Pathological Delta Oscillations in Hallucinogen Persisting Perception Disorder: A Case Report

David Haslacher, Nikola Novkovic, Maria Buthut, Andreas Heinz and Surjo R. Soekadar*

Department of Psychiatry and Neurosciences, Clinical Neurotechnology Lab, Neuroscience Research Center, Charité – Universitätsmedizin Berlin, Berlin, Germany

Background: Hallucinogen persisting perception disorder (HPPD) is characterized by spontaneous recurrence of visual hallucinations or disturbances after previous consumption of hallucinogens, such as lysergic acid diethylamide (LSD). The underlying physiological mechanisms are unknown and there is no standardized treatment strategy available.

Case Presentation: A 33-year-old male patient presented with persistent visual distortions (halos around objects, intensified colors, positive after images, and trails following moving objects) that developed after repeated use of hallucinogenic drugs at the age of 18. Symptoms developed gradually and worsened several months later, resulting in various pharmacological and psychosocial treatment attempts that remained unsuccessful, however. At presentation, 32-channel electroencephalography (EEG) showed increased delta activity over the occipital brain regions, reminiscent of occipital intermittent rhythmic delta activity (OIRDA) usually seen in children. Two sessions of cathodal (inhibitory) transcranial direct current stimulation (tDCS) over 30 min attenuated visual hallucinations and occipital delta activity by approximately 60%. The response persisted for over four weeks.

Conclusion: Pathological delta activity over occipital brain regions may play an important role in the development and perpetuation of HPPD and can be attenuated by non-invasive brain stimulation.

Keywords: hallucinogen persisting perception disorder (HPPD), transcranial direct current stimulation (tDCS), delta oscillations, excitation/inhibition, EEG, non-invasive brain stimulation (NIBS)

BACKGROUND

The consumption of hallucinogens such as lysergic acid diethylamide (LSD) or methylenedioxymethamphetamine (MDMA) can result in long-lasting and possibly permanent occurrence of perceptual, mainly visual, and disturbances. Prevalence of such hallucinogen-persisting perception disorder (HPPD) may further increase due to the growing diffusion of novel psychoactive substances able to cause the onset of the disorder (1, 2). HPPD was first described by Sandison et al. in the 1950s when the therapeutic value of LSD in mental illness was more

Abbreviations: tDCS, transcranial direct current stimulation; EEG, electroencephalogram; HPPD, hallucinogen persistent perception disorder; MDMA, methylenedioxymethamphetamine; LSD, lysergic acid diethylamide; OIRDA, occipital intermittent rhythmic delta activity.
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**CASE PRESENTATION**

A 32-year-old man presented with complaints of visual hallucinations that he characterized as “golden glitter” and “glowing translucent patches” in his total visual field. He also complained about seeing trails that follow moving objects. Particularly, loud colors, such as neon-colored objects or clothes, would intimidate him due to their intensity and could also trigger more severe episodes of visual distortions over several hours.

He reported that symptoms started gradually in the months after he repeatedly consumed hallucinogenic drugs at the age of 18. Due to the symptoms, he withdrew from social contacts and became increasingly insecure. At the age of 19, he sought professional help. Cranial magnetic resonance imaging (cMRI) remained unremarkable (except for a left cerebellar arachnoid cyst). A clinical EEG was interpreted as normal. To attenuate symptoms of depression with difficulties to sleep, he received citalopram and quetiapine that improved these symptoms, but not the visual hallucinations. About 8 years later, he developed an acute psychiatric crisis with anxiety and irritability as well as increased perceptual disturbances. During this time, he did not feel safe in his apartment anymore and had increasing suicidal ideations resulting in admission to a psychiatric hospital. At admission, he also mentioned distortions of sound for the time of one day that were classified as akasms. The reported symptoms were interpreted as signs of an acute (schizophreniform) psychotic episode. During inpatient treatment, the daily dose of quetiapine was increased, which led to an improvement of symptoms. The leading tentative diagnoses over the coming years were a suspected schizophrenic psychosis that alternated with episodes of depression.

During this time, he became treated with various neuroleptics, including clozapine, haloperidol, amisulpride, ziprasidone, risperidone, quetiapine, aripiprazole, perazine, and promethazine, but did not experience any lasting improvement of visual hallucinations. Due to side-effects, including akathisia and other extrapyramidal motor symptoms (EPMS), neuroleptics were discontinued. Out of his despair, he contacted numerous physicians and therapists, including the Center for Neuromodulation at the Department of Psychiatry and Psychotherapy of the Charité – Universitätsmedizin Berlin where he was diagnosed with HPPD at the age of 32 based on his self-report and course of disease. A 32-channel EEG was performed and showed diffuse slowing of brain oscillations across broad areas of cortex with high power in the delta range over occipital electrodes (Figure 1A). Resting state EEG did not show a clear alpha-peak with eyes open and no alpha blockage during eyes closed. Delta activity did not exhibit any notable lateralization. The patient was asked to rate occurrence and intensity of visual hallucinations or distortions using a visual analog scale (VAS, ranging from 1 = minimal to 10 = extreme) three times a day daily (Figure 2).

Based on the large body of literature showing reduced cortical excitability after cathodal transcranial direct current stimulation (tDCS) (19, 20), we delivered tDCS at 2 mA to the occipital lobe using large rubber electrodes (5 cm × 7 cm). The electrodes were placed perpendicularly to the midline, such that the cathode was centered to electrode position Oz and the anode was centered to position Fpz according to the international 10–20 system. Two 30-min sessions of tDCS each were performed, separated by an intermission of 30 min. EEG was obtained immediately before the first and after the second session of tDCS.

During the session, the patient reported that his visual hallucinations gradually improved. After the second session, the
patient reported an improvement of visual hallucinations or distortions by approximately 60% which sustained for 10 days (Figure 2). A Mann–Whitney U test comparing baseline VAS values provided for the 10 days before intervention with VAS values provided for the 10 days after intervention was highly significant ($p < 0.001$). Evaluation of the EEG recorded after the second session showed that abnormal delta activity over the occipital region disappeared (Figures 1B,C). Over the coming 4 weeks attenuation of delta activity remained reduced by approximately 40% relative to the pre-tDCS level (Figure 2). During this time, also symptoms of depression improved, and the patient reported alleviation of anxiety and agitation. Although visual distortions did not completely disappear and their intensity remained at a level of 3–4 on a VAS, the patient underlined that he felt great relief because tDCS provided him a mechanistic tool to control his symptoms.

**DISCUSSION AND CONCLUSION**

In the presented case diagnosed with HPPD, we found that pathological delta activity was causally linked to visual hallucinations. While occipital delta hypersynchrony was described earlier in HPPD (16), this is the first case report in which clinical symptoms were successfully treated with non-invasive brain stimulation to attenuate such pathological delta activity.

It has been proposed that symptoms of HPPD are caused by damage to inhibitory interneurons expressing 5-HT$_{2A}$ serotonin receptors to which most hallucinogens bind. This loss of cortical inhibition (21, 22) may manifest in aberrant occipital delta oscillations (23–25) associated with visual hallucinations. Our results support this model and suggest that disinhibition can be restored with cathodal (inhibitory) tDCS. Future studies should investigate whether the reported findings can be generalized to larger cohorts diagnosed with HPPD.

While two sessions of cathodal tDCS had an immediate effect on clinical symptoms and pathological delta activity, the exact mechanisms by which tDCS affected pathological delta activity are not entirely clear.

The most plausible and accepted primary effect of tDCS relates to modulation of resting membrane potentials (RMP), with anodal stimulation resulting in decreased RMP and cathodal stimulation in increased RMP reducing likelihood of action
FIGURE 2 | Intensity of visual hallucinations rated on a visual analog scale (VAS) ranging from 1 = minimal to 10 = extreme before and after intervention. While VAS scores ranged at around 5 before intervention, tDCS resulted in a highly significant decrease of VAS scores for 10 days (Mann–Whitney U test, \( p < 0.001^{***} \)) and remained reduced for more than 40 days.

Data availability statement
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement
Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patient provided his written informed consent to participate in this study.

Author contributions
DH performed tDCS treatment, data analysis, and wrote the manuscript. NN performed neuropsychological evaluation, data analysis, and wrote the manuscript. MB and AH evaluated the medical history and revised the manuscript. