Asian Journal of Psychiatry 92 (2024) 103887

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

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

Lesion network guided delta frequency neuromodulation improves cognition in patients with psychosis spectrum disorders: A pilot study

Willa Molho [a,b,*], Nicolas Raymond [a,b,*], Robert M.G. Reinhart [c], Rebekah Trotti [a,b], Shrey Grover [b], Matcheri Keshavan [a,d], Paulo Lizano [a,b,d,*]

[a] Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA, USA
[b] Division of Translational Neuroscience, Beth Israel Deaconess Medical Center, Boston, MA, USA
[c] Department of Psychological and Brain Science, Boston University, Boston, MA, USA
[d] Department of Psychiatry, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Keywords:
Cognition
Transcranial Electrical Stimulation
Lesion Network Mapping
Psychosis

ABSTRACT

Background: Transcranial electric stimulation (tES) may improve cognition in psychosis spectrum disorders. However, few studies have used novel tES approaches, such as high definition tES (HD-tES) to target specific brain circuits. Recently, the extrastriate visual cortex (V5/MT) has been causally linked to visual hallucinations through lesion network mapping and this may be a promising approach for improving cognition.
Objective: We aim to determine if causal lesion network guided HD-tES to V5/MT improves cognitive performance as measured by the Brief Assessment of Cognition in Schizophrenia (BACS).
Methods: A single-blind pilot study with a within-subjects crossover design was performed to characterize the effect of cathodal HD-transcranial direct current stimulation (tDCS) and 2 Hz HD-transcranial alternating current stimulation (tACS) on cognition. Enrolled patients received 20 mins of HD-tES twice daily for 5 consecutive days applied bilaterally to V5/MT with a washout between conditions. BACS assessments were performed at baseline, day-5, and 1-month.
Results: 6 participants with psychosis spectrum disorder were enrolled. 6 individuals received cathodal HD-tDCS. 4 individuals received 2 Hz HD-tACS. HD-tACS resulted in significant ($p < 0.1$ baseline to 1-month improvements for Digit Sequencing, Verbal Fluency, and Tower of London. HD-tDCS did not result in significant improvement on any task.
Conclusions: HD-tACS targeting V5/MT may be a promising treatment to improve cognitive abilities in individuals with psychosis. By promoting delta oscillations, tACS may enhance cortico-cortico communications across brain networks to improve verbal working memory, processing speed, and executive function. Large-scale investigations are needed to replicate these results.

1. Introduction

Psychosis spectrum disorders such as schizophrenia, schizoaffective disorder, and schizophreniform disorder affect approximately 3% of individuals (Perälä et al., 2007). Psychosis stems from a disconnection and distortion of reality and is characterized by hallucinations, delusions, psychomotor disturbances, cognitive impairments, and negative symptoms such as emotional flattening, withdrawal, depression, and anxiety (Arciniegas, 2015). Cognitive impairments include deficits in information processing, working memory, executive function, attention, motor functioning, and verbal fluency (Arciniegas, 2015; Begemann MJ et al.). Moreover, cognitive deficits in psychosis are associated with delusions and hallucinations (Petrolini et al., 2020), may exacerbate negative symptom severity (Türközer et al., 2019),and are strongly predictive of worsening community functioning in individuals with psychosis (McCleery and Nuechterlein, 2019).

Current treatments for cognitive deficits in psychotic disorders are limited but typically include a combination of psychotherapy and psychopharmacology (Perrotta, 2020). Psychotherapy is aimed at increasing an individual's knowledge and awareness of what they are experiencing and increasing the early recognition of symptomology (Perrotta, 2020). Pharmacological treatment includes medications

* Corresponding authors at: Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA, USA
E-mail addresses: wmolho@gmail.com (W. Molho), njraymon@bidmc.harvard.edu (N. Raymond), plizano@bidmc.harvard.edu (P. Lizano).

https://doi.org/10.1016/j.ajp.2023.103887
Received 3 October 2023; Received in revised form 5 December 2023; Accepted 18 December 2023
Available online 26 December 2023

aimed at decreasing the severity of positive symptoms; however, pharmacological interventions rarely improve cognition (Perrotta, 2020). In fact, relatively few options exist to manage cognitive deficits in psychosis outside of cognitive enhancement therapy. Cognitive therapy includes Cognitive Behavioral Therapy (CBT), Cognitive Remediation Therapy (CR) and Cognitive Enhancement Therapy (CET), which are aimed at improving daily cognitive ability and functioning (Medalia et al., 2019; Eack et al., 2009). Cognitive therapies are often successful (Wykes et al., 2011), but burdensome and they are not standardized, effective, or accessible for everyone (Hofmann et al., 2012; Lopez and Basco, 2015).

Over the past decade, transcranial electric stimulation (tES) and transcranial magnetic stimulation (TMS) have been successful as rehabilitation tools to enhance cognition (Bello et al., 2023). Compared to cognitive therapies, tES requires significantly less time and effort from individuals, which can be particularly helpful for people with symptoms of avolition and fatigue (Begemann MJ et al.). Furthermore, recent technological developments now allow for high definition tES (HD-tES) which focalizes current to specific brain regions by employing a higher number of stimulation electrodes (Focal Transcranial Electrical Stimulation, 2023). By using HD-tES, researchers may target specific regions of the cortex associated with symptoms. Of the few studies that employ tES to improve cognition in psychosis, most target the dorsolateral prefrontal cortex (DLPFC) due to its involvement in working memory. Studies targeting the region have shown improvement in multiple aspects of cognition (Begemann MJ et al.), including working memory in psychosis (Schwippel et al., 2018; Papazova et al., 2018). However, many regions of the brain are involved in cognitive processing, and very few tES investigations targeting other areas have examined its effect on cognitive ability.

Deficits and dysfunction of the visual cortex are heavily implicated in psychosis and may be related to cognitive functioning. MRI studies note decreased cortical thickness (Türközer et al., 2019; Adhan et al., 2020; Sugranyes et al., 2021) and grey matter volume in the visual cortex of individuals with psychosis (Onitsuka et al., 2007). Electro- and magnetoencephalography (E/MEG) studies, which measure activity at the cortical level, describe visual processing impairments and delays involving both visual processing and cognition in individuals with psychosis (Tan et al., 2013; Sur and Sinha, 2009). More importantly, the cognitive role of the visual cortex spans a range of cognitive tasks including visual perception, working memory (Supèr, 2003), imagery, decision making (Roelfsema and de Lange, 2016), and facial recognition (Grill-Spector et al., 2017). A 2020 study found that tACS applied to the extrastriate visual cortex (V5/MT), an area responsible for higher level visual processing, reduced temporal perception and made patients with psychosis more likely to perceive and integrate consecutive stimuli as one combined representation (Battaglini et al., 2020). Therefore, tES to the extrastriate visual cortex may have effects on cognitive ability in psychosis.

Previously, we investigated the effects of cathodal HD-tDCS and 2 Hz HD-tACS targeting V5/MT on psychosis symptoms in individuals with psychosis spectrum disorders (Lizano, 2023). V5/MT in the visual cortex was used as a target because it was causally implicated in the production of visual hallucinations in Kim et al., 2021. This paper describes a causal lesion network mapping study of otherwise healthy individuals who had brain injuries and then developed visual hallucinations (VH). Results showed that 98% of all the lesions were part of a cortical network involving V5/MT. In addition, decreased slow waves during motion related tasks have been associated with decreased cognitive performance and reduced V5/MT activation, highlighting the importance of oscillatory mechanisms in the extrastriate visual cortex (Martínez et al., 2018). This prompted the current study to incorporate frequency specific stimulation (2 Hz) as a means to increase this activity. In our previous investigation, significant reductions in EEG visual evoked potentials and PANSS general symptoms were observed after 5 days of tDCS treatment (Lizano, 2023). Intriguingly, HD-tACS treatment resulted in a greater long-term effect, showing a significant improvement in PANSS general symptoms 1 month after treatment (Lizano, 2023). This study also demonstrated that stimulation to the extrastriate visual cortex via HD-tDCS or HD-tACS was well tolerated (Lizano, 2023).

Based on the intersections between deficits in the visual cortex and deficits in cognition in psychosis, this research seeks to investigate if cathodal HD-tDCS and 2 Hz HD-tACS applied to V5/MT will improve cognition in individuals with psychosis spectrum disorders. We hypothesize that HD-tES will improve cognition as measured by BACS. Based on the results of our previous study, we hypothesize that HD-tDCS will be more efficacious over the short term (immediately after 5 days of stimulation), and that HD-tACS will be more efficacious in the long term (up to 1 month after stimulation). We also aim to determine if one method of stimulation is more effective than the other at improving cognition.

2. Materials and methods

A pilot study with a within-subjects, single blind, crossover design was conducted in order to characterize the efficacy of cathodal HD-tDCS and 2 Hz HD-tACS for psychosis treatment. The within-subjects control was pre-stimulation compared to post-stimulation. Participants received 20 mins of tES twice daily applied bilaterally to V5/MT for five consecutive days. Each participant received HD-tDCS stimulation and then HD-tACS stimulation separated by a washout period of four weeks. During the stimulation procedure for both HD-tDCS and HD-tACS, participants were asked to remain awake but not to engage in any tasks. Participants completed assessments at Baseline, Day 5, 1 month. See Fig. 1**A** for study design.

Six participants with psychosis spectrum disorder received cathodal HD-tDCS and four received 2 Hz HD-tACS (Supplementary Figure 1). Inclusion criteria for the pilot study included: a diagnosis of schizophrenia, schizoaffective disorder, or bipolar I disorder with psychosis by SCID-V (First et al., 2015), a lifetime history of hallucinations, ages between 18 and 55, no relevant changes to antipsychotic medications in the month before participation, and a sufficient level of English fluency. Exclusion criteria included: pregnancy or breastfeeding, an IQ less than 60, a diagnosis of current substance use disorder, a history of moderate to severe visual impairment, other serious medical illness, relevant skin allergies, and metallic or electronic implants.

Both HD-tDCS and HD-tACS stimulation procedures used 12-mm-diameter Ag-AgI electrodes in high-definition electrode holders provided by Soterix Medical which were filled with conductive gel. Electric field modeling was performed on HD-Explore by Soterix Medical in order to guide electrode placement. Electrode placement and stimulation intensity for tES were guided by current flow modeling with the goal of delivering a focalized current to coordinates from the Montreal Neurologic Institute (MNI) (−50, −78, 30) and (50, −74, 4) (Kim et al., 2021) in order to stimulate the extrastriate visual cortex bilaterally. For both HD-tDCS and HD-tACS, stimulation parameters including sensor location and stimulation intensity were: AF6, 0.333 mA; AF8, 0.35 mA; P6, − 0.325 mA; P9, 0.333 mA; P10, 0.65 mA; PO7, − 1.00 mA; PO8, − 0.675 mA; O1, 0.334 mA. Overall current intensity (peak to baseline) was set to 2 mA. HD-tDCS and HD-tACS operate through different mechanisms (HD-tDCS is cathodal stimulation and HD-tACS is 2 Hz delta in phase stimulation) despite having the same placements and charge densities (Fig. 1**B**).

The measure of cognition used in this study was the Brief Assessment of Cognition (BAC). The BAC assessment is performed by the participant on an iPad (VeraSci, WCG Clinical) (Atkins et al., 2017), guided by a research assistant. BAC is composed of 6 different tasks that assess 5 different aspects of cognition (Kaneda et al., 2007): Verbal Memory Task (VM) which measures recall of words by asking the participant to repeat as many words as they remember back to the researcher after hearing a list of unrelated words; Digit Sequencing Task (DS) which measures verbal working memory by asking participants to repeat a series of

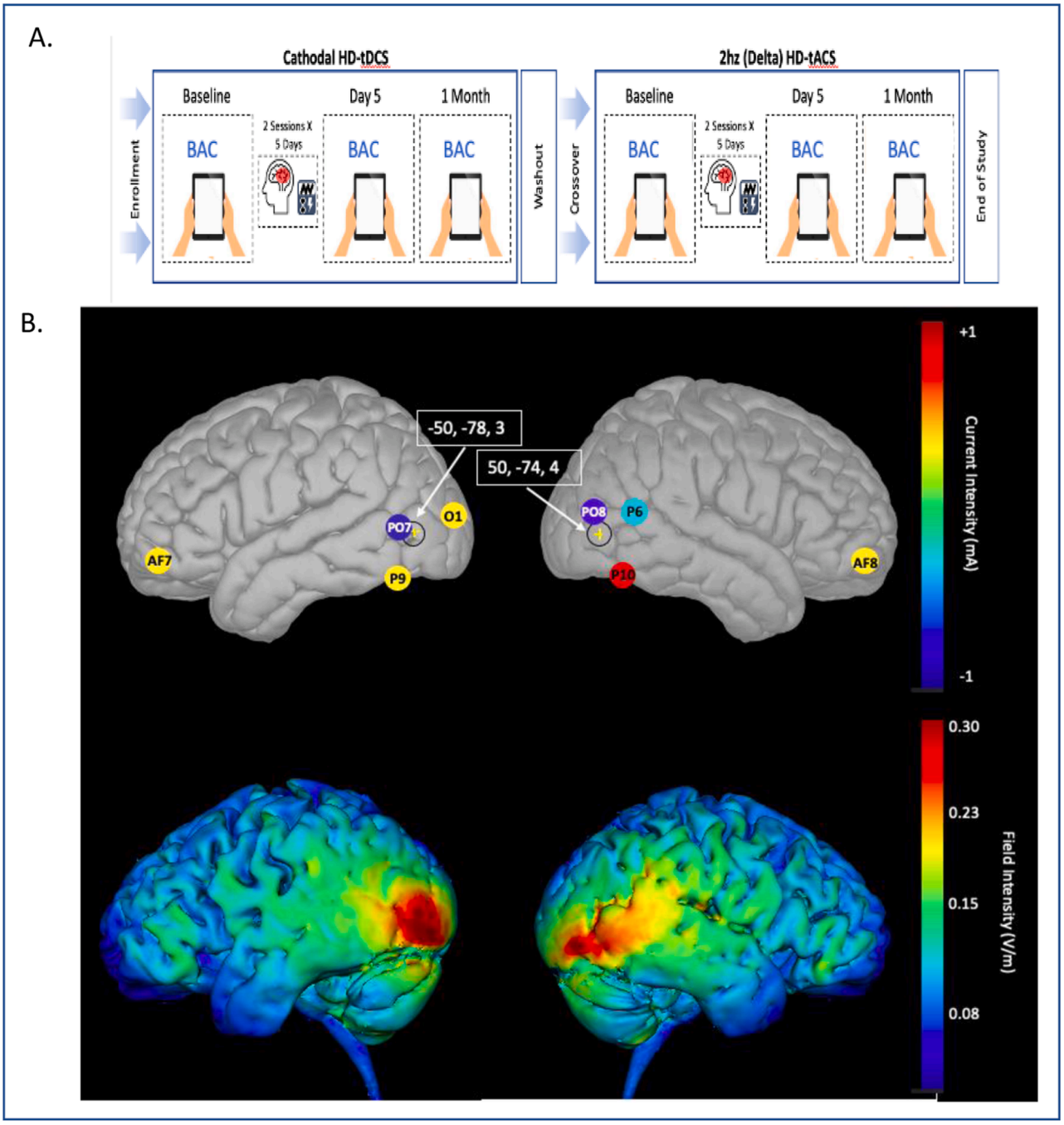

Fig. 1. A) Study design; EEG as well as clinical, visual, and cognitive assessments were performed at Baseline, Day-5, and, 1-Month. **B)** Stimulation electrode montage and coordinates in Montreal Neurologic Institute (MNI) space for the bilateral extrastriate visual cortex. The current intensity and the current flow modeling (field intensity) are depicted in the heatmap. Notes: HD-tDCS, High Definition Transcranial Direct Current Stimulation; HD-tACS, High Definition Transcranial Alternating Stimulation; BAC, Brief Assessment of Cognition.

numbers that they hear back to the administrator after putting the numbers in order from lowest to highest; Token Motor Task (TM) which measures motor coordination and motor speed by asking participants to use both hands in unison to place two chips into a bin as quickly as they can; Verbal Fluency Tasks (VF), measures of lexical access and recall from long term memory as well as processing speed, composed of Semantic Fluency (SF): which asks participants to name all the animals they can in 60 s and two measures of Letter Fluency (LF-F and LF-S): which ask participants to name all the words they can that start with the letter "F" for 60 s and then again with words beginning with the letter "S"; Symbol Coding Task (SC) which measures attention, processing speed and executive function (Shao et al., 2023) by asking participants to use a key to match a particular symbol to a number and encode a list of numbers from corresponding list of symbols as quickly as they can; and Tower of London Task (TL) which measures overall executive function and attention; particularly problem-solving, planning-ability and processing speed (Unterrainer et al., 2004) by showing participants an image of colored blocks arranged on 3 pegs and asking the participants the minimum number of moves it would take to arrange the blocks on the pegs so they are in the same arrangement as they appear on a reference image. The VM assessments were randomized for repeated BAC testing; different sets of words were used for assessments

at each session. Scores were converted to z-scores from normative data and adjusted for age and sex (Hochberger et al., 2016; HILL et al., 2008).

Data and analyses were performed with R Software (v4.1.2) and R Studio using "ggstatplot" for statistical analysis and plots (Patil, 2021). The Amelia package was used to impute missing values for individuals unable to return for their 1-month assessments (HD-tDCS n = 1, HD-tACS n = 1) (Honaker et al., 2011). CPZ was calculated using the ChlorprozamineR package on R (Convert, 2023). A p-value of 0.1 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 (Kim and Choi, 2021), which in turn substantially increases the power of the effect. Friedman tests (Friedman, 2023) were performed to investigate within-group differences in performance across the six domains of BAC (VM; DS; TM; VF; SC; TL) as well as the composite score across sessions (baseline, day-5, 1-month) for HD-tDCS and HD-tACS treatment. Effect size was calculated using Kendall's W in order to help determine clinical significance (Friedman, 2023). Pairwise comparisons were performed using the Durbin Conover test and Rank Biserial estimation was used to calculate effect sizes (Kloke and McKean, 2012). Post-hoc power analyses were calculated using pairwise testing and effect sizes for significant findings on G*Power (University of Düsseldorf: G*Power, 2023).

3. Results

Six participants with a DSM-5 diagnosis of a psychosis spectrum disorder were included in the study. All six participants received HD-tDCS, while four received 2 Hz HD-tACS. All participants remained on stable medications from 1 month prior to the first stimulation through the 1 month follow up of the last stimulation. Baseline demographic and clinical characteristics are summarized in Table 1.

In the HD-tDCS condition, no significant differences in BAC composite score or sub-scores were identified (Table 2). Likewise, further investigations revealed that no significant pairwise comparison between session were found for any BAC subdomains in the HD-tDCS condition (Table 3).

In the HD-tACS condition, BAC composite z-scores were not significant (Table 2), however post-hoc pairwise comparisons showed significant improvements in BACS Composite z-scores from baseline to 1 month of HD-tACS stimulation [$p_{unadj.}$= 0.09, rank biserial= −0.50; 95% CI − 0.88, 0.29, power= 0.31] (Fig. 2). However, this value did not remain significant after FDR adjustment (Murray and Blume, 2021) [p_{fdr} = 0.23] (Table 3). A Freidman test was conducted to determine whether there were learning effects across the HD-tDCS and HD-tACS conditions (sessions 1–6), which indicated that there was no learning effect of repeated BAC testing (Supplementary Figures 2 and 3) Additionally, no significant improvement was observed between the 1 month HD-tDCS time point (session 3) and the Baseline HD-tACS timepoint (session 4) (Supplementary Figures 2 and 3), indicating that HD-tDCS treatment was not responsible for the improvement in BAC observed during HD-tACS. The trajectory of the change in z-scores for each participant has been demonstrated for BAC Composite and tasks that significantly improved with HD-tACS in Supplementary Figures 4 and 5.

Additionally, significant improvements were found in three BAC subdomains in the HD-tACS condition: Digit Sequencing, Verbal Fluency, and Tower of London. No significant changes were found in the Verbal Memory, Token Motor, or Symbol Coding BAC subdomains in the HD-tACS condition.

Table 1
Demographic and Clinical Information.

	HD-tDCS (N = 6)	HD-tACS (N = 4)
Sex(M/F/Other)	2/3/1	1/2/1
Race/Ethnicity		
African American	2	2
White	3	2
Other	1	0
Age, Mean (SD)	29.7 (2.6)	29.8 (3.1)
Primary Diagnosis	3	2
Schizophrenia		
Schizoaffective	1	1
Bipolar	2	1
CPZ Equivalence, Mean (SD)	260.9 (269.6)	314.4 (279.0)
Years of Education, Mean (SD)	14.8 (1.3)	15.0 (1.2)
Years of Illness Duration, Mean (SD)	11.8 (3.7)	9.5 (1.0)
SFS, Mean (SD)	128.5 (12.4)	117.0 (10.9)
BAC Composite z-score	-0.46	-1.28

Notes: HD-tDCS, High-Definition Transcranial Direct Current Stimulation; HD-tACS, High-Definition Transcranial Alternating Current Stimulation; CPZ, chlorpromazine; SFS, Social Functioning Scale; SD, Standard Deviation; BAC, Brief Assessment of Cognition

3.1. Digit sequencing

In the HD-tACS condition, z-scores for the Digit Sequencing subdomain of the BAC assessment significantly improved [p = 0.08; Kendall's W = 0.62] (Table 2, Fig. 2). Pairwise comparisons for the Digit Sequencing subdomain in the HD-tACS condition showed significant improvements from baseline to 1-month [p = 0.04, p_{FDR}= 0.06, rank biserial= −0.56] and 5 day to 1-month [p = 0.03, $p_{FDR.}$= 0.06, rank biserial= −0.38], but not baseline to day-5 [p = 0.81, p_{FDR}= 0.81, rank biserial= −0.19] (Table 3). However, no significant interactions related to condition by session were found when a two way ANOVA model was performed. Post-hoc power analyses using effect size= 0.62 provided a power= 0.42. Based on this pilot study, 18 participants would be needed to achieve 80% power with a p = 0.05 and a 0.62 effect size in future studies.

3.2. Verbal fluency

In the HD-tACS condition, z-scores for the Verbal Fluency subdomain of the BAC assessment significantly improved [p = 0.02; Kendall's W = 1.00] (Table 2, Fig. 2). Pairwise comparisons for the Verbal Fluency subdomain in the HD-tACS condition showed significant improvements from baseline to 1-month [p = 0.03, p_{FDR}= 0.09, rank biserial= −0.38], but not from baseline to day 5 [p = 0.21, p_{FDR}= 0.21, rank biserial= −0.38] or from day-5 to 1-month [p = 0.21, p_{FDR}= 0.21, rank biserial= −0.31] (Table 3). However, no significant interactions related to condition by session were found when a two way ANOVA model was performed. Post-hoc power analyses using effect size= 1.00 provided a power= 0.66. Based on this pilot study, 8 participants would be needed to achieve 80% power with a p = 0.05 and a 1.00 effect size in future studies.

3.3. Tower of London

In the HD-tACS condition, z-scores for the Tower of London subdomain of the BAC assessment significantly improved [p = 0.06; Kendall's W = 0.70,] (Table 2, Fig. 2). Pairwise comparisons for the Tower of London subdomain in the HD-tACS condition showed significant improvements from baseline to day-5 [p = 0.01, p_{FDR}= 0.04, rank biserial= −0.50] and baseline to 1-month [p = 0.04, p_{FDR}= 0.06, rank biserial= −0.44], but not from 5 day to 1 month [p = 0.41, p_{FDR}= 0.41, rank biserial= 0.25] (Table 3). However, no significant interactions related to condition by session were found when a two way ANOVA model was performed. Post-hoc power analyses using effect size= 0.70 provided a power= 0.46. Based on this pilot study, 15 participants would be needed to achieve 80% power with a p = 0.05 and a 0.70 effect size in future studies.

4. Discussion

This study suggests that 2 Hz HD-tACS stimulation, but not HD-tDCS to V5/MT bilaterally, may improve attention, processing speed, verbal

Table 2
Cognition Results for HD-tDCS and HD-tACS.

		HD-tDCS			HD-tACS		
		Median (IQR)	Friedman P Value	Kendall Effect Size	Median (IQR)	Friedman P Value	Kendall Effect Size
BAC Composite	Baseline	-0.465 [− 0.958, 0.005]			-1.280 [− 1.488, − 0.623]		
	Day 5	0.095 [− 0.790, 0.545]	0.85	0.03	-0.555 [− 1.198, 0.335]	0.17	0.44
	1 Month	-0.185 [− 0.950, 0.655]			-0.170 [− 0.635, 0.388]		
Verbal Memory	Baseline	-0.545 [− 1.470, 0.462]			-0.315 [− 0.688, − 0.033]		
	Day 5	-0.050 [− 0.858, 0.683]	0.96	0.007	0.120 [− 0.633, 0.525]	0.78	0.06
	1 Month	-0.025 [− 0.928, 0.510]			0.125 [− 0.313, 0.375]		
Digit Sequencing	Baseline	-0.880 [− 1.698, − 0.438]			-1.625 [− 1.995, − 0.780]		
	Day 5	-0.735 [− 1.555, 0.258]	0.83	0.03	**-0.885 [− 1.703, − 0.008]**	**0.08**	**0.62**
	1 Month	-0.880 [− 1.998, 0.185]			-0.285 [− 0.805, 0.338]		
Token Motor	Baseline	1.355 [− 0.670, 3.845]			1.845 [− 0.445, 4.000]		
	Day 5	2.660 [1.805, 3.583]	0.68	0.07	1.060 [− 0.493, 2.823]	0.72	0.08
	1 Month	1.060 [− 0.310, 3.007]			1.430 [− 0.860, 2.140]		
Verbal Fluency	Baseline	0.210 [− 0.590, 1.040]			-0.470 [− 0.995, 0.315]		
	Day 5	0.450 [− 0.035, 0.590]	0.51	0.11	0.125 [− 0.588, 1.033]	**0.018**	**1.00**
	1 Month	1.140 [− 0.445, 1.720]			0.220 [− 0.445, 1.125]		
Symbol Coding	Baseline	-0.325 [− 0.463, − 0.210]			-0.780 [− 0.955, − 0.070]		
	Day 5	-0.560 [− 1.135, 0.315]	0.74	0.05	-0.955 [− 1.023, − 0.338]	0.37	0.25
	1 Month	-0.520 [− 1.025, − 0.015]			-0.865 [− 0.910, − 0.245]		
Tower of London	Baseline	-0.660 [− 0.660, 0.225]			-0.660 [− 0.935, − 0.473]		
	Day 5	0.305 [− 0.473, 1.015]	0.47	0.13	**0.260 [− 0.198, 0.670]**	**0.06**	**0.70**
	1 Month	0.085 [− 0.198, 0.353]			0.080 [− 0.105, 0.083]		

Notes: HD-tDCS, High Definition Transcranial Direct Current Stimulation; HD-tACS, High Definition Transcranial Alternating Stimulation; IQR, Interquartile Range; BAC, Brief Assessment of Cognition

Table 3
Cognition Results by Session for HD-tDCS and HD-tACS.

		HD-tDCS			HD-tACS		
		Durbin-Conover P Value	FDR Corrected P Value	Rank biserial	Durbin-Conover P Value	FDR Corrected P Value	Rank biserial
BAC Composite	Baseline- Day 5	0.79	0.79	-0.22	0.15	0.23	-0.38
	Day 5- 1 Month	0.79	0.79	-0.06	0.70	0.70	-0.25
	Baseline- 1 Month	0.60	0.60	-0.17	**0.09**	0.23	**-0.50**
Digit Sequencing	Baseline- Day 5	0.59	0.59	-0.03	0.81	0.81	-0.19
	Day 5- 1 Month	0.79	0.79	0.03	**0.03**	**0.06**	**-0.38**
	Baseline- 1 Month	0.79	0.79	-0.03	**0.04**	**0.06**	**-0.56**
Tower of London	Baseline- Day 5	0.56	0.56	-0.17	**0.01**	**0.04**	**-0.50**
	Day 5- 1 Month	0.56	0.56	0.17	0.41	0.41	0.25
	Baseline- 1 Month	0.26	0.26	-0.31	**0.04**	**0.06**	**-0.44**
Verbal Fluency	Baseline- Day 5	0.59	0.59	-0.06	0.21	0.21	-0.38
	Day 5- 1 Month	0.59	0.59	-0.19	0.21	0.21	-0.31
	Baseline- 1 Month	0.29	0.59	-0.22	**0.03**	**0.09**	**-0.38**

Notes: HD-tDCS, High Definition Transcranial Direct Current Stimulation; HD-tACS, High Definition Transcranial Alternating Stimulation; BAC, Brief Assessment of Cognition

working memory, and executive function. Additionally, the effect of 2 Hz HD-tACS on DS demonstrated a stepwise improvement in performance until the 1-month assessment, while performance on the TL task plateaued after at the 5 day assessment, and VF improvement was only significant after 1 month. Most importantly, the improvement in performance on the DS, VF, and TL tasks came close to that observed in age and gender matched controls based on normative data. These finding highlight that oscillatory mechanisms, particularly slow waves, play an important role in cognitive processes and may be an important target for future tES investigations. However, the post-hoc power for this pilot study ranges from 0.42 to 0.6, suggesting that at least 18 participants per arm would be needed in future studies investigating the effects of V5/MT tES on cognition.

As noted above, improvement in the BAC assessment was observed with HD-tACS stimulation for the DS, VF, and TL tasks. These tasks assess verbal working memory, executive function, and attention capacities. While more research is necessary, there are potential mechanisms that may have resulted in HD-tACS improving cognitive ability over HD-tDCS. First, HD-tACS has been shown to alter long range cortical communication (Elyamany et al., 2021), influencing connected brain regions other than the one directly stimulated (Grover et al., 2022). Delta waves in the brain (or slow waves in general) are necessary in cognitive processes involving working memory (Harmony, 2023) and executive functioning (Bong et al., 2020). During tasks that require concentration, delta waves increase in the frontal cortex (Harmony, 2023) and sleep research shows that slow wave sleep (2–4 Hz) aids in storing long-term information in cortical structures (Girardeau and Lopes-dos-Santos, 2021). Slow wave delta frequency (2–7 Hz) was also

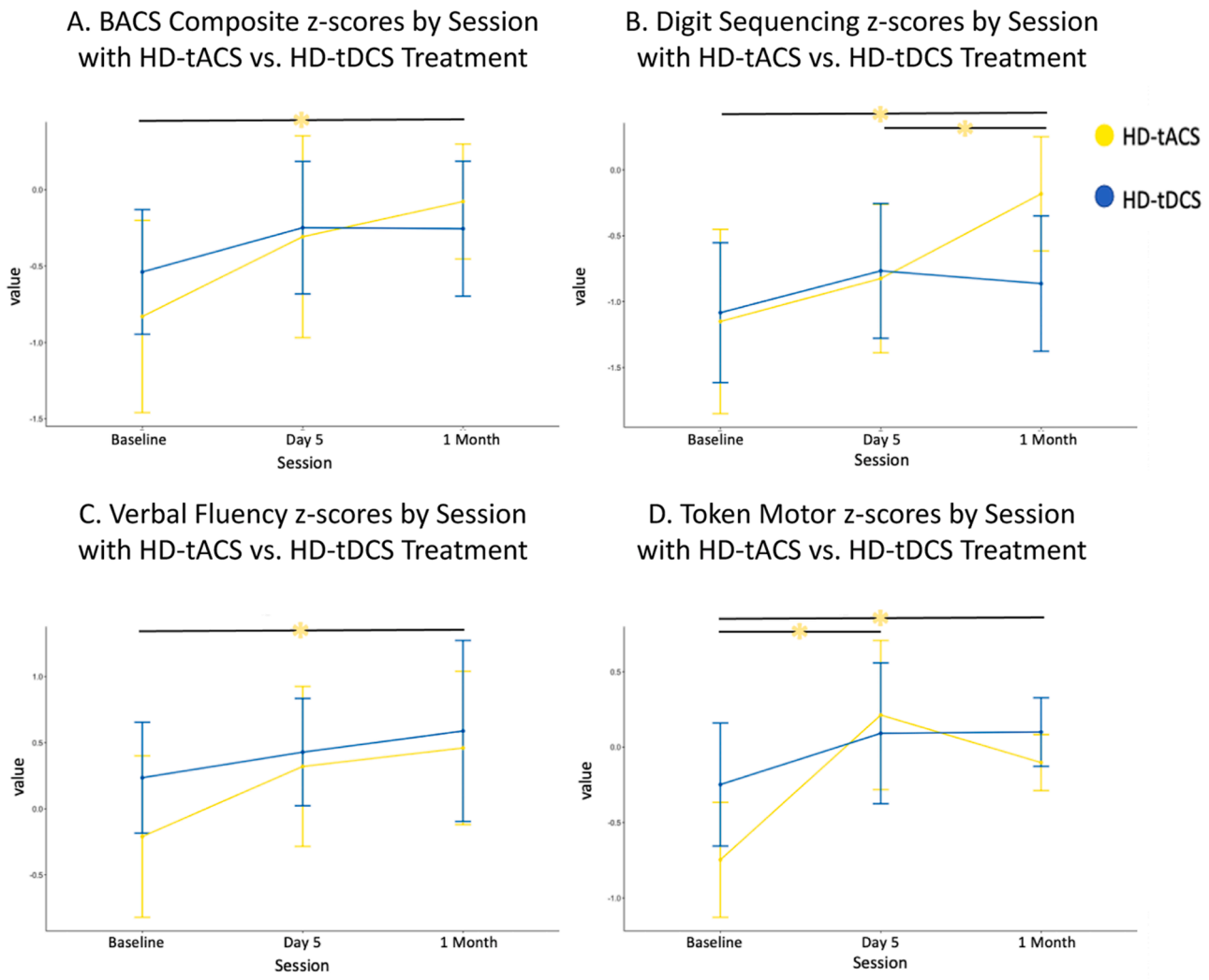

Fig. 2. BACS Composite and Significant Subcategory z-scores by session with HD-tACS (n = 4) vs. HD-tDCS (n = 6) Treatment. Changes in subdomain scores of the BACS (Brief Assessment of Cognition in Schizophrenia) are demonstrated for A) Composite, B) Digit Sequencing, C) Verbal Fluency, and D) Tower of London across 3 time points (baseline, day 5, and 1 month) and two groups (HD-tDCS and HD-tACS). * Depict significant ($p < 0.1$) findings between time points for the HD-tACS group.

found to play a major role in encoding auditory and visual sensory information, particularly coordinating information across auditory and visual streams (Luo et al., 2010). Patients with psychosis display slow wave abnormalities relative to healthy individuals (Zhang et al., 2020). Moreover, clozapine treatment has been shown to increase slow wave activity (Raymond et al., 2022) and individuals have been shown to have increased cognitive ability after receiving clozapine (Lee et al., 1994).

Because the three BAC tasks that improved with HD-tACS stimulation heavily rely on visualization abilities (The human imagination, 2023), it is possible that HD-tACS stimulation to the visual cortex helped to improve the "visuospatial sketchpad" and working memory aspects of cognition, as well as other aspects more attributed to the frontal cortex. It is possible that our stimulation montage boosted delta oscillations and ultimately improved working memory and executive functioning processes through a mechanism such as delta-gamma coupling (Gągol et al., 2018).

It is conceivable that the functionality of the visual cortex and neighboring brain regions may explain the observed improvement in cognition after HD-tACS. Studies have implicated the lateral parietal cortex in goal directed behavior (Tumati et al., 2019), the posterior parietal cortex in attention capabilities (Whitlock, 2017), and the occipital-parietal and visual cortices in motion processing (Martínez et al., 2018). Since stimulation to V5/MT may also affect surrounding areas and other nodes associated with cognitive networks, HD-tACS may have been able to enhance these aspects of cognition and result in improved performance on specific BACS tasks.

The disparate results obtained from HD-tDCS and HD-tACS stimulation emphasizes the importance of stimulating not only at the correct location, but also with the optimal frequency in order to have an effect (Grover et al., 2022). The improvements observed with HD-tACS stimulation may be due to HD-tACS interacting with the relevant brain networks to rectify altered connectivity, while HD-tDCS stimulation by its design does not specifically target particular brain networks. For example, HD-tDCS cathodal stimulation is expected to decrease cortical excitability of the targeted brain region (Eskandari et al., 2019) and this was demonstrated in our initial study where visual evoked response potentials were decreased after cathodal HD-tDCS stimulation to V5/MT (Raymond et al., 2023). In this study, HD-tDCS was used to target V5/MT based on previous studies that implicate an overactivation of the visual cortex in individuals with psychosis spectrum disorders (Braithwaite et al., 2015; Coltheart, 2018). HD-tDCS did not result in improved cognition, but aspects of this study design including stimulation frequency and brain target could potentially be altered to produce the desired results.

The improvements seen on these BAC tasks with HD-tACS

stimulation to V5/MT are promising in terms of clinical utility. Attention, working memory, and executive functions are particularly impaired cognitive domains in individuals with psychosis spectrum disorders (Bralet et al., 2008). Based on the results of this study, low frequency HD-tACS may become a viable stimulation approach to improve specific aspects of cognition in individuals with psychosis not enhanced by the antipsychotic drugs, which primarily address hallucinations and delusions. However, further studies are necessary to replicate these results. Furthermore, time intervals at which cognition improved with HD-tACS treatment suggest that HD-tACS may have a long-term positive effect on cognition in psychosis spectrum disorders. These results are consistent with literature suggesting that tACS has a more long-term effect on individuals working memory and other aspects of cognition (Grover et al., 2021, 2023) If these results are replicated in larger and longer term studies, then HD-tACS may become a viable treatment option for cognitively-impaired patients with psychosis.

5. Limitations

Limitations of this pilot study include a small number of participants (n = 6) and limited diversity of patients, as this study was performed at a single site. Sample size was limited by the study falling at the height of the COVID-19 pandemic, but take-home stimulation units and collaborations with multiple collection sites provide opportunities to maximize recruitment and regional/demographic variability in the future. Additionally, recruited subjects did not have active positive symptoms at their baseline assessments, and 2 subjects were unable to return for their one month follow-up assessment (one after HD-tDCS and one after HD-tACS). However, the included subjects demonstrated significant cognitive deficits at baseline, allowing for noticeable improvements. Performing this intervention in an acute population could show even larger effects, so future studies should aim to recruit from recent inpatient, treatment-naïve, and treatment resistant populations.

Lastly, this study had a single blind crossover design, providing only preliminary data towards stimulation efficacy. The use of a single blind is likely a minor issue for the digital BAC test, as it is a relatively objective measure that would be less sensitive to bias than a clinician-rated measurement. However, most previous research has used a paper and pen version of the BAC assessment as opposed to the tablet version, and our BAC composite results to do not take into account differences in nonsignificant tasks on the iPad vs. on paper. Additionally, the Verbal Memory BAC task is susceptible to learning effects after repeated use (Keefe et al., 2008), however this BAC task did not improve with either type of stimulation so it likely did not inflate our results. For the crossover, each participant received HD-tDCS, underwent a washout period, and then received HD-tACS. In future studies, the order of the interventions will be counterbalanced and compared to a sham or active control condition to better control for practice effects. Lastly, future studies may want to incorporate a longer washout period and additional follow up timepoints in order to assess whether cognitive improvements may last for longer than one month after stimulation (Grover et al., 2022). Despite the limitations associated with the pilot study, the results identified herein set the framework for more thorough analyses in the future.

6. Conclusions

In this study, the aim was to explore the relationship between V5/MT and cognition in psychosis spectrum disorders using two different stimulation paradigms. Two methods of altering cortical electrical activity were employed (HD-tDCS and 2 Hz HD-tACS). HD-tACS stimulation was associated with a stepwise improvement in cognition on the BAC DS task up to 1 month post-treatment, improvement in the VF task 1 month post treatment, while performance plateaued after 5 days on the TL task. There were no cognitive changes associated with HD-tDCS treatment to V5/MT, despite the fact that we have previously demonstrated neural target engagement with visual event related potentials (Raymond et al., 2023). Ultimately, delta wave HD-tACS may be able to improve cognition in psychosis by altering cortico-cortico communication between relevant brain structures. Future large-scale investigations are needed to validate these results.

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

I declare that the disclosed information is correct and that no other situation of real, potential or apparent conflict of interest is known to me.

Acknowledgements

The authors would like to thank everyone who contributed to this research. We would also like to thank the participants in our pilot study who made this research possible.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2023.103887.

References

Adhan, I., Lizano, P., Bannai, D., et al., 2020. Visual cortical alterations and their association with negative symptoms in antipsychotic-naïve first episode psychosis. Psychiatry Res. 288, 112957 https://doi.org/10.1016/j.psychres.2020.112957.

Arciniegas, D.B., 2015. Psychosis. Contin. Minne Minn. 21 (3 Behavioral Neurology and Neuropsychiatry), 715–736. https://doi.org/10.1212/01.CON.0000466662.89908.e7.

Atkins, A.S., Tseng, T., Vaughan, A., et al., 2017. Validation of the tablet-administered Brief Assessment of Cognition (BAC App). Schizophr. Res 181, 100–106. https://doi.org/10.1016/j.schres.2016.10.010.

Battaglini, L., Mena, F., Ghiani, A., Casco, C., Melcher, D., Ronconi, L., 2020. The Effect of Alpha tACS on the temporal resolution of visual perception. Front Psychol. 11, 1765 https://doi.org/10.3389/fpsyg.2020.01765.

Begemann M.J., Brand B.A., Ćurčić-Blake B., Aleman A., Sommer I.E. Efficacy of non-invasive brain stimulation on cognitive functioning in brain disorders: a meta-analysis. *Psychol Med.* 50(15):2465–2486. doi:10.1017/S0033291720003670.

Bello, U.M., Wang, J., Park, A.S.Y., et al., 2023. Can visual cortex non-invasive brain stimulation improve normal visual function? A systematic review and meta-analysis. Accessed August 14 *Front Neurosci.* 2023;17. Accessed August 14. ⟨https://www.frontiersin.org/articles/10.3389/fnins.2023.1119200⟩. Accessed August 14.

Bong, S.H., Choi, T.Y., Kim, K.M., Lee, J., Kim, J.W., 2020. Correlation between executive function and quantitative EEG in patients with anxiety by the Research Domain Criteria (RDoC) framework. Sci. Rep. 10 (1), 18578 https://doi.org/10.1038/s41598-020-75626-0.

Braithwaite, J.J., Mevorach, C., Takahashi, C., 2015. Stimulating the aberrant brain: evidence for increased cortical hyperexcitability from a transcranial direct current stimulation (tDCS) study of individuals predisposed to anomalous perceptions. Cortex J. Devoted Study Nerv. Syst. Behav. 69, 1–13. https://doi.org/10.1016/j.cortex.2015.03.023.

Bralet, M.C., Navarre, M., Eskenazi, A.M., Lucas-Ross, M., Falissard, B., 2008. [Interest of a new instrument to assess cognition in schizophrenia: the Brief Assessment of Cognition in Schizophrenia (BACS)]. L'Encephale 34 (6), 557–562. https://doi.org/10.1016/j.encep.2007.12.005.

Coltheart, M., 2018. Charles bonnet syndrome: cortical hyperexcitability and visual hallucination. Curr. Biol. 28 (21), R1253–R1254. https://doi.org/10.1016/j.cub.2018.09.007.

Convert Antipsychotic Doses to Chlorpromazine Equivalents • chlorpromazineR. Accessed August 25, 2023. https://docs.ropensci.org/chlorpromazineR/.

Eack, S.M., Greenwald, D.P., Hogarty, S.S., et al., 2009. Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. Psychiatr. Serv. 60 (11), 1468–1476. https://doi.org/10.1176/ps.2009.60.11.1468.

Elyamany, O., Leicht, G., Herrmann, C.S., Mulert, C., 2021. Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry. Eur. Arch. Psychiatry Clin. Neurosci. 271 (1), 135–156. https://doi.org/10.1007/s00406-020-01209-9.

Eskandari, Z., Dadashi, M., Mostafavi, H., Armani Kia, A., Pirzeh, R., 2019. Comparing the efficacy of anodal, cathodal, and sham transcranial direct current stimulation on brain-derived neurotrophic factor and psychological symptoms in opioid-addicted patients. Basic Clin. Neurosci. 10 (6), 641–650. https://doi.org/10.32598/BCN.10.6.1710.1.

First M., Williams J., Karg R., Spitzer R. Structured Clinical Interview for DSM-5—Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV). Published online 2015.

Focal Transcranial Electrical Stimulation (High Definition Transcranial Direct Current Stimulation). Brainbox. Accessed February 13, 2023. https://brainbox-neuro.com/techniques/focal-tes-hd-tdcs.

Friedman Test - an overview | ScienceDirect Topics. Accessed August 17, 2023. https://www.sciencedirect.com/topics/medicine-and-dentistry/friedman-test.

Friedman Test Effect Size (Kendall's W Value) — friedman_effsize. Accessed February 27, 2023. https://rpkgs.datanovia.com/rstatix/reference/friedman_effsize.html.

Gągol, A., Magnuski, M., Kroczek, B., et al., 2018. Delta-gamma coupling as a potential neurophysiological mechanism of fluid intelligence. Intelligence 66, 54–63. https://doi.org/10.1016/j.intell.2017.11.003.

Girardeau, G., Lopes-dos-Santos, V., 2021. Brain neural patterns and the memory function of sleep. Science 374 (6567), 560–564. https://doi.org/10.1126/science.abi8370.

Grill-Spector, K., Weiner, K.S., Kay, K., Gomez, J., 2017. The functional neuroanatomy of human face perception. Annu Rev. Vis. Sci. 3, 167–196. https://doi.org/10.1146/annurev-vision-102016-061214.

Grover, S., Nguyen, J.A., Viswanathan, V., Reinhart, R.M.G., 2021. High-frequency neuromodulation improves obsessive-compulsive behavior. Nat. Med 27 (2), 232–238. https://doi.org/10.1038/s41591-020-01173-w.

Grover, S., Wen, W., Viswanathan, V., Gill, C.T., Reinhart, R.M.G., 2022. Long-lasting, dissociable improvements in working memory and long-term memory in older adults with repetitive neuromodulation. Nat. Neurosci. 25 (9), 1237–1246. https://doi.org/10.1038/s41593-022-01132-3.

Grover, S., Fayzullina, R., Bullard, B.M., Levina, V., Reinhart, R.M.G., 2023. A meta-analysis suggests that tACS improves cognition in healthy, aging, and psychiatric populations. Sci. Transl. Med 15 (697), eabo2044. https://doi.org/10.1126/scitranslmed.abo2044.

Harmony, T., 2023. The functional significance of delta oscillations in cognitive processing. Accessed February 2 Front Integr. Neurosci. 2013 (7). Accessed February 2. ⟨https://www.frontiersin.org/articles/10.3389/fnint.2013.00083⟩. Accessed February 2.

HILL, S.K., SWEENEY, J.A., HAMER, R.M., et al., 2008. Efficiency of the CATIE and BACS neuropsychological batteries in assessing cognitive effects of antipsychotic treatments in schizophrenia. J. Int Neuropsychol. Soc. JINS 14 (2), 209–221. https://doi.org/10.1017/S1355617708080570.

Hochberger, W.C., Hill, S.K., Nelson, C.L.M., et al., 2016. Unitary construct of generalized cognitive ability underlying BACS performance across psychotic disorders and in their first-degree relatives. Schizophr. Res 170 (1), 156–161. https://doi.org/10.1016/j.schres.2015.11.022.

Hofmann, S.G., Asnaani, A., Vonk, I.J.J., Sawyer, A.T., Fang, A., 2012. The efficacy of cognitive behavioral therapy: a review of meta-analyses. Cogn. Ther. Res 36 (5), 427–440. https://doi.org/10.1007/s10608-012-9476-1.

Honaker, J., King, G., Blackwell, M., 2011. **Amelia** II: a program for missing data. J. Stat. Softw. 45 (7) https://doi.org/10.18637/jss.v045.i07.

Kaneda, Y., Sumiyoshi, T., Keefe, R., Ishimoto, Y., Numata, S., Ohmori, T., 2007. Brief assessment of cognition in schizophrenia: validation of the Japanese version. Psychiatry Clin. Neurosci. 61 (6), 602–609. https://doi.org/10.1111/j.1440-1819.2007.01725.x.

Keefe, R.S.E., Harvey, P.D., Goldberg, T.E., et al., 2008. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). Schizophr. Res 102 (1), 108–115. https://doi.org/10.1016/j.schres.2008.03.024.

Kim, J.H., Choi, I., 2021. Choosing the level of significance: a decision-theoretic approach. Abacus 57 (1), 27–71. https://doi.org/10.1111/abac.12172.

Kim, N.Y., Hsu, J., Talmasov, D., et al., 2021. Lesions causing hallucinations localize to one common brain network. Mol. Psychiatry 26 (4), 1299–1309. https://doi.org/10.1038/s41380-019-0565-3.

Kloke, J.D., McKean, J.W., 2012. Rfit: rank-based estimation for linear models. R. J. 4 (2), 57–64.

Lee, M.A., Thompson, P.A., Meltzer, H.Y., 1994. Effects of clozapine on cognitive function in schizophrenia. J. Clin. Psychiatry 55 (Suppl B), 82–87.

Lizano P. *Improving Visual Hallucinations by Targeting the Visual Cortex With Electrical Stimulation: A Feasibility Study*. clinicaltrials.gov; 2022. Accessed February 7, 2023. https://clinicaltrials.gov/ct2/show/NCT04870710.

Lopez, M.A., Basco, M.A., 2015. Effectiveness of cognitive behavioral therapy in public mental health: comparison to treatment as usual for treatment -resistant depression. Adm. Policy Ment. Health 42 (1), 87–98. https://doi.org/10.1007/s10488-014-0546-4.

Luo, H., Liu, Z., Poeppel, D., 2010. Auditory cortex tracks both auditory and visual stimulus dynamics using low-frequency neuronal phase modulation. PLoS Biol. 8 (8), e1000445 https://doi.org/10.1371/journal.pbio.1000445.

Martínez, A., Gaspar, P.A., Hillyard, S.A., et al., 2018. Impaired motion processing in schizophrenia and the attenuated psychosis syndrome: etiological and clinical implications. Am. J. Psychiatry 175 (12), 1243–1254. https://doi.org/10.1176/appi.ajp.2018.18010072.

McCleery, A., Nuechterlein, K.H., 2019. Cognitive impairment in psychotic illness: prevalence, profile of impairment, developmental course, and treatment considerations. Dialog-. Clin. Neurosci. 21 (3), 239–248. https://doi.org/10.31887/DCNS.2019.21.3/amccleery.

Medalia, A., Beck, A.T., Grant, P.M., 2019. Cognitive therapies for psychosis: advances and challenges. Schizophr. Res 203, 1–2. https://doi.org/10.1016/j.schres.2018.05.021.

Murray, M.H., Blume, J.D., 2021. FDRestimation: flexible false discovery rate computation in R. F1000Research 10, 441. https://doi.org/10.12688/f1000research.52999.2.

Onitsuka, T., McCarley, R.W., Kuroki, N., et al., 2007. Occipital lobe gray matter volume in male patients with chronic schizophrenia: A quantitative MRI study. Schizophr. Res 92 (1-3), 197–206. https://doi.org/10.1016/j.schres.2007.01.027.

Papazova, I., Strube, W., Becker, B., et al., 2018. Improving working memory in schizophrenia: effects of 1 mA and 2 mA transcranial direct current stimulation to the left DLPFC. Schizophr. Res 202, 203–209. https://doi.org/10.1016/j.schres.2018.06.032.

Patil, I., 2021. Visualizations with statistical details: The "ggstatsplot" approach. J. Open Source Softw. 6 (61), 3167. https://doi.org/10.21105/joss.03167.

Perälä, J., Suvisaari, J., Saarni, S.I., et al., 2007. Lifetime Prevalence of Psychotic and Bipolar I Disorders in a General Population. Arch. Gen. Psychiatry 64 (1), 19–28. https://doi.org/10.1001/archpsyc.64.1.19.

Perrotta, G., 2020. Psychotic spectrum disorders: definitions, classifications, neural correlates and clinical profiles. Ann. Psychiatry Treat. 4 (1), 070–084. https://doi.org/10.17352/apt.000023.

Petrolini, V., Jorba, M., Vicente, A., 2020. The role of inner speech in executive functioning tasks: schizophrenia with auditory verbal hallucinations and autistic spectrum conditions as case studies. Front Psychol. 11, 572035 https://doi.org/10.3389/fpsyg.2020.572035.

Raymond, N., Lizano, P., Kelly, S., et al., 2022. What can clozapine's effect on neural oscillations tell us about its therapeutic effects? A scoping review and synthesis. Biomark. Neuropsychiatry 6, 100048. https://doi.org/10.1016/j.bionps.2022.100048.

Raymond N., Reinhart R.M.G., Trotti R., et al. Efficacy and Tolerability of Lesion Network Guided Transcranial Electrical Stimulation in Outpatients with Psychosis Spectrum Illness: A Nonrandomized Controlled Trial. medRxiv. Published online April 3, 2023:2023.03.31.23287980. doi:10.1101/2023.03.31.23287980.

Roelfsema, P.R., de Lange, F.P., 2016. Early visual cortex as a multiscale cognitive blackboard. Annu Rev. Vis. Sci. 2, 131–151. https://doi.org/10.1146/annurev-vision-111815-114443.

Schwippel, T., Papazova, I., Strube, W., Fallgatter, A.J., Hasan, A., Plewnia, C., 2018. Beneficial effects of anodal transcranial direct current stimulation (tDCS) on spatial working memory in patients with schizophrenia. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 28 (12), 1339–1350. https://doi.org/10.1016/j.euroneuro.2018.09.009.

Shao, Z., Janse, E., Visser, K., Meyer, A.S., 2023. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. Accessed February 3 *Front Psychol.* 2014;5. Accessed February 3. ⟨https://www.frontiersin.org/articles/10.3389/fpsyg.2014.00772⟩. Accessed February 3.

Sugranyes, G., de la Serna, E., Ilzarbe, D., et al., 2021. Brain structural trajectories in youth at familial risk for schizophrenia or bipolar disorder according to development of psychosis spectrum symptoms. J. Child Psychol. Psychiatry 62 (6), 780–789. https://doi.org/10.1111/jcpp.13321.

Supèr, H., 2003. Working Memory in the Primary Visual Cortex. Arch. Neurol. 60 (6), 809–812. https://doi.org/10.1001/archneur.60.6.809.

Sur, S., Sinha, V.K., 2009. Event-related potential: An overview. Ind. Psychiatry J. 18 (1), 70–73. https://doi.org/10.4103/0972-6748.57865.

Tan H.R.M., Lana L., Uhlhaas P. High-frequency neural oscillations and visual processing deficits in schizophrenia. *Front Psychol*. 2013;4. Accessed May 9, 2023. https://www.frontiersin.org/articles/10.3389/fpsyg.2013.00621.

The human imagination: the cognitive neuroscience of visual mental imagery | Nature Reviews Neuroscience. Accessed February 2, 2023. https://www.nature.com/articles/s41583–019-0202–9.

Tumati, S., Martens, S., de Jong, B.M., Aleman, A., 2019. Lateral parietal cortex in the generation of behavior: implications for apathy. Prog. Neurobiol. 175, 20–34. https://doi.org/10.1016/j.pneurobio.2018.12.003.

Türközer, H.B., Hasoğlu, T., Chen, Y., et al., 2019. Integrated assessment of visual perception abnormalities in psychotic disorders and relationship with clinical characteristics. Psychol. Med 49 (10), 1740–1748. https://doi.org/10.1017/S0033291718002477.

*University of Düsseldorf: G*Power. Accessed December 5, 2023. https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower.

Unterrainer, J.M., Rahm, B., Kaller, C.P., et al., 2004. Planning abilities and the Tower of London: is this task measuring a discrete cognitive function? J. Clin. Exp. Neuropsychol. 26 (6), 846–856. https://doi.org/10.1080/13803390490509574.

Whitlock, J.R., 2017. Posterior parietal cortex. Curr. Biol. 27 (14), R691–R695. https://doi.org/10.1016/j.cub.2017.06.007.

Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am. J. Psychiatry 168 (5), 472–485. https://doi.org/10.1176/appi.ajp.2010.10060855.

Zhang, Y., Quiñones, G.M., Ferrarelli, F., 2020. Sleep spindle and slow wave abnormalities in schizophrenia and other psychotic disorders: recent findings and future directions. Schizophr. Res 221, 29–36. https://doi.org/10.1016/j.schres.2019.11.002.