Asian Journal of Psychiatry 88 (2023) 103750

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

A pilot study to investigate the efficacy and tolerability of lesion network guided transcranial electrical stimulation in outpatients with psychosis spectrum illness

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ARTICLE INFO

Keywords:
Positive Symptoms
Transcranial Electrical Stimulation
Lesion Network Mapping

ABSTRACT

Background: Transcranial electrical stimulation (tES) may improve psychosis symptoms, but few investigations have targeted brain regions causally linked to psychosis symptoms. We implemented a novel montage targeting the extrastriate visual cortex (eVC) previously identified by lesion network mapping in the manifestation of visual hallucinations.

Objective: To determine if lesion network guided High Definition-tES (HD-tES) to the eVC is safe and efficacious in reducing symptoms related to psychosis.

Methods: We conducted a single-blind crossover pilot study (NCT04870710) in patients with psychosis spectrum disorders. Participants first received HD-tDCS (direct current), followed by 4 weeks of wash out, then 2 Hz HD-tACS (alternating current). Participants received 5 days of daily (2×20 min) stimulation bilaterally to the eVC. Primary outcomes included the Positive and Negative Syndrome Scale (PANSS), biological motion task, and Event Related Potentials (ERP) from a steady state visual evoked potential (SSVEP) paradigm. Secondary outcomes included the Montgomery-Asperg Depression Rating Scale, Global Assessment of Functioning (GAF), velocity discrimination and visual working memory task, and emotional ERP.

Results: HD-tDCS improved PANSS general psychopathology in the short-term ($d=0.47$; $p_{fdr}=0.03$), with long-term improvements in general psychopathology ($d=0.62$; $p_{fdr}=0.05$) and GAF ($d=-0.56$; $p_{fdr}=0.04$) with HD-tACS. HD-tDCS reduced SSVEP P1 ($d=0.25$; $p_{fdr}=0.005$), which correlated with general psychopathology ($\beta = 0.274$, $t = 3.59$, $p = 0.04$). No significant differences in safety or tolerability measures were identified.

Conclusion: Lesion network guided HD-tES to the eVC is a safe, efficacious, and promising approach for reducing general psychopathology via changes in neuroplasticity. These results highlight the need for larger clinical trials implementing novel targeting methodologies for the treatments of psychosis.

1. Introduction

Transcranial electrical stimulation (tES) modulates cortical activity and influences cognition (Sun et al., 2021), perception (Schülke and Straube, 2019), and positive symptoms in psychosis (Gupta et al., 2018). Few researchers have integrated recent neuroimaging findings to identify optimal stimulation targets, such as location, frequency, and circuits (Raymond et al., 2022). Innovations in tES hardware and software now allows for more focal stimulation (using high definition tES, HD-tES) compared to sponge montages (Solomons and Shanmugasundaram,

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https://doi.org/10.1016/j.ajp.2023.103750
Received 26 July 2023; Received in revised form 9 August 2023; Accepted 17 August 2023
Available online 22 August 2023

2020) and greater spatial target engagement using current flow models (Edwards et al., 2013). While HD-tES advances have been effective for the treatment of neuropsychiatric disorders (Parlikar et al., 2021) few studies have used HD-tES in psychosis (Sun et al., 2021; Raymond et al., 2022; Nayok et al., 2021; Bose et al., 2017).

Psychotic disorders consist of negative symptoms (Correll and Schooler, 2020), positive symptoms (Pienkos et al., 2019), cognitive deficits (Fett et al., 2020) and disorganized thoughts and/or behavior (Ventura et al., 2010). Positive symptoms, such as hallucinations are often debilitating with visual hallucinations (VH) associated with more severe morbidity, delusions, suicidal behavior, and catatonia (Chouinard et al., 2019). Estimations related to the prevalence of VH in psychosis have been reported to be upwards of 27% in individuals diagnosed with schizophrenia, 15% in affective psychosis and roughly 7% in the general population (Waters et al., 2014). In addition, others have shown that the prevalence of VH can be as high as 33% in first-episode of psychosis (Allen et al., 2023). Lifetime prevalence rates have been estimated to be between 23% and 31% (McCarthy-Jones et al., 2017). While antipsychotics treat positive symptoms, ~30% of individuals are treatment resistant (Caspi et al., 2004), which may result in metabolic dysregulation (Pillinger et al., 2020), agranulocytosis, and risk of seizures (Molden, 2021). Thus, there is a critical need for novel, neurobiologically informed, non-invasive, and safe treatments for psychosis symptom management, such as HD-tES.

To optimize tES parameters we used a combination of neuroimaging, neurophysiological, and cause-effect studies. The extrastriate visual cortex (eVC) was of particular importance due to its role in motion perception, neurocognition, and social cognition (Chen, 2011; Tong, 2003). For instance, in a large cross-sectional neuroimaging study we identified thinning of the eVC (V5/MT) across the psychosis spectrum compared to controls, which correlated with poor cognition and response inhibition (Türközer et al., 2022). In fMRI studies examining active visual and/or auditory hallucinations in drug-free adolescents with brief psychotic disorders or adults with psychosis spectrum disorders, the authors found activation of the primary and secondary visual cortices (van Ommen et al., 2023; Jardri et al., 2013). Results from a lesion networking mapping (LNM) study, a powerful tool used to make causal inferences from lesions causally linked to symptoms (Fox, 2018), identified the eVC to be implicated in VH (Kim et al., 2021). Pathologically elevated eVC activity has also been demonstrated in psychosis (Goebel et al., 2001). Lastly, a study examining the neural basis of motion perception in schizophrenia found that reduced V5/MT activation was associated with lower delta (2 Hz) evoked amplitude during motion related tasks and poorer cognitive performance (Martínez et al., 2018). While brain frequency specific characteristics have not been utilized in past tES targeting of the visual cortex, results such as those from Martinez et al., 2018 (Martínez et al., 2018) highlight the importance of oscillatory mechanisms in the eVC. This convergent body of work highlights the importance of the eVC and delta frequency in psychosis and provides a framework for neurobiologically informed treatment with HD-tES.

To examine the translational value of the eVC in psychosis, we conducted a proof-of-concept single blind crossover study at a single site to characterize the efficacy and safety of using cathodal HD-tDCS (transcranial direct current stimulation) or delta frequency (2hz) HD-tACS (transcranial alternating current stimulation) in improving psychosis symptoms, visual processing, and visual evoked potentials.

2. Methods

2.1. Participants

This study enrolled outpatients beginning October 1, 2020 with the final study visit completed on January 2, 2022. This study was approved by the Institutional Review Board at Beth Israel Deaconess Medical Center, Massachusetts. Participants signed written informed consent and were compensated for their participation (see trial protocol in Supplement 1).

We intended to recruit 10 individuals (5 sham and 5 HD-tDCS) between the ages of 18–55 years with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder using the Structured Clinical Interview for DSM-V, and with a lifetime history of VH and/or experiencing mild to moderate symptoms of VH. Since recruitment efforts were hindered due to institutional restrictions during the COVID-19 pandemic, we removed the VH requirement and sham condition. Instead, the study was transitioned to a crossover design using HD-tDCS followed by 2 Hz HD-tACS.

Participants had no antipsychotic medication change in the month prior to participation. Participants were excluded if they had an intelligence quotient < 60, any major medical or neurologic condition, a diagnosis of substance abuse or positive urine drug screen, history of moderate-to-severe visual impairment secondary to glaucoma, cataract or macular degeneration, serious medical illness or instability requiring hospitalization within the last year, relevant skin allergies, metallic or electronic implants, or if they were pregnant or breastfeeding.

2.2. Procedure

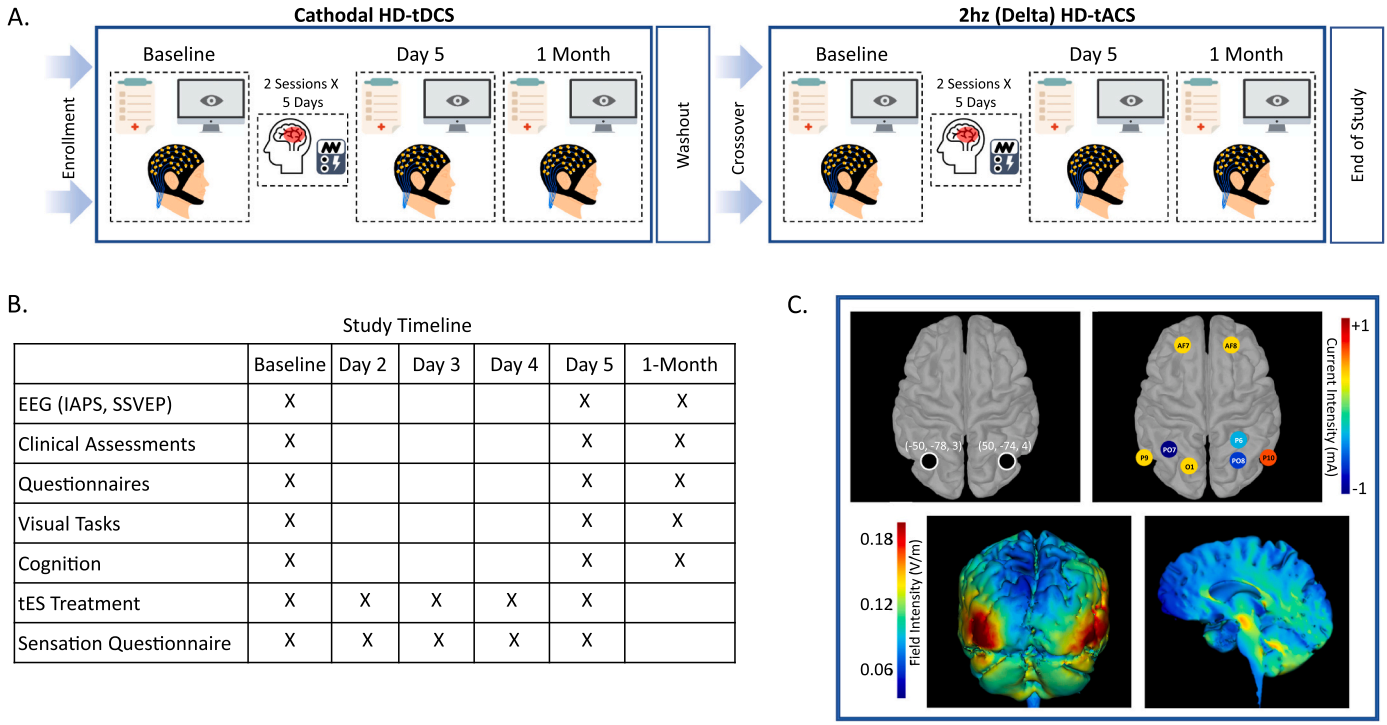
This proof-of-concept study used a between-participants, single blind, non-randomized, crossover design, with two tES treatment conditions. Participants first received HD-tDCS, followed by 4 weeks of wash out (beginning the following week after day 5 of HD-tDCS treatment), then received 2 Hz HD-tACS (Fig. 1 A). Clinical assessments were performed by a psychiatrist at baseline, day 5 and 1-month. Participants arrived at the hospital on a Monday, were briefed on study procedures by a research assistant, followed by electroencephalography (EEG) including a steady-state visual evoked potential (SSVEP) task, and emotional scene processing task (International Affective Picture System; IAPS). Visual processing tasks were conducted while seated in a dark room under the supervision of study staff (Fig. 1B). Then, 2 sessions of 20 min HD-tDCS was administered daily for 5 days while the participant sat comfortably, quietly and without disruption. A 15–20 min break was provided between the 2 sessions and participants were asked to complete a brief sensation questionnaire related to sensations felt during the administration of tES. On a Friday, and after 5 days of treatment, baseline assessments were repeated. These assessments were performed again after 1-month. Participants then received HD-tACS, which consisted of the same study procedures as HD-tDCS.

2.3. Treatment

HD-tDCS and HD-tACS was delivered by a Soterix MXN-9 High Definition-Transcranial Electrical Current Stimulator, Model 9002 A (Supplement 2). The stimulation montage was designed to target the lesion network mapping findings associated with VH, which identified the bilateral eVC (Kim et al., 2021) (Fig. 1C). The delta (2 Hz) frequency peak for this study was extracted from the Maritnez et al., 2018 paper, which conducted a time-frequency analysis of a motion processing task in patients with schizophrenia (Supplement 3). Electrical current field modeling (Edwards et al., 2013) using HD-Explore and HD-Targets (Soterix Medical) guided decision-making about where to place electrodes, with the goal of delivering focalized current to the bilateral eVC. The montage consisted of cathodal PO7 and anodal P9, O1, AF7 on the left, and cathodal P6, P08 and anodal P10, AF8 on the right according to the International 10–10 System. HD-tACS used the same montage but with 2hz in-phase alternating current being delivered (Fig. 1C).

2.4. Outcome measures

The North-East Visual Hallucination Interview (NEVHI) was employed to establish participants with a past history of VH (Holiday et al., 2017; Mosimann et al., 2008). The questionnaire includes 3 binary



	Baseline	Day 2	Day 3	Day 4	Day 5	1-Month
EEG (IAPS, SSVEP)	X				X	X
Clinical Assessments	X				X	X
Questionnaires	X				X	X
Visual Tasks	X				X	X
Cognition	X				X	X
tES Treatment	X	X	X	X	X	
Sensation Questionnaire	X	X	X	X	X	

Fig. 1. : Study Design, Timeline and Transcranial Electrical Stimulation (tES) Montage: A. Depicts the experimental crossover study design. B. Demonstrates the study timeline showing when the primary and secondary outcomes were collected, as well as the days participants received electrical stimulation. C. Shows the stimulation coordinates in Montreal Neurologic Institute (MNI) space for the bilateral extrastriate visual cortex target, stimulation electrode montage (current intensity depicted in heatmap), and the current flow modeling (field intensity depicted in heatmap). **Note**: HD-tDCS, High-Definition Transcranial Direct Current Stimulation; HD-tACS, HHD-Transcranial Alternating Current Stimulation; EEG, Electroencephalogram; IAPS, International Affective Picture System; SSVEP, Steady State Visual Evoked Potential.

responses related to VH. If answered 'yes' to one of these questions, the participant is identified as having VH. See Table 1 for count of participants with past VH. It is important to note, that no individuals were experiencing active VH.

The primary outcomes examined were the Positive and Negative Syndrome Scale (PANSS), biological motion detection, and SSVEP between timepoints and stimulation montages. PANSS total, positive, negative, and general scores were used. Visual processing outcomes were obtained by a biological motion task to assess the accuracy for determining the direction of motion (Türközer et al., 2019) (Supplement 4). Event Related Potential (ERP) measures were obtained through a SSVEP task to assess changes in biomarkers of the early visual response, the P1 and N1 (Supplement 5).

Table 1
Baseline Demographic Characteristics.

	HD-tDCS	HD-tACS
Sex (M/F)	3/3 (N = 6)	2/2 (N = 4)
Race/Ethnicity		
Black	2	2
White	3	2
Other	1	0
Age, mean (SD)	29.7 (2.6)	29.8 (3.1)
DSM-V Diagnosis	3	2
Schizophrenia		
Schizoaffective	1	1
Bipolar	2	1
NEVHI Q1–3: VH+ /VH-	4/2	2/2
CPZ Equivalence, Mean (SD)	260.9 (269.6)	314.4 (279.0)
Illness Duration in Years, Mean (SD)	11.8 (3.7)	9.5 (1.0)

Notes: HD-tDCS, High-Definition Transcranial Direct Current Stimulation; HD-tACS, High-Definition Transcranial Alternating Current Stimulation; NEVHI, North-East Visual Hallucination Interview; VH+ , visual hallucinations present; VH-, no visual hallucinations; CPZ, chlorpromazine; SD, Standard Deviation

The secondary outcomes examined included the Montgomery-Asberg Depression Rating Scale (MADRS), Global Assessment of Functioning (GAF), visual processing behavioral tasks, and emotional processing ERPs. Visual processing measures were obtained through a velocity discrimination and a visuospatial working memory task to assess accuracy of speed detection and visual working memory, respectively (Türközer et al., 2019) (Supplementary 4). Emotional ERP measures were obtained using the IAPS, which consists of unpleasant, pleasant, and neutral scene stimuli, to assess changes in a motivationally-relevant early visual biomarker, the early posterior negativity (EPN) (Lang et al., 1997) (Supplementary 5).

Exploratory analyses included determining whether significant ($p < 0.1$) target engagement of EEG measures using tES would be correlated with significant ($p < 0.1$) changes in clinical or behavioral measures.

