect pathophysiological differences between out- and chronically hospitalized inpatients that affect their ability to benefit from tDCS. It has recently been reported that such patients may benefit from more extensive treatment [28], further supported by meta-analysis support efficacy of longer treatments [37].

We have previously observed that patients drawn from primarily inpatient sites have significantly impaired early auditory processing (EAP) and greater cognitive deficits relative to those drawn from primarily outpatient sites who show unimpaired EAP performance [57]. This differential finding between in- and outpatients has recently been replicated using neurophysiological measures both by ourselves [58] and others [59,60]. As previously reviewed [61], tDCS may have a specific role in modulating EAP deficits related to overall cognitive function. Most recently, we shown that high levels of cognitive symptoms may serve as a proxy measure of EAP [44].

Table 3
Target Engagement: Regions with Suprathreshold Field strength (>2 V/m).

Cortical region	Region #[a]	Mean[b]	N	Std. Deviation
Cathodal				
Auditory Association	11	0.35	8	0.16
Lateral temporal	14	0.33	9	0.14
Posterior opercular	9	0.32	6	0.11
Temporoparietal occipital junction	15	0.27	5	0.10
Inferior parietal cortex	17	0.27	10	0.11
Early auditory	10	0.25	5	0.03
Anodal				
Inferior frontal	21	0.35	8	0.09
Premotor	8	0.31	7	0.10
Somatosensory/Motor	6	0.27	5	0.14
Dorsolateral prefrontal	22	0.27	13	0.06
Orbital/Polar frontal	20	0.27	11	0.08
Insula/frontal opercular cortex	12	0.22	13	0.03

[a] Glasser region (11).
[b] Field strength (V/m).

Table 4
Safety.

	Active (n = 47)	Sham (n = 42)	t, p
Brunoni Headache	1.1 ± 0.2	1.1 ± 0.2	0.03,0.98
Brunoni Neck pain	1.0 ± 0.1	1.0 ± 0.1	0.71,0.48
Brunoni Scalp pain	1.2 ± 0.3	1.2 ± 0.3	0.4,0.69
Brunoni Tingling	1.6 ± 0.4	1.7 ± 0.4	1.08,0.28
Brunoni Itching	1.5 ± 0.4	1.4 ± 0.5	0.27,0.79
Brunoni Burning sensation	1.5 ± 0.4	1.4 ± 0.5	0.64,0.53
Brunoni Skin redness	1.3 ± 0.4	1.2 ± 0.3	1.08,0.28
Brunoni Sleepiness	1.2 ± 0.3	1.2 ± 0.2	0.04,0.97
Brunoni Trouble concentrating	1.1 ± 0.1	1.0 ± 0.1	1.23,0.22
Brunoni Acute mood change	1.1 ± 0.1	1.1 ± 0.2	0.06,0.96
Brunoni Mean	1.2 ± 0.2	1.2 ± 0.2	0.42,0.67
WBPFRS	0.8 ± 0.9	0.8 ± 0.8	0.03,0.98

Scores averaged across all 10 tDCS sessions.
Brunoni: Brunoni tDCS Adverse Effects Questionnaire; 0 to 4 scale, with 4 being the worst.
WBFRS: Wong-Baker Faces Pain Rating Scale; 0 to 5 scale, with 5 being the worst.

Although explicit tests of cognition or EAP were not incorporated in the present study, when our cognitive-symptom proxy [44] was applied to the sample, significant beneficial effects of tDCS were observed only in the low cognitive-symptom, putatively EAP-intact subgroup (d = 0.61). Moreover, when this same proxy was applied post hoc to subjects studied by Brunelin [23], 14 of 15 (93%) subjects in the active group met low cognitive-symptom criteria (Brunelin, personal communication).

The magnitude of effect we observed in our low cognitive-symptom subjects (28.9 ± 43.0%) was highly similar to the values observed by Brunelin et al. (31 ± 14.4%), although our effect size (d = 0.48) remained smaller, relating to a higher placebo response rate. Since this low cognitive-symptom, putative EAP intact subgroup included both in- and outpatients, we hypothesize that these patient characteristics better explain the differential response as compared to hospital status. Consistent with this hypothesis, we note that in one recent negative study [29], the active group was significantly more cognitively impaired than the sham group. While other recent studies did not report direct cognitive outcomes, another recent negative study [30] had a significantly longer duration of illness in the active group, while in a recent positive study [27], the active group had less negative symptoms, potentially consistent with between group differential functional and cognitive outcomes. To test this hypothesis, we advocate explicit inclusion of both treatment setting and EAP measures in future tDCS studies.

Finally, in the present study, we included individuals with both schizophrenia and schizoaffective disorder in order to assess generalizability of the effect. Although we did not have sufficient statistical power to evaluate the schizoaffective subgroup separately, we saw no evidence of differential effect between the diagnostic subtypes, consistent with prior review [62]. Inclusion of both schizophrenia and schizoaffective disorder thus appears warranted in future studies.

Target engagement: The present low-definition ("1X1") montage was implemented prior to the availability of methodology to model intracranial current flow or to implement high-definition approaches to precisely target brain regions of interest. We therefore applied modeling *post hoc* to evaluate the degree to which the montage achieved an adequate field strength within regions implicated in the pathophysiology of AVH. To permit comparison with other studies, results were mapped using a recently developed multimodal parcellation scheme [38].

Suprathreshold cathodal field strength was achieved in the two parcels of TPOJ (PSL, STV) that are most related to language processing, as well as the A4 and A5 regions of auditory association and the early auditory cortex. Nevertheless, relatively larger field strength was achieved in lateral temporal and posterior opercular regions, which may have little language function. Thus, while effective, the present montage may not be optimized to target AVH-related brain regions [63].

In addition, in the present montage, it is necessary to place the anodal electrode over DLPFC, which induces significant radially inward field strength within frontal regions. In several regions, near the anode we observed parcels in which greater field strength led to significantly worse clinical response, including both insula (AVI) and inferior frontal gyrus (IFJa), which fall within cortical language networks [38] and which may be hyperactive in AVH + subjects. A similar inverse correlation was also observed for premotor Area 6 anterior (6a), which has recently been observed to participate in visual imagery [64], suggesting that inward field strength of these regions by tDCS may impede treatment effectiveness.

Limitations: As above, the main limitation of this study was that the stimulation montage, in retrospect, may not be optimized to target brain regions thought to be most associated with AVH. Although the results were significant and clinically noticeable, nevertheless, the majority of subjects did not achieve remission. Second, the MANCOVA required co-variation for CPZE, which was not prespecified.

Finally, an unexpected finding was that individuals with putative high cognitive-symptom, putative EAP deficits responded less well than those without. Such individuals account for ~50% of schizophrenia patients [44]. However, because EAP deficits are associated with worse functional outcome [59,65,66], such subjects are overrepresented in samples drawn from inpatient/residential care facilities, possibly explaining the high sham effects in the inpatient sample and potentially limiting the efficacy of tDCS.

In the present study, tone matching or other measures of EAP (e.g. mismatch negativity: MMN) were not implemented [65,67], so that status was inferred based upon symptom profile. Future studies should thus incorporate explicit EAP measures to permit more precise patient stratification and as biomarkers of treatment. Alternative montages may also be needed to explicitly target negative symptoms [68]. Finally, we caution that these subgroup analyses were *post hoc* in small subsamples, and should be considered preliminary.

Conclusions: In conclusion, we replicate prior reports of significant beneficial effects of tDCS applied 2/day X 5 days using a left TPOJ/DLPFC montage on persistent AVH, although not on negative symptoms. In addition, we show feasibility of individual subject mapping of electric field strength. Over recent years, methods for designing and implementing MR-guided multi-electrode, high definition arrays have increased dramatically [16], potentially permitting more effective targeting of posterior and anterior language regions in future studies. Future studies using individualized, field-strength guided high-definition tDCS approaches to more precisely target language sensitive regions may be warranted [69,70].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.03.003.

Disclosures

Dr. Kantrowitz reports having received consulting payments within the last 24 months from Krog & Partners Incorporated, IQVIA, Alphasights, Charles River Associates, Semantics MR LTD, Putnam Associates, LifeSci Capital and BVF Partners. He has served on the Schizophrenia Advisory Board for Alkermes.

