

Complete resolution of treatment-refractory auditory verbal hallucinations in a patient with schizophrenia following transcranial direct current stimulation therapy

Całkowite ustąpienie lekoopornych omamów słuchowych u pacjentki ze schizofrenią po zastosowaniu przezczaszkowej stymulacji prądem stałym

Department of Old Age Psychiatry and Psychotic Disorders, Medical University of Lodz, Łódź, Poland

Correspondence: Adam Wysokiński, Department of Old Age Psychiatry and Psychotic Disorders, Medical University of Lodz, Czechosłowacka 8/10, 92-216 Łódź, Poland, e-mail: adam.wysokinski@umed.lodz.pl

Klinika Psychiatrii Wieku Podeszłego i Zaburzeń Psychotycznych, Uniwersytet Medyczny w Łodzi, Łódź, Polska

Adres do korespondencji: Adam Wysokiński, Klinika Psychiatrii Wieku Podeszłego i Zaburzeń Psychotycznych, Uniwersytet Medyczny w Łodzi, ul. Czechosłowacka 8/10, 92-216 Łódź, e-mail: adam.wysokinski@umed.lodz.pl

 <https://doi.org/10.15557/PiPK.2025.0046>

ORCID iDs

1. Adam Wysokiński  <https://orcid.org/0000-0002-6159-6579>

2. Michał Pazdrak  <https://orcid.org/0000-0003-4828-4754>

Abstract

The prevalence of auditory verbal hallucinations in schizophrenia is high, and many patients achieve no improvement despite adequate pharmacological treatment. This case report describes a 59-year-old female schizophrenia patient with chronic, treatment-refractory auditory verbal hallucinations. A total of 15 transcranial direct current stimulation procedures were administered over the left dorsolateral prefrontal cortex and left superior temporal gyrus. Following treatment, the patient achieved complete remission of auditory verbal hallucinations that lasted at least two weeks after the therapy was completed. Electroencephalogram-based analyses of power spectra and coherence are presented, demonstrating potential mechanisms that may underlie clinical effects of transcranial direct current stimulation in auditory verbal hallucinations.

Keywords: schizophrenia, electroencephalogram, auditory hallucinations, transcranial direct current stimulation

Streszczenie

Częstość występowania słownych omamów słuchowych wśród pacjentów ze schizofrenią jest wysoka, a u wielu z nich nie obserwuje się poprawy pomimo odpowiedniego leczenia farmakologicznego. Przedstawiono opis przypadku 59-letniej pacjentki ze schizofrenią, u której występowały przewlekłe i odporne na leczenie halucynacje słuchowe. Wykonano 15 zabiegów przezczaszkowej stymulacji prądem stałym, ukierunkowanych na lewą grzbietowo-boczną korę przedczołową i lewy zakręt skroniowy górny. Po zakończeniu leczenia odnotowano całkowite ustąpienie halucynacji słuchowych, utrzymujące się przez co najmniej dwa tygodnie. Przedstawiono analizę spektralną i koherencji opartą na elektroencefalografii, pokazujące potencjalne mechanizmy odpowiedzialne za efekty kliniczne przezczaszkowej stymulacji prądem stałym w leczeniu słownych omamów słuchowych.

Słowa kluczowe: schizofrenia, elektroencefalografia, halucynacje słuchowe, przezczaszkowa stymulacja prądem stałym

INTRODUCTION

This case report describes a female schizophrenia patient with chronic, treatment-refractory auditory verbal hallucinations (AVH) that achieved complete remission following transcranial direct current stimulation (tDCS) treatment.

AVH are present in approximately 60% of individuals with schizophrenia. More than 30% of patients are resistant to treatment with antipsychotic drugs. Increased spontaneous neuronal activity in the auditory cortex has been proposed as an underlying mechanism of AVH formation (Allen et al., 2008). Lahti et al. (2006) studied two cohorts of patients with schizophrenia using positron emission tomography. The study provided evidence that limbic dysfunction may contribute to the development of positive symptoms, with hallucinations correlating positively with resting activation in the anterior cingulate cortex and negatively with hippocampal activity. Also, reduced fronto-temporal connectivity was found to be involved in AVH in schizophrenia (Sommer et al., 2012). Recent studies have also shown that low-frequency (1 Hz) transcranial magnetic stimulation (TMS) over the temporal cortex may improve abnormal functional connectivity between the superior frontal gyrus and other brain areas, including the frontal cortex (Xie et al., 2023).

tDCS is a modern, safe, and effective method of non-invasive brain stimulation (NIBS) (Cirilo et al., 2017). Typically, two electrodes (anode and cathode) are used to apply a current to the surface of the patient's head. After penetration into the brain, there is a change in the resting potential of neurons located within the stimulation area. Following tDCS, within the area stimulated by the positive electrode (anode), there is an increase in the resting potential (neuronal excitation), which increases the likelihood of triggering an action potential in response to the incoming electrical/chemical stimulus. This effect is the opposite in the area supplied by the negative electrode (cathode), where the resting potential is lowered (inhibitory hyperpolarisation), making it less likely to induce a resting potential. Cathodal tDCS stimulation thus produces a similar effect to low-frequency TMS treatment.