2.5. Statistical analysis

All statistics were performed using R software (v4.1.2) and RStudio. For individuals missing 1-month assessments (HD-tDCS n = 1, HD-tACS n = 1), values were imputed using the Amelia package (Honaker et al., 2011) while accounting for scores across sessions. Modeling constraints were considered for imputation and implemented using the polynomial to account for the effect of time. One imputation model was run to obtain imputed values. The "ggstatsplot" package was used for statistical analysis and plots (Patil, 2021). The "WRS2″ package was used for two-way ANOVA (Mair and Wilcox, 2020). Chlorpromazine equivalents was calculated using "chlorpromazineR" and the Leucht et al. methodology (Leucht et al., 2020). We used non-parametric tests consisting of the Friedman and Durbin Conover tests to examine within group differences. Trimmed means (20%) two-way ANOVA models were used to examine group (HD-tDCS, HD-tACS) by session (baseline, day 5 &

1-month) interactions. To assess the relationship between changes (follow up - baseline) in clinical and EEG measurements, rank-based estimation regression while controlling for skewness (Kloke and McKean, 2012) was used with baseline clinical measurements used as a covariate. An alpha value of 0.10 was set for significance due to the sample size of the study and to help identify effect sizes to power future large scale trials (Kim and Choi, 2021). An alpha value of 0.10 was used to determine significance throughout the analysis for this study in order to achieve a balance between the probabilities of committing Type I and II errors when working with small sample sizes, which in turn substantially increases the power of the effect (Kim and Choi, 2021). Kendall (*W*) and Rank Biserial Effect Size (RBES) was calculated. False discovery rate (FDR) corrected p-values are reported for pairwise comparisons. To confirm significant results, analyses were re-run using the non-imputed dataset and are reported in the supplement.

3. Results

A total of 6 participants with a psychosis spectrum disorder were enrolled in the study. All 6 received HD-tDCS and 4 received 2 Hz HD-tACS (Fig. 2). Baseline demographic and clinical characteristics are summarized in Table 1.

3.1. Primary outcomes

There were significant differences across sessions for PANSS general symptoms in the HD-tDCS (W=0.42; p = 0.04) and HD-tACS condition (W=0.58; p = 0.07), but not for total, positive or negative symptoms (Table 2A, Fig. 3A). Post hoc comparisons in the HD-tDCS showed a significant reduction from baseline to day 5 for PANSS general scores (RBES=0.47; p_{fdr}=0.03) and significant increase from day 5 to 1-month (RBES=−0.50; p_{fdr}=0.03). For HD-tACS, significant reductions in PANSS general score between day 5 and 1-month (RBES=0.69; p_{fdr}=0.05) and from baseline to 1-month (RBES=0.62; p_{fdr}=0.05) was observed. There were no significant differences between HD-tDCS 1-month and HD-tACS baseline nor between HD-tDCS baseline and HD-tACS 1-month (eFigure 1). These analyses were repeated without imputed data and results were similar for the HD-tDCS and HD-tACS findings (Supplement 6). Post hoc analyis showed a signficant group by session interaction (F=12.42, p = 0.02) between HD-tDCS and HD-tACS (eTable 1, Fig. 3). An exploratory analysis was conducted for PANSS P3 Hallucination score despite these participants not having acute hallucinatory symptoms, but there were no significant difference noted in either the HD-tDCS or HD-tACS group. eTable 1.

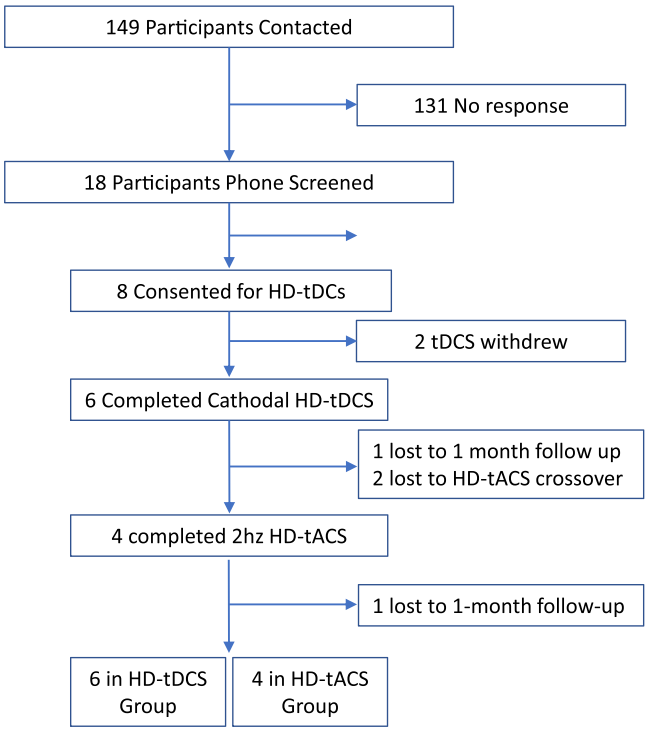


Fig. 2. . CONSORT Flow Diagram.

There were significant differences across sessions for the SSVEP P1 voltage in the HD-tDCS group for bilateral trials at POz (W=0.65; p = 0.02) (Table 2A, Fig. 3A,C). HD-tDCS post hoc analyses showed a significant decrease in voltage for P1 from baseline to 5 day (RBES=0.25; p_{fdr}=0.005) and baseline to 1-month (RBES=0.33; p_{fdr}=0.008). The SSVEP N1 voltage was significantly different across sessions in the HD-tDCS group for bilateral POz (W=0.69; p = 0.02). HD-tDCS post hoc analyses showed a significant increase in voltage for N1 from baseline to 5 day (RBES=−0.56; p_{fdr}=0.002) and baseline to 1-month (RBES=−0.28; p_{fdr}=0.04), as well as a significant decrease from 5 day to 1-month (RBES=0.39; p_{fdr}=0.04). There were no significant session differences noted for P1 and N1 in the HD-tACS group. There was no significant group by session effect noted for P1 or N1 (eTable 1, Fig. 3C). These results were repeated without imputed values and the results were similar (Supplement 6).

There were no significant differences observed on the biological motion task for either treatment condition (eTable 2).

In exploratory analyses, a significant relationship was identified between the improvement in PANSS general score and the reduction in P1 observed between day 5 and baseline (β = 0.274, t = 3.59, p = 0.04) (eTable 3, Fig. 3D).

3.2. Secondary outcomes

There were significant differences across sessions for GAF scores in the HD-tACS condition (W=0.44; p = 0.06) (Table 2B, Fig. 4A). Post hoc comparisons in the HD-tACS showed a significant increase in GAF from day 5–1-month (RBES=−0.56; p_{fdr}=0.05) and baseline to 1-month (RBES=−0.56; p_{fdr}=0.04). These analyses were repeated without imputed data and results were similar for the HD-tACS findings (Supplement 6). There was no group by session effect observed for GAF (eTable 1, Fig. 4B). There were no significant differences noted for MADRS within or between conditions (Table 2B, eTable 1).

There were significant differences across sessions for the IAPS EPN voltages in the HD-tDCS condition for both unpleasant (W=0.84; p = 0.01) and neutral (W=0.52; p = 0.07) stimuli, but not for pleasant (Table 2B, Fig. 4C). Pairwise comparisons in the HD-tDCS condition showed a significant decrease in response amplitude to unpleasant stimuli from baseline to day 5 (RBES=−0.68; p_{fdr}=0.07), day 5–1-month (RBES=0.76; p_{fdr}=0.004) and baseline to 1-month (RBES=0.84; p_{fdr}=0.0007). Pairwise comparisons showed that response amplitudes to neutral stimuli decreased from baseline to 1-month (RBES=0.76; p_{fdr}=0.06). These analyses were repeated without imputed IAPS data and results were similar for the HD-tDCS findings in the unpleasant stimuli, but not significant for neutral stimuli (Supplement 6).

There were no significant differences observed on the visual spatial working memory or velocity discrimination task for either treatment condition (eTable 2).

In exploratory analyses, no significant relationship was identified between the improvement in PANSS general score and the reduction in unpleasant (β = 0.529, t = 2.18, p = 0.16) or neutral (β = 0.173, t = 0.37, p = 0.75) stimuli observed between day 5 and baseline (eTable 3).

There were no serious adverse events reported in either stimulation condition and no participant withdrew from the study due to side effects. The stimulation montage was well tolerated and no participant reported above a moderate sensation on the sensation scale (eFigure 2).

Table 2A
Primary Outcome Results.

	HD-tDCS				HD-tACS			
	Median (IQR)	Friedman P Value	Kendall Effect Size	Confidence Intervals (95%)	Median (IQR)	Friedman P Value	Kendall Effect Size	Confidence Intervals (95%)
PANSS Total								
Baseline	49.50 [43.50–59.25]				59.50 [54.50–67.50]			
Day 5	44.00 [40.50–49.75]	0.11	0.34	[0.15, 1.00]	56.50 [50.50–64.75]	0.47	0.19	[0.00,1.00]
1 Month	50.00 [48.25–54.75]				47.50 [43.75–52.00]			
PANSS Positive								
Baseline	14.50 [11.75–16.50]				13.50 [11.00–18.00]			
Day 5	12.50 [8.75–15.50]	0.17	0.26	[0.08, 1.00]	14.50 [11.75–17.25]	0.53	0.14	[0.00,1.00]
1 Month	10.00 [9.25–13.75]				13.00 [10.00–16.25]			
PANSS Negative								
Baseline	11.00 [8.50–13.50]				19.50 [13.00–24.00]			
Day 5	11.00 [8.50–13.50]	0.17	0.19	[0.03, 1.00]	20.00 [13.00–26.00]	0.53	0.11	[0.02,1.00]
1 Month	14.00 [13.00–18.00]				11.50 [10.25–12.75]			
PANSS General								
Baseline	25.00 [22.25–29.25]				28.50 [26.50–31.50]			
Day 5	20.50 [18.50–23.25]	**0.04**	**0.42**	**[0.19, 1.00]**	27.50 [25.25–30.00]	**0.07**	**0.58**	**[0.44,1.00]**
1 Month	25.50 [23.50–27.50]				22.50 [21.75–24.25]			
SSVEP P100 Voltage								
Baseline	1.725 [0.910–3.035]				1.160 [0.480–2.933]			
Day 5	1.180 [0.503–2.053]	**0.02**	**0.65**	**[0.51, 1.00]**	1.005 [0.483–3.238]	0.78	0.06	[0.06,1.00]
1 Month	1.160 [0.218–2.860]				2.560 [1.035–4.412]			
SSVEP N100 Voltage								
Baseline	-2.240[− 3.710- − 1.055]				-1.275[− 1.900- − 0.855]			
Day 5	-0.600[− 1.135- − 0.478]	**0.02**	**0.69**	**[0.53, 1.00]**	-1.760[− 2.277- − 1.433]	0.82	0.05	[0.05,1.00]
1 Month	-1.090[− 2.000- − 0.630]				-2.050[− 2.353- − 1.545]			

4. Discussion

This is the first tES intervention for psychosis to precisely target the eVC, guided by lesion network mapping and HD-tES current flow models. We demonstrated that stimulating this region using HD-tDCS may improve general psychopathology in the short-term (5 days), with longer-term (1-month) improvements in general psychopathology and functioning noted with HD-tACS. Furthermore, eVC stimulation with HD-tDCS may induce a sustained reduction in early visual ERPs from visual steady-state and emotional scene paradigms, but this effect was not observed using HD-tACS. Regression analysis in the HD-tDCS condition indicates that general psychopathology and electrophysiological reductions are linked, suggesting that engaging the eVC with HD-tES may play a role in the alleviation of psychosis symptoms. Lastly, both HD-tES montages used in this study were well tolerated (eFigure 2).

The HD-tDCS general psychopathology results are consistent with findings in the literature from randomized control trials with 8 studies demonstrating short-term improvements (SMD=0.31), while 4 studies did not show longer-term benefits at 4–12 weeks (SMD=0.15) (Lee et al., 2022). These studies used 2 mA stimulation intensity, anodal to the left dorsolateral prefrontal cortex (F3) and cathodal to right frontal (F4) or left temporoparietal junction (T3, P3), stimulation area ranged from 25 to 35 cm^2, and sessions ranged from 5–10 sessions. Further support comes from a case report of a patient with treatment resistant auditory hallucinations and VH who underwent cathodal tDCS to Oz for 10 sessions and then the temporoparietal area for 10 sessions, and they experienced a 29% reduction in general psychopathology symptoms at 1-month (Shiozawa et al., 2013). The HD-tACS general psychopathology findings are also consistent with a case series of 3 clozapine resistant patients with schizophrenia receiving theta (4.5 Hz) tACS demonstrating an 18% improvement in symptoms (Kallel et al., 2016). This study used 2 mA stimulation intensity, F3 and F4 electrode placement, 25 cm^2 area, for 20 sessions over 4 weeks. While these studies are promising they were conducted using sponge montages, which decrease the focality of stimulation, and traditional montages were used targeting primarily frontal, temporal, and parietal regions, which don't specifically target networks associated with behavior or psychosis symptomatology. Our study expands on this literature by demonstrating that HD-tDCS to the eVC which is causally linked to VH (Kim et al., 2021) and motion processing (Martínez et al., 2018), resulted in a larger short-term effects size change (RBES=0.47) for general psychopathology than has been reported previously. We are also the first to demonstrate that 2 Hz tACS to the eVC can result in a long-term moderate effect size (RBES=0.62) improvement at 1-month, which may be due to neuroplastic changes induced by phase locking of intrinsic brain rhythms (Krause et al., 2019), but further work is needed in this area.

The mechanism through which HD-tDCS or HD-tACS decreases general psychopathology is not fully understood. However, the findings

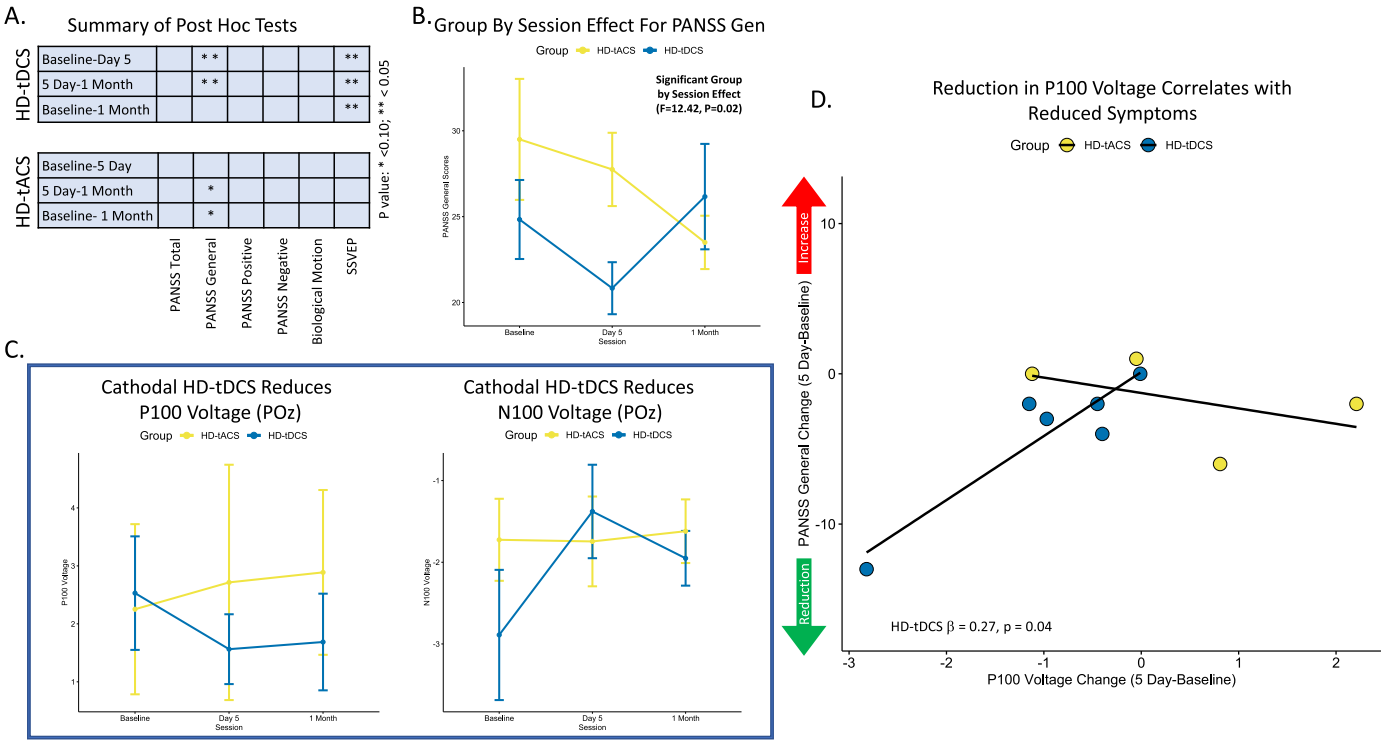


Fig. 3. : Primary Outcome Results: A. Demonstrates the summary of post-hoc pairwise comparisons by session contrasts for both HD-tDCS and HD-tACS. B. Depicts the group by session interaction effect for the PANSS General score. C. Shows the SSVEP P100 and N100 results at the POz sensor across sessions. D. Demonstrates the regression results between change scores (5 Day-Baseline) for P100 Voltage and PANSS General score with a significant result in the HD-tDCS condition. **Notes:** High-Definition Transcranial Current Stimulation; HD-tACS, High-Definition Transcranial Alternating Current Stimulation; PANSS, Positive and Negative Syndrome Scale; SSVEP, Steady State Visual Evoked Potential.

Table 2B
Secondary Outcome Results.

GAF								
Baseline	70.00 [62.00–78.75]				65.00 [60.00–66.25]			
Day 5	68.50 [61.25–78.75]	0.93	0.006	[0.006, 1.00]	65.00 [61.75–66.25]	**0.06**	**0.44**	**[0.19,1.00]**
1 Month	63.00 [53.50–65.00]				68.00 [65.75–72.50]			
MADRS								
Baseline	6.00 [4.25–15.25]				5.50 [3.75–10.00]			
Day 5	3.50 [3.00–5.50]	0.38	0.15	[0.02, 1.00]	4.00 [2.25–8.00]	0.53	0.11	[0.02,1.00]
1 Month	6.00 [2.00–7.75]				2.50 [0.00–5.50]			
IAPS Unpleasant EPN								
Baseline	6.525 [6.348–6.787]							
Day 5	5.751 [5.139–5.856]	**0.01**	**0.84**	**[0.76, 1.00]**				
1 Month	3.25 [3.247–4.348]							
IAPS Pleasant EPN								
Baseline	6.127 [5.946–6.298]							
Day 5	5.19 [5.087–5.229]	0.25	0.28	[0.04, 1.00]				
1 Month	5.300 [3.685–5.731]							
IAPS Neutral EPN								
Baseline	6.216 [5.740–6.319]							
Day 5	6.164 [4.529–6.823]	**0.07**	**0.52**	**[0.36, 1.00]**				
1 Month	4.052 [3.745–5.002]							

Notes: HD-tDCS, High-Definition Transcranial Current Stimulation; HD-tACS, HD Transcranial Alternating Current Stimulation; PANSS, Positive and Negative Syndrome Scale; SSVEP, Steady State Evoked Potential; GAF, Global Assessment of Functioning; MADRS, Montgomery–Åsberg Depression Rating Scale; IAPS, International Affective Picture System; EPN, Early Posterior Negativity; IQR, Interquartile Range. Statistics reported here include individuals with imputed values for follow-up visits

of the present study suggest that HD-tDCS to the eVC induces a neuroplastic change to the SSVEP P1 and IAPS EPN ERPs with the former being correlated with a change in general psychopathology, however, this effect was not observed with HD-tACS. This observation may be explained by the fact that tDCS can modulate cortical excitability using anodal stimulation which tends to increase (i.e. the resting potential becomes less negative), while cathodal stimulation tends to decrease the underlying membrane potential (i.e. the resting potential becomes more negative) (Stagg and Nitsche, 2011; Creutzfeldt et al., 1962). Furthermore, studies have demonstrated that tDCS can modulate visual cortical function in a polarity-dependent manner, where anodal stimulation can increase and cathodal stimulation can decrease the amplitude of the N70 component from the visual-evoked potential (Antal et al., 2004). While there is no study to date examining the relationship between P1 and

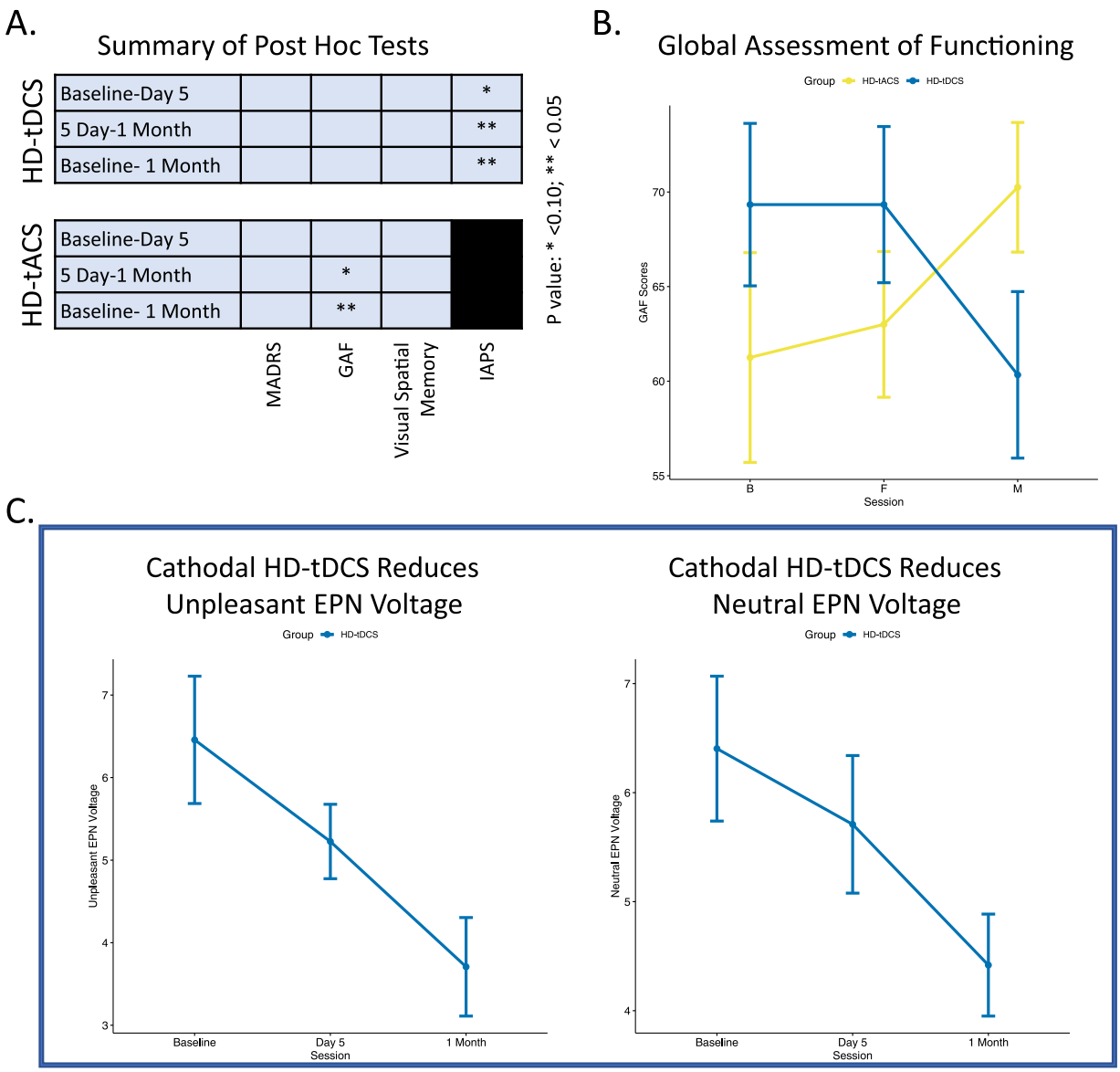


Fig. 4. : Secondary Outcome Results: A. Demonstrates the summary of post-hoc pairwise comparisons by session contrasts for both HD-tDCS and HD-tACS. B. Depicts the results for GAF scores across sessions for both HD-tDCS and HD-tACS with a significant reduction in the HD-tACS group at 1 Month. C. Shows the IAPS EPN Voltage for Unpleasant and Neutral stimuli at P6, P7, PO6, PO7, O1, and O2 sensors across sessions. **Notes:** HD-tDCS, High-Definition Transcranial Current Stimulation; HD-tACS, HD Transcranial Alternating Current Stimulation; GAF, Global Assessment of Functioning; IAPS, International Affective Picture System; EPN, Early Posterior Negativity. 1 participant in the HD-tDCS condition was not able to complete IAPS assessments.

general psychopathology, a study using dynamic facial expressions to examine ERP responses in schizophrenia, found that greater N200 latency was associated with lower general psychopathology scores (Fukuta et al., 2014). Different from tDCS, tACS is known to modulate endogenous neural oscillations by applying oscillating electrical current with a periodic waveform to the brain (Elyamany et al., 2021). Using tACS to target the occipital cortex, it was demonstrated that different stimulation frequencies can interact with endogenous rhythmic activities in a frequency-specific manner to induce phosphenes (Kanai et al., 2008). While these studies are informative, more research is needed to better understand the mechanisms underlying the improvement in general psychopathology.

5. Limitations

We acknowledge several important limitations in understanding our results. First, due to institutional restrictions surrounding the COVID-19, recruitment efforts were significantly hindered and thus a sham condition was not conducted. However, there is significant power in this cross-over design, which demonstrated differential effects on symptoms and electrophysiology. Additionally, due to our small sample size we were forced to allocate treatment protocols in one order (HD-tDCS and then HD-tACS). While this was not ideal, we believe that stimulation effects from HD-tDCS and HD-tACS are still apparent since we implemented a stringent washout period of 4 weeks and implemented an electrophysiological readout at 5 days and 1 month. Moreover, our results suggested that the effects from HD-tDCS were no longer significantly related to our variables of interest at the 1-month follow up. Second, our single blind design may have introduced a potential bias in clinical measures; however, the combination of objective markers such as EEG and behavioral tasks can be seen as control measures for this phenomenon. Third, imputed data was used for 1-month assessments, but the results were similar when repeated using unimputed data. Fourth, subjects were stable outpatients not experiencing clinically

significant symptoms and future studies should be performed in an acute population. Furthermore, future studies should employ and validate a wide range of clinical assessments such as the NEVHI or University of Miami Parkinson's Disease Hallucinations Questionnaire (UM-PDHQ) to ensure they are capturing key features of symptoms (Mosimann et al., 2008; Papapetropoulos et al., 2008). Fifth, velocity discrimination is likely a better behavioral target than biological motion when stimulating the eVC (Vaina and Gross, 2004), but future studies should conduct brain stimulation online while the patient is performing the task as compared to offline, which is how it was conducted in the current study. Additionally, the lack of change in biological motion scores from the two stimulations arms suggest that this task may be a reliable way to measure the absence of off target effects. Fifth, the lack of positive psychosis symptom findings may be due to a lack of self-reported psychosis symptoms scales, which may be a more accurate measure of predicting outcomes (Biancosino et al., 2007; Kaiser and Oswald, 2022). Lastly, we did not use each individuals structural MRI, which would have allowed us to personalize the stimulation location and current flow (Datta et al., 2012; Thair et al., 2017), as well as maximize the effects of HD-tES. Despite these limitations, this is an important proof of concept study that lays the foundation for future studies investigating the treatment of positive and general symptoms of psychosis with HD-tES.

6. Conclusions

Findings from the present study suggest that lesion network guided HD-tES to the eVC is a safe, efficacious, and promising approach for reducing general psychopathology via changes in neuroplasticity. These results highlight the need for larger clinical trials implementing novel targeting methodologies and montages with the hopes of identifying effective future treatments for psychosis.

Funding

This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

Declaration of Competing Interest

The authors report no conflicts of interest.

Acknowledgements

The authors would like to thank the individuals who participated in this research and for their willingness to complete study visits during the COVID-19 pandemic. In addition, we would like to thank all study team members for their supporting roles in this research.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2023.103750.

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