He has conducted clinical research supported by the NIMH, the Stanley Foundation, Takeda, Taisho, Lundbeck, Boehringer Ingelheim, NeuroRX, Teva, Merck, and Lilly within the last 24 months. He owns a small number of shares of common stock in GlaxoSmithKline.

Dr. Girgis reports research support from Genentech, Allergan and Bioadvantex.

Dr. Javitt reports having received consulting payments within the last 2 years from Pfizer, FORUM, Autifony, Glytech, Lundbeck, Concert, and Cadence. He holds intellectual property rights for use of NMDA modulators in treatment of neuropsychiatric disorders. He holds equity in Glytech, AASI, and NeuroRx, and serves on the

advisory board of Promentis, Phytec and NeuroRx. All other co-authors report no conflicts.

References

[1] Andreasen NC, Flaum M. Schizophrenia: the characteristic symptoms. Schizophr Bull 1991;17(1):27–49.
[2] Goghari VM, Harrow M, Grossman LS, Rosen C. A 20-year multi-follow-up of hallucinations in schizophrenia, other psychotic, and mood disorders. Psychol Med 2013;43(6):1151–60.
[3] Heilbronner U, Samara M, Leucht S, Falkai P, Schulze TG. The longitudinal course of schizophrenia across the lifespan: clinical, cognitive, and neurobiological aspects. Harv Rev Psychiatry 2016;24(2):118–28.
[4] Bohlken MM, Hugdahl K, Sommer IE. Auditory verbal hallucinations: neuroimaging and treatment. Psychol Med 2017;47(2):199–208.
[5] Berman BA, Duffy K, Serper MR. Beliefs about voices and aggressive behavior in inpatients in an acute psychiatric setting. J Clin Psychiatry 2010;71(4):497–501.
[6] Cheung P, Schweitzer I, Crowley K, Tuckwell V. Violence in schizophrenia: role of hallucinations and delusions. Schizophr Res 1997;26(2–3):181–90.
[7] Mancevski B, Keilp J, Kurzon M, Berman RM, Ortakov V, Harkavy-Friedman J, et al. Lifelong course of positive and negative symptoms in chronically institutionalized patients with schizophrenia. Psychopathology 2007;40(2):83–92.
[8] Barta PE, Pearlson GD, Powers RE, Richards SS, Tune LE. Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. Am J Psychiatry 1990;147(11):1457–62.
[9] Silbersweig D, Stern E. Functional neuroimaging of hallucinations in schizophrenia: toward an integration of bottom-up and top-down approaches. Mol Psychiatr 1996;1(5):367–75.
[10] Suzuki M, Yuasa S, Minabe Y, Murata M, Kurachi M. Left superior temporal blood flow increases in schizophrenic and schizophreniform patients with auditory hallucination: a longitudinal case study using 123I-IMP SPECT. Eur Arch Psychiatry Clin Neurosci 1993;242(5):257–61.
[11] Vercammen A, Knegtering H, den Boer JA, Liemburg EJ, Aleman A. Auditory hallucinations in schizophrenia are associated with reduced functional connectivity of the temporo-parietal area. Biol Psychiatry 2010;67(10):912–8.
[12] Curcic-Blake B, Ford JM, Hubl D, Orlov ND, Sommer IE, Waters F, et al. Interaction of language, auditory and memory brain networks in auditory verbal hallucinations. Prog Neurobiol 2017;148:1–20.
[13] Powers AR, Mathys C, Corlett PR. Pavlovian conditioning-induced hallucinations result from overweighting of perceptual priors. Science (New York, NY) 2017;357(6351):596–600.
[14] Powers III AR, Kelley M, Corlett PR. Hallucinations as top-down effects on perception. Biol Psychiatr Cogn Neurosci Neuroimaging 2016;1(5):393–400.
[15] Cassidy CM, Balsam PD, Weinstein JJ, Rosengard RJ, Slifstein M, Daw ND, et al. A perceptual inference mechanism for hallucinations linked to striatal dopamine. Curr Biol : CB 2018;28(4):503–514 e4.
[16] Bikson M, Brunoni AR, Charvet LE, Clark VP, Cohen LG, Deng ZD, et al. Rigor and reproducibility in research with transcranial electrical stimulation: an NIMH-sponsored workshop. Brain Stimul 2018;11(3):465–80.
[17] Horga G, Schatz KC, Abi-Dargham A, Peterson BS. Deficits in predictive coding underlie hallucinations in schizophrenia. J Neurosci : Off J Soc Neurosci 2014;34(24):8072–82.
[18] Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. Am J Psychiatry 2011;168(1):73–81.
[19] Bindman LJ, Lippold OC, Redfearn JW. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. JPhysiol 1964;172:369–82.
[20] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol 2000;527(Pt 3):633–9.
[21] Brunoni AR, Shiozawa P, Truong D, Javitt DC, Elkis H, Fregni F, et al. Understanding tDCS effects in schizophrenia: a systematic review of clinical data and an integrated computation modeling analysis. Expert Rev Med Devices 2014;11(4):383–94.
[22] Voroslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernandez-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun 2018;9(1):483.
[23] Brunelin J, Mondino M, Gassab L, Haesebaert F, Gaha L, Suaud-Chagny MF, et al. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am J Psychiatry 2012;169(7):719–24.
[24] Kay SR, Opler LA. The positive-negative dimension in schizophrenia: its validity and significance. Psychiatr Dev 1987;5(2):79–103.
[25] Mondino M, Jardri R, Suaud-Chagny MF, Saoud M, Poulet E, Brunelin J. Effects of fronto-temporal transcranial direct current stimulation on auditory verbal hallucinations and resting-state functional connectivity of the left temporo-parietal junction in patients with schizophrenia. Schizophr Bull 2016;42(2):318–26.
[26] Mondino M, Haesebaert F, Poulet E, Suaud-Chagny MF, Brunelin J. Fronto-temporal transcranial Direct Current Stimulation (tDCS) reduces source-monitoring deficits and auditory hallucinations in patients with schizophrenia. Schizophr Res 2015;161(2–3):515–6.
[27] Bose A, Shivakumar V, Agarwal SM, Kalmady SV, Shenoy S, Sreeraj VS, et al. Efficacy of fronto-temporal transcranial direct current stimulation for refractory auditory verbal hallucinations in schizophrenia: a randomized, double-blind, sham-controlled study. Schizophr Res 2018;195:475–80.
[28] Lindenmayer JP, Kulsa MKC, Sultana T, Kaur A, Yang R, Ljuri I, et al. Transcranial direct-current stimulation in ultra-treatment-resistant schizophrenia. Brain Stimul 2019;12(1):54–61.
[29] Koops S, Blom JD, Bouachmir O, Slot MI, Neggers B, Sommer IE. Treating auditory hallucinations with transcranial direct current stimulation in a double-blind, randomized trial. Schizophr Res 2018.
[30] Chang CC, Tzeng NS, Chao CY, Yeh CB, Chang HA. The effects of add-on fronto-temporal transcranial direct current stimulation (tDCS) on auditory verbal hallucinations, other psychopathological symptoms and insight in schizophrenia: a randomized, double-blind, sham-controlled trial. Int J Neuropsychopharmacol/Off Sci J Coll Int Neuropsychopharmacologicum (CINP) 2018;21(11). 979-87.
[31] Ponde PH, de Sena EP, Camprodon JA, de Araujo AN, Neto MF, DiBiasi M, et al. Use of transcranial direct current stimulation for the treatment of auditory hallucinations of schizophrenia - a systematic review. Neuropsychiatric Dis Treat 2017;13:347–55.
[32] Kennedy NI, Lee WH, Frangou S. Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: a meta-analysis of randomized controlled trials. Eur Psychiatry : J Assoc Eur Psychiatrists 2018;49:69–77.
[33] Lee EHM, Chan PY, Law EYL, Lin JJX, Hui CLM, Chang WC, et al. Efficacy of transcranial direct current stimulation (tDCS) as a treatment for persistent hallucinations in patients with schizophrenia: a systematic review and meta-analysis. Schizophr Res 2018.
[34] Fitzgerald PB, McQueen S, Daskalakis ZJ, Hoy KE. A negative pilot study of daily bimodal transcranial direct current stimulation in schizophrenia. Brain Stimul 2014;7(6):813–6.
[35] Frohlich F, Burrello TN, Mellin JM, Cordle AL, Lustenberger CM, Gilmore JH, et al. Exploratory study of once-daily transcranial direct current stimulation (tDCS) as a treatment for auditory hallucinations in schizophrenia. Eur Psychiatry : J Assoc Eur Psychiatrists 2016;33:54–60.
[36] Smith RC, Boules S, Mattiuz S, Youssef M, Tobe RH, Sershen H, et al. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. Schizophr Res 2015;168(1–2):260–6.
[37] Kim J, Iwata Y, Plitman E, Caravaggio F, Chung JK, Shah P, et al. A meta-analysis of transcranial direct current stimulation for schizophrenia: “Is more better?”. J Psychiatr Res 2019;110. 117-26.
[38] Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, et al. A multi-modal parcellation of human cerebral cortex. Nature 2016;536(7615):171–8.
[39] Kantrowitz JT, Beggel O, Horga G, Moreno-Ortega M, Kangarlu A, Silipo G, et al. Replication of significant improvement in auditory verbal hallucinations after 5 days of double-blind, sham controlled Inhibitory (cathodal) tDCS in schizophrenia patients treatment resistant to antipsychotics. Neuropharmacology 2016;41(13 Supp):M206.
[40] First MB, Spitzer RL, Gibbon M, Williams J. Structural clinical interview for DSM-IV Axis I disorders (SCID-IV). New York: Biometrics Research Department, New York State Psychiatric Institute; 1997.
[41] Hoffman RE, Gueorguieva R, Hawkins KA, Varanko M, Boutros NN, Wu YT, et al. Temporoparietal transcranial magnetic stimulation for auditory hallucinations: safety, efficacy and moderators in a fifty patient sample. Biol Psychiatry 2005;58(2):97–104.
[42] Foundation W-BF. Wong-baker FACES® pain rating scale. 2016.
[43] Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol 2011;14(8):1133–45.
[44] Donde C, Martinez A, Kantrowitz JT, Silipo G, Dias E, Medalia A, et al. Bimodal distribution of tone matching deficits indicates discrete pathophysiological entities within the syndrome of schizophrenia. submitted.
[45] Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, et al. The minimal preprocessing pipelines for the human connectome project. Neuroimage 2013;80:105–24.
[46] Huang Y, Datta A, Bikson M, Parra L. Realistic vOlumetric-Approach to Simulate Transcranial Electric Stimulation – ROAST – a fully automated open-source pipeline. bioRxiv 2017. https://doi.org/10.1101/217331.
[47] Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003;64(6):663–7.
[48] Egbewale BE, Lewis M, Sim J. Bias, precision and statistical power of analysis of covariance in the analysis of randomized trials with baseline imbalance: a simulation study. BMC Med Res Methodol 2014;14:49.
[49] Zhang S, Paul J, Nantha-Aree M, Buckley N, Shahzad U, Cheng J, et al. Empirical comparison of four baseline covariate adjustment methods in analysis of continuous outcomes in randomized controlled trials. Clin Epidemiol 2014;6:227–35.
[50] Woodward TS, Jung K, Hwang H, Yin J, Taylor L, Menon M, et al. Symptom dimensions of the psychotic symptom rating scales in psychosis: a multisite study. Schizophr Bull 2014;40(Suppl 4):S265–74.

[51] Vercammen A, Knegtering H, Bruggeman R, Aleman A. Subjective loudness and reality of auditory verbal hallucinations and activation of the inner speech processing network. Schizophr Bull 2011;37(5):1009–16.
[52] Lehman AF, Kreyenbuhl J, Buchanan RW, Dickerson FB, Dixon LB, Goldberg R, et al. The schizophrenia patient outcomes research team (PORT): updated treatment recommendations 2003. Schizophr Bull 2004;30(2):193–217.
[53] Sommer IE, Slotema CW, Daskalakis ZJ, Derks EM, Blom JD, van der Gaag M. The treatment of hallucinations in schizophrenia spectrum disorders. Schizophr Bull 2012;38(4):704–14.
[54] Sim K, Su HC, Fujii S, Yang SY, Chong MY, Ungvari G, et al. High-dose antipsychotic use in schizophrenia: a comparison between the 2001 and 2004 research on east asia psychotropic prescription (REAP) studies. Br J Clin Pharmacol 2009;67(1):110–7.
[55] Barbui C, Biancosino B, Esposito E, Marmai L, Dona S, Grassi L. Factors associated with antipsychotic dosing in psychiatric inpatients: a prospective study. Int Clin Psychopharmacol 2007;22(4):221–5.
[56] Agarwal SM, Bose A, Shivakumar V, Narayanaswamy JC, Chhabra H, Kalmady SV, et al. Impact of antipsychotic medication on transcranial direct current stimulation (tDCS) effects in schizophrenia patients. Psychiatr Res 2016;235:97–103.
[57] Rabinowicz EF, Silipo G, Goldman R, Javitt DC. Auditory sensory dysfunction in schizophrenia: imprecision or distractibility? Arch Gen Psychiatr 2000;57(12):1149–55.
[58] Lee M, Sehatpour P, Dias EC, Silipo GS, Kantrowitz JT, Martinez AM, et al. A tale of two sites: differential impairment of frequency and duration mismatch negativity across a primarily inpatient versus a primarily outpatient site in schizophrenia. Schizophr Res 2018;191:10–7.
[59] Thomas ML, Green MF, Hellemann G, Sugar CA, Tarasenko M, Calkins ME, et al. Modeling deficits from early auditory information processing to psychosocial functioning in schizophrenia. JAMA Psychiatr 2017;74(1):37–46.
[60] Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, et al. Identification of distinct psychosis biotypes using brain-based biomarkers. Am J Psychiatry 2016;173(4):373–84.
[61] Kantrowitz JT, Swerdlow NR, Dunn W, Vinogradov S. Auditory system target engagement during plasticity-based interventions in schizophrenia: a focus on modulation of N-Methyl-D-Aspartate-Type glutamate receptor function. Biol Psychiatr Cogn Neurosci Neuroimaging 2018;3(7):581–90.
[62] Kantrowitz JT, Citrome L. Schizoaffective disorder: a review of current research themes and pharmacological management. CNS Drugs 2011;25(4):317–31.
[63] Lee WH, Kennedy NI, Bikson M, Frangou S. A computational assessment of target engagement in the treatment of auditory hallucinations with transcranial direct current stimulation. Front Psychiatry 2018;9:48.
[64] Winlove CIP, Milton F, Ranson J, Fulford J, MacKisack M, Macpherson F, et al. The neural correlates of visual imagery: a co-ordinate-based meta-analysis. Cortex; a journal devoted to the study of the nervous system and behavior. 2018.
[65] Kantrowitz JT. N-methyl-d-aspartate-type glutamate receptor modulators and related medications for the enhancement of auditory system plasticity in schizophrenia. Schizophr Res 2018. https://doi.org/10.1016/j.schres.2018.02.003.
[66] Kantrowitz JT, Hoptman MJ, Leitman DI, Moreno-Ortega M, Lehrfeld JM, Dias E, et al. Neural substrates of auditory emotion recognition deficits in schizophrenia. J Neurosci : Off J Soc Neurosci 2015;35(44):14909–21.
[67] Perrin MA, Kantrowitz JT, Silipo G, Dias E, Jabado O, Javitt DC. Mismatch negativity (MMN) to spatial deviants and behavioral spatial discrimination ability in the etiology of auditory verbal hallucinations and thought disorder in schizophrenia. Schizophr Res 2018;191:140–7.
[68] Kantrowitz JT. Managing negative symptoms of schizophrenia: how far have we come? CNS Drugs 2017;31(5):373–88.
[69] Kuo HI, Bikson M, Datta A, Minhas P, Paulus W, Kuo MF, et al. Comparing cortical plasticity induced by conventional and high-definition 4 x 1 ring tDCS: a neurophysiological study. Brain Stimul. 2013;6(4):644–8.
[70] Sreeraj VS, Dinakaran D, Parlikar R, Chhabra H, Selvaraj S, Shivakumar V, et al. High-definition transcranial direct current simulation (HD-tDCS) for persistent auditory hallucinations in schizophrenia. Asian J Psychiatr 2018;37:46–50.