Typically, hallucinations are associated with sensory modality-specific activation in cerebral areas involved in normal sensory processing (temporal cortex for auditory hallucinations and occipital cortex for visual hallucinations) (Weiss and Heckers, 1999). Thus, tDCS stimulation of these modality-specific areas might reduce the severity of hallucinations originating in overactive cortical regions. This phenomenon has been reported for both visual (Koops and Sommer, 2017) and auditory (Kantrowitz et al., 2019) hallucinations. A recent meta-analysis of adjunctive tDCS for treatment-refractory auditory hallucinations in schizophrenia confirmed a small positive effect of tDCS in protocols involving twice-daily stimulation or ≥ 10 stimulation sessions (Jiang et al., 2022).

MATERIALS AND METHODS

The patient is a 59-year-old female, with a 35-year history of psychiatric treatment for schizophrenia. The major clinical symptom was chronic auditory verbal hallucinations, which the patient had been reporting for many months prior to hospitalisation and included command auditory hallucinations for suicide (CAHS). In the past, she had been medicated with the majority of available antipsychotics (including clozapine), with no significant clinical improvement. Due to the lack of therapeutic alternatives, a course of tDCS stimulations of the left dorsolateral prefrontal cortex (IDL-PFC) (anode) and the left superior temporal gyrus (ISTG) (cathode) was performed. The spread of the electric field over the brain surface with these electrode locations was modelled using SimNIBS 4.0 software.

tDCS was performed using DC-Stimulator PLUS (neuroCare, Germany). This tDCS stimulation protocol has an experimental status, as it is not registered for schizophrenia. All stimulations were delivered using 5×7 cm rubber electrodes placed in 0.9% saline-soaked sponge pads. For all sessions, a current of 2.0 mA was applied, resulting in a current density of 0.057 A/m^2 . The anode was positioned at point F3 (according to the international EEG 10/20 system), and the cathode at point T7 (T3 according to the older nomenclature), with electrode placement according to Beam and Borckardt (Beam et al., 2009). Stimulation duration was 1,200 seconds for all sessions, with 20-second ramp-in and ramp-out. The total number of tDCS sessions was 15 (one session per day, for three weeks, Monday to Friday). Tolerability of each session was evaluated by the patient using a standard protocol. Only mild tingling/itching sensation was reported by the patient, with no impact on the general condition of the patient. The severity of AVH was assessed using the Auditory Vocal Hallucination Rating Scale (AVHRS) (Jenner and van de Willige, 2002) and items 1–11 of the Psychotic Symptoms Rating Scale (PSYRATS) (Haddock et al., 1999). Clinical assessments were performed at baseline (V1) and consecutively after the 5th, 10th and 15th (V2) tDCS procedure.

Prior to tDCS (V1) and at the end of the treatment (V2), a standard 19-channel resting EEG was recorded. EEG data were processed using the NeuroAnalyzer 0.24.4 toolbox (Wysokiński, 2024; <https://neuroanalyzer.org>). The processing pipeline included high-pass FIR filtering (0.5 Hz, attenuation: 32 dB, transition bandwidth: 0.002 Hz), notch filtering at 50 Hz, low-pass FIR filtering (45 Hz, attenuation: 32 dB, transition bandwidth: 0.0439 Hz). Electrocardiography (ECG) artifacts were removed using independent component analysis (ICA) (ECG component percent variance accounted for: 77.0 for the V1 recording and 57.11 for the V2 recording). Next, artifacts were removed manually upon visual inspection. Common average referencing and epoching into 20-second segments was performed. Next, epochs were visually examined and rejected if containing artifacts. A total of 52 20-second epochs were retained for

each EEG recording. Next, EEG epochs were analysed for spectral power across 0.1–30 Hz spectrum at F3 and T7 locations (IDPFC and lSTG, respectively) and F4 and T8 (rDPFC and rSTG). Total band power was calculated using the Welch periodogram and integrated using the composite Simpson's rule for delta (0.1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (14–30 Hz) frequency ranges. Coherence was calculated per each EEG band separately, using multi-taper (7 tapers) method.

The study was approved by a suitably constituted Ethics Committee of the Medical University of Lodz (RNN/244/19/KE). The study conforms to the provisions of the Declaration of Helsinki (1995; revised in Edinburgh 2000). The study subject provided informed consent for the tDCS treatment and for the use of acquired data for research purposes. During the tDCS procedures, the patient continued her previous pharmacological treatment (olanzapine 20 mg/day, lurasidone 148 mg/day).

RESULTS

Baseline (V1) scores were AVHRS: 39 and PSYRATS: 29, indicating high symptom severity. After completing the three-week tDCS course, no AVH were reported by a patient. At the endpoint (V2), the scores were AVHRS: 8 and PSYRATS: 4 (equivalent to minimal to no symptoms). Resolution of symptoms was gradual, and improvement started during the second week of treatment. Two weeks after the end of the treatment course, a follow-up assessment was performed. The patients maintained complete recovery of AVH (AVHRS: 8, PSYRATS: 4). After the follow-up examination, the patient was discharged home with improved mood and affect, with no presence of positive symptoms.

An unequal-variance two sample *t*-test or Mann-Whitney *U* test was used to compare band powers between V1 and V2 recordings (see Fig. 1). Compared to V1, there was a significant (Bonferroni-adjusted significant threshold: 0.0031) decrease of delta band power at F3 ($t = 4.04$, $df = 53.05$, $p < 0.001$), F4 ($t = 11.32$, $df = 58.40$, $p < 0.001$) and T8 ($t = 15.50$, $df = 61.22$, $p < 0.001$), but not at T7 ($U = 1266.0$, $df = 102.0$, $p = 0.578$). Similarly, theta and alpha powers were reduced at F3 (theta: $t = 4.19$, $df = 52.04$, $p < 0.001$; alpha: $t = 3.92$, $df = 65.88$, $p < 0.001$), F4 (theta: $t = 7.54$, $df = 53.10$, $p < 0.001$; alpha: $t = 13.31$, $df = 75.84$, $p < 0.001$) and T8 (theta: $t = 7.54$, $df = 53.10$, $p < 0.001$; alpha: $t = 4.80$, $df = 94.78$, $p < 0.001$), but not at T7 (theta: $t = 2.24$, $df = 51.36$, $p = 0.029$; alpha: $U = 1657.0$, $df = 102.0$, $p = 0.048$). There was a significant reduction of beta power in the frontal locations (F3: $t = 4.53$, $df = 53.55$, $p < 0.001$ and F4: $t = 7.73$, $df = 94.04$, $p < 0.001$), but not in the temporal ones (T7: $t = 0.78$, $df = 62.01$, $p = 0.44$ and T8: $U = 1,384.00$, $df = 102.00$, $p = 0.84$), see Fig. 2.

Fig. 3 shows coherence values for individual bands and channel pairs (F3–T8, F3–F4, F4–T8, and T7–T8). Tab. 1 shows the comparison between V1 and V2, all differences were statistically significant (*p*-values adjusted for 16

comparisons, equal-variance two sample *t*-test). For each analysed channel pair, there was a reduction (V2–V1) in coherence: delta F3–F4: -0.275 , delta F3–T7: -0.339 , delta F4–T8: -0.068 , theta F3–F4: -0.275 , theta F3–T7: -0.339 , theta F4–T8: -0.068 , alpha F3–F4: -0.275 , alpha F3–T7: -0.339 , alpha F4–T8: -0.068 , beta F3–F4: -0.275 , beta F3–T7: -0.339 , beta F4–T8: -0.068 . Next, the reduction in coherence was mapped onto a topographical representation of channel locations. Fig. 4 shows that for each analysed EEG band, the strongest reduction in coherence occurred between the anodal and cathodal locations of stimulation (F3 and T7, respectively).

DISCUSSION

A case report is presented of a female schizophrenia patient with chronic, treatment-refractory auditory verbal hallucinations (AVH) who achieved complete remission after tDCS treatment.

The effectiveness of auditory hallucination treatment using the tDCS method is assessed in a patient already receiving pharmacotherapy, as discontinuation of medication in drug-resistant schizophrenia could lead to global deterioration of the mental state and exacerbation of psychosis. Lindenmayer et al. (2019) reported that tDCS combined with pharmacological intervention can provide clinical gains over pharmacological intervention alone. Bose et al. (2018), in a randomised, double-blind, sham-controlled study, also demonstrated beneficial effects of add-on tDCS for refractory AVH in schizophrenia. Thus, tDCS is evaluated here as a complementary method to pharmacotherapy.

Interestingly, there were no changes at the T7 location, despite expectations (based on previous studies, e.g. To et al., 2018), that cathodal stimulation of this region would produce increased theta activity there. Otherwise, the observed EEG changes were mostly consistent with already reported alterations in the EEG spectrum, e.g. by Schestatsky et al. (2013), although there is large variability of reported effects. The profile of observed EEG alterations might indicate that anodal stimulation of the prefrontal cortex might be responsible for the symptomatic improvement.

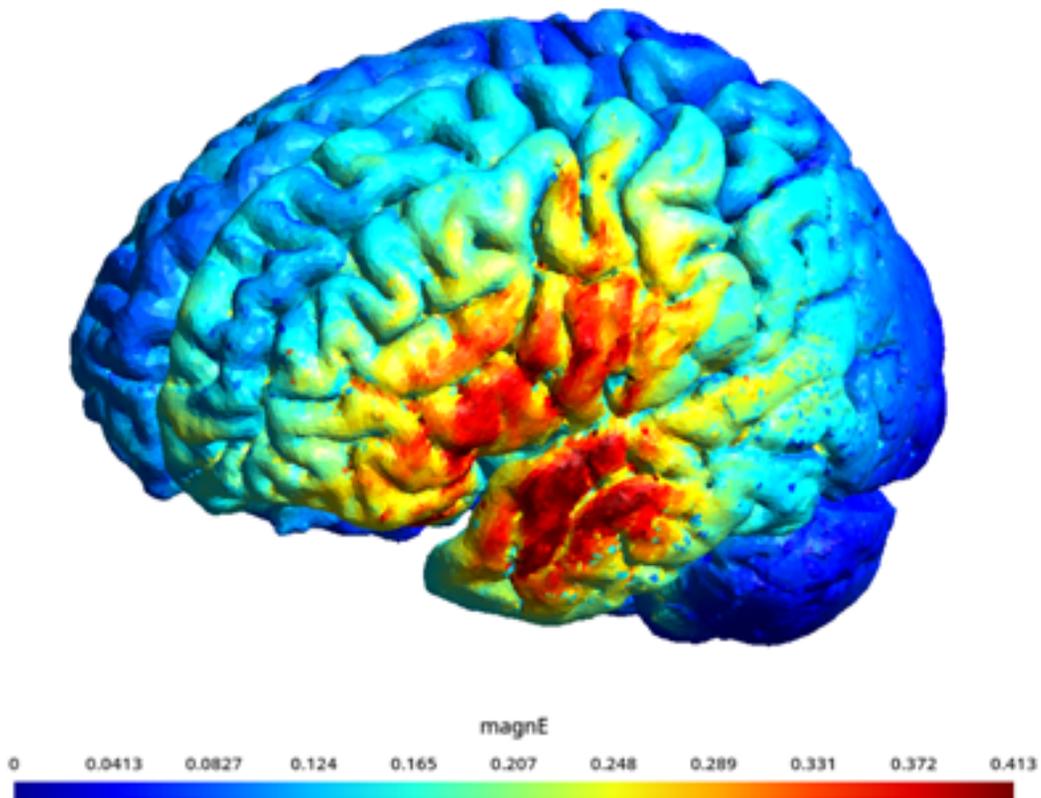
The coherence between the anodal and cathodal locations of stimulation is notable. It may support the view that the severity of auditory hallucinations is related not only to the activity of the temporal lobes but also to the quality of communication between temporal and frontal brain areas. Particularly remarkable is the linkage between the F3 and T7 areas, suggesting that disintegration between these regions may lead to an increase in the severity of auditory hallucinations. This promising finding indicates the need to further analyse these connections and their relevance to the severity of the patient's auditory hallucinations.

After two weeks, the patient maintained the therapeutic effect – complete absence of auditory hallucinations (AVHRS: 8, PSYRATS: 4), which supports the assumption

Band	Channels pair	V1	V2	Test statistics	p
Delta	F3–T7	0.83 ± 0.01	0.49 ± 0.05	$t = 71.1$ [95% CI: 0.33, 0.35], $df = 159.1$	<0.001
Delta	F3–F4	0.72 ± 0.06	0.44 ± 0.07	$t = 30.9$ [95% CI: 0.26, 0.29], $df = 250.0$	<0.001
Delta	T7–T8	0.48 ± 0.09	0.46 ± 0.06	$t = 2.1$ [95% CI: 0.01, 0.04], $df = 219.7$	0.002
Delta	F4–T8	0.77 ± 0.06	0.70 ± 0.03	$t = 10.5$ [95% CI: 0.01, 0.04], $df = 219.7$	0.002
Theta	F3–T7	0.77 ± 0.02	0.41 ± 0.02	$t = 112.5$ [95% CI: 0.35, 0.37], $df = 244.6$	<0.001
Theta	F3–F4	0.67 ± 0.03	0.42 ± 0.02	$t = 62.5$ [95% CI: 0.24, 0.26], $df = 228.8$	<0.001
Theta	F4–T8	0.74 ± 0.02	0.65 ± 0.03	$t = 21.9$ [95% CI: 0.08, 0.09], $df = 238.4$	<0.001
Theta	T7–T8	0.45 ± 0.03	0.45 ± 0.02	$t = -0.4$ [95% CI: -0.01, 0.01], $df = 215.0$	0.04
Alpha	F3–T7	0.70 ± 0.02	0.43 ± 0.03	$t = 83.2$ [95% CI: 0.27, 0.28], $df = 308.2$	<0.001
Alpha	F3–F4	0.64 ± 0.05	0.44 ± 0.02	$t = 39.9$ [95% CI: 0.18, 0.20], $df = 216.4$	<0.001
Alpha	F4–T8	0.77 ± 0.02	0.64 ± 0.04	$t = 34.2$ [95% CI: 0.12, 0.14], $df = 243.0$	<0.001
Alpha	T7–T8	0.60 ± 0.03	0.47 ± 0.02	$t = 37.6$ [95% CI: 0.13, 0.14], $df = 256.1$	<0.001
Beta	F3–T7	0.76 ± 0.02	0.39 ± 0.02	$t = 261.2$ [95% CI: 0.37, 0.37], $df = 996.6$	<0.001
Beta	F3–F4	0.63 ± 0.03	0.49 ± 0.02	$t = 69.9$ [95% CI: 0.13, 0.14], $df = 921.2$	<0.001
Beta	F4–T8	0.75 ± 0.03	0.71 ± 0.03	$t = 16.5$ [95% CI: 0.03, 0.04], $df = 1,024.0$	<0.001
Beta	T7–T8	0.52 ± 0.02	0.46 ± 0.02	$t = 39.6$ [95% CI: 0.06, 0.07], $df = 1,024.0$	<0.001

Data presented as mean ± standard deviation. 95% confidence interval (CI) values are given for t -test statistics. p -values were adjusted for 16 comparisons. **V1** – visit 1 (pre-tDCS); **V2** – visit 2 (post-tDCS).

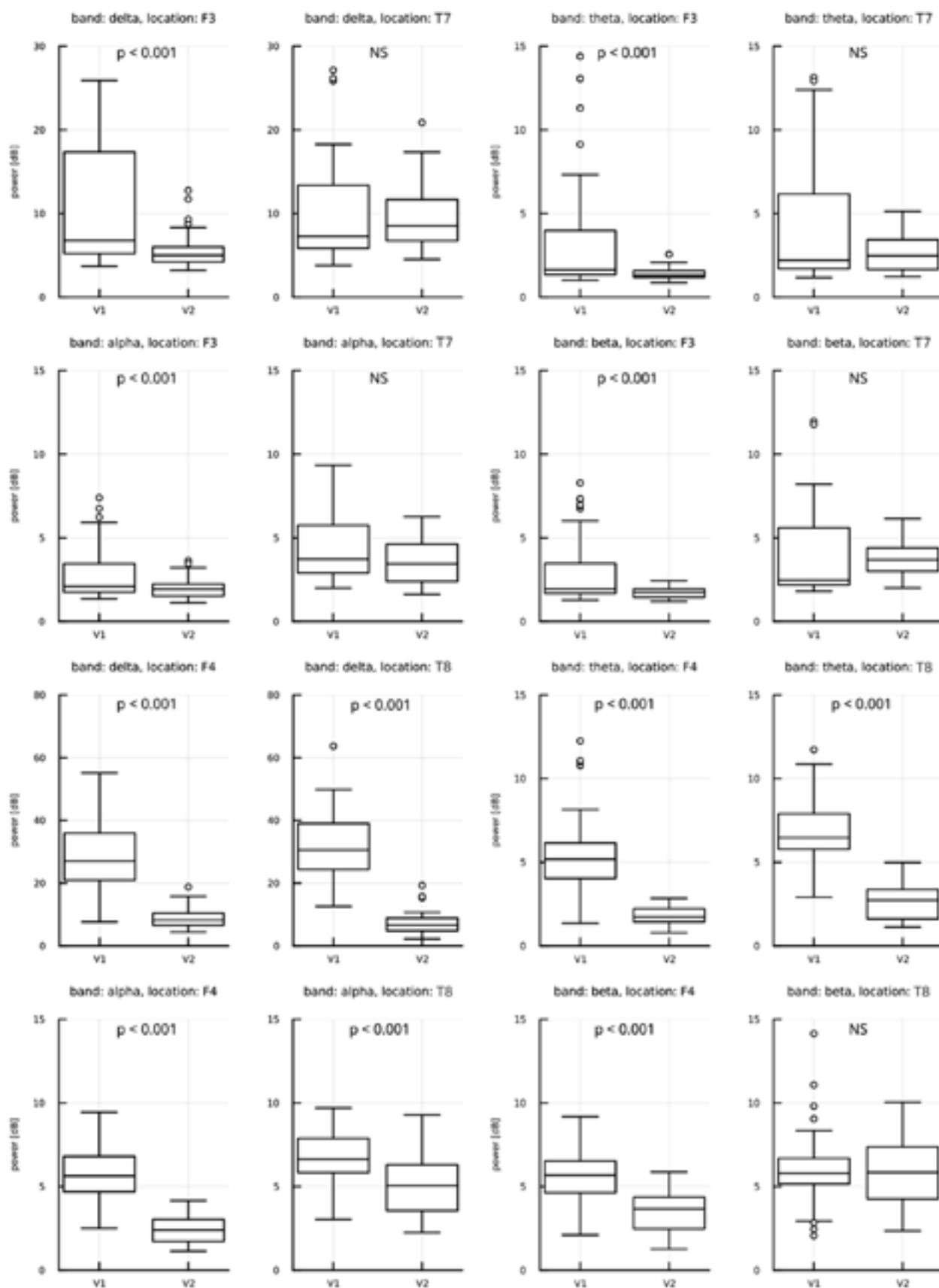
Tab. 1. Coherence values for EEG bands and channel pairs



magnE – magnitude of the electric field (V/m).

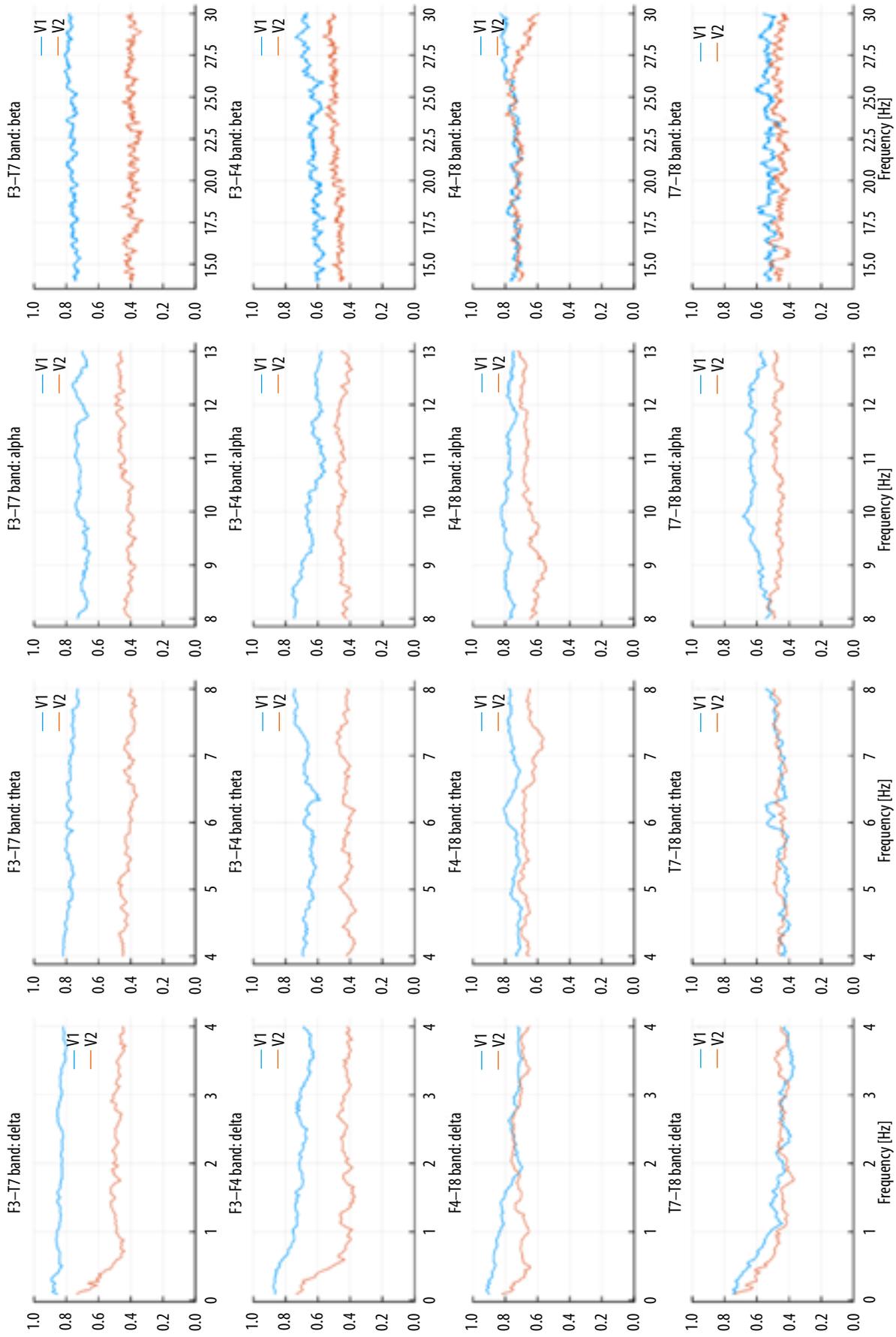
Note: red colour indicates higher magnitude of the electric field, while its magnitude over the blue areas is diminishing. It is expected that the most potent tDCS effects are within the red-to-yellow regions of the cerebral cortex.

Fig. 1. Distribution of the electric field for tDCS electrode placement used in the study



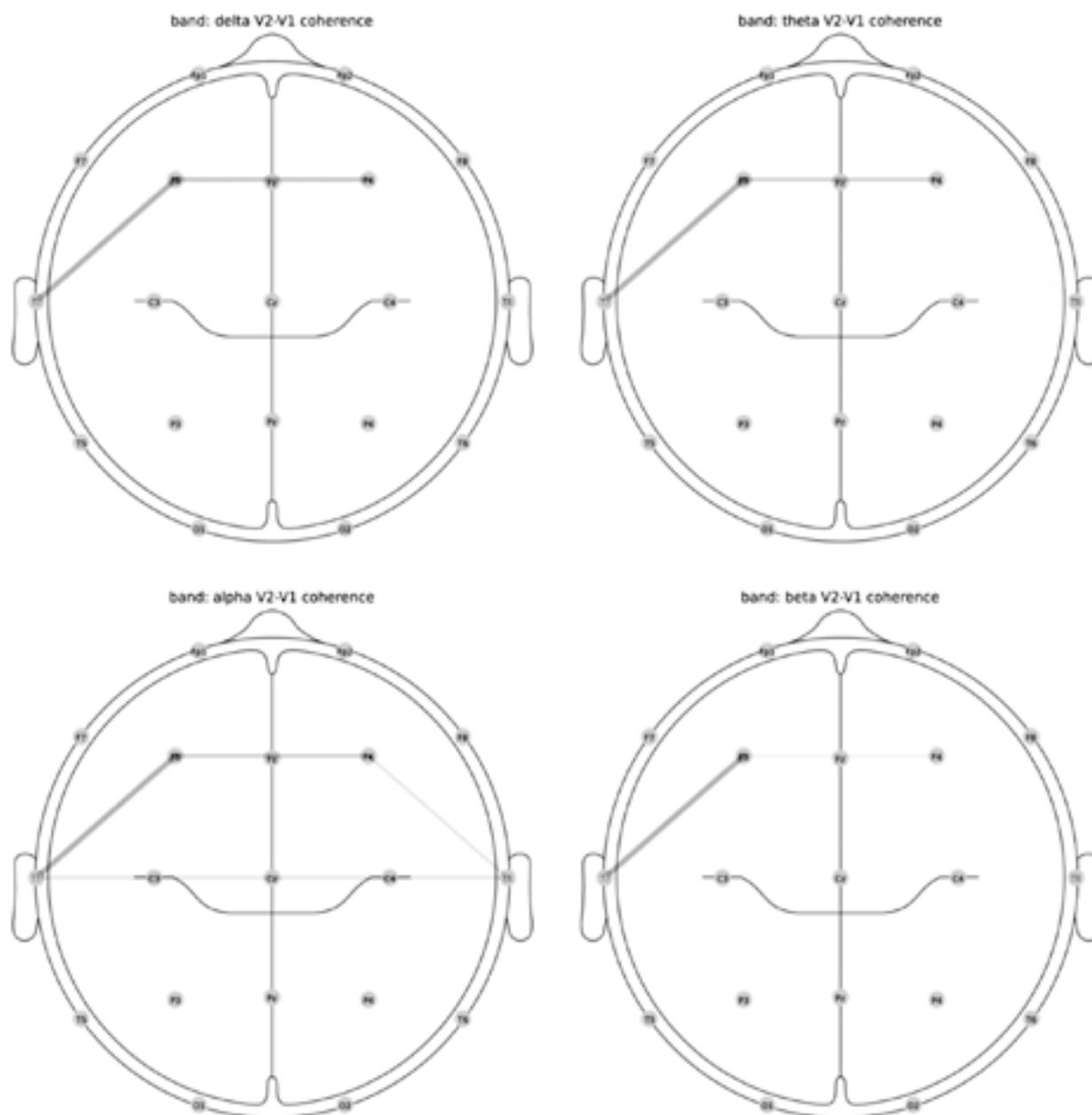
V1 – visit 1 (pre-tDCS); V2 – visit 2 (post-tDCS).

388 Fig. 2. Delta, theta, alpha, and beta powers at F3, F4, T7, and T8 locations before (V1) and after (V2) tDCS treatment



V1 – visit 1 (pre-tDCS); V2 – visit 2 (post-tDCS).
Y axes: inter-channel coherence value.

Fig. 3. Coherence between F3, F4, T7, and T8 channels



V1 – visit 1 (pre-tDCS); **V2** – visit 2 (post-tDCS).

Line width represents degree of reduction.

Fig. 4. Topographical map of reduction in coherence (V2–V1)

of durability of the therapeutic response and requires further observation in subsequent studies, also with the use of EEG.

The number of reports on the efficacy of tDCS for AVH in treatment-refractory schizophrenia remains limited. This, combined with the remarkable improvement observed in the patient, makes this case report significant for the psychiatric community. In summary, fronto-temporal tDCS stimulation might be a therapeutic alternative for schizophrenia

patients with treatment-refractory AVH. Based on clinical experience and previous reports, the number of tDCS stimulations should be ≥ 10 to achieve clinical effects.

A significant limitation of this report is its nature as a single case study, providing only limited evidence. Also, the tDCS procedure was not blinded, there was a potential impact of placebo effects associated with tDCS. Finally, the short duration of follow-up in this case does not allow conclusions regarding long-term outcomes.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study; analysis and interpretation of data: AW. Collection, recording and/or compilation of data; critical review of manuscript: MP. Writing of manuscript; final approval of manuscript AW, MP.

References

- Allen P, Larøi F, McGuire PK et al.: The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. *Neurosci Biobehav Rev* 2008; 32: 175–191.
- Beam W, Borckardt JJ, Reeves ST et al.: An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimul* 2009; 2: 50–54.
- Bose A, Shivakumar V, Agarwal SM 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: 475–480.
- Cirillo G, Di Pino G, Capone F et al.: Neurobiological after-effects of non-invasive brain stimulation. *Brain Stimul* 2017; 10: 1–18.
- Haddock G, McCarron J, Tarrrier N et al.: Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychol Med* 1999; 29: 879–889.
- Jenner JA, van de Willige G: The Auditory Vocal Hallucination Rating Scale (AVHRS). University Medical Center Groningen, Groningen 2002.
- Jiang WL, Cai DB, Sun CH et al.: Adjunctive tDCS for treatment-refractory auditory hallucinations in schizophrenia: a meta-analysis of randomized, double-blinded, sham-controlled studies. *Asian J Psychiatr* 2022; 73: 103100.
- Kantrowitz JT, Sehatpour P, Avissar M et al.: 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. *Brain Stimul* 2019; 12: 981–991.
- Koops S, Sommer IEC: Transcranial direct current stimulation (tDCS) as a treatment for visual hallucinations: a case study. *Psychiatr Res* 2017; 258: 616–617.
- Lahti AC, Weiler MA, Holcomb HH et al.: Correlations between rCBF and symptoms in two independent cohorts of drug-free patients with schizophrenia. *Neuropsychopharmacology* 2006; 31: 221–230.
- Lindenmayer JP, Kulska MKC, Sultana T et al.: Transcranial direct-current stimulation in ultra-treatment-resistant schizophrenia. *Brain Stimul* 2019; 12: 54–61.
- Schestatsky P, Morales-Quezada L, Fregni F: Simultaneous EEG monitoring during transcranial direct current stimulation. *J Vis Exp* 2013: 50426.
- Sommer IE, Clos M, Meijering AL et al.: Resting state functional connectivity in patients with chronic hallucinations. *PLoS One* 2021; 7: e43516.
- To WT, Eroh J, Hart J et al.: Exploring the effects of anodal and cathodal high definition transcranial direct current stimulation targeting the dorsal anterior cingulate cortex. *Sci Rep* 2018; 8: 4454.
- Weiss AP, Heckers S: Neuroimaging of hallucinations: a review of the literature. *Psychiatry Res* 1999; 92: 61–74.
- Wysokiński A: NeuroAnalyzer. 2024. Available from: <https://doi.org/10.5281/zenodo.7985829>.
- Xie Y, Guan M, Wang Z et al.: Alterations in brain connectivity patterns in schizophrenia patients with auditory verbal hallucinations during low frequency repetitive transcranial magnetic stimulation. *Psychiatry Res* 2023; 328: 115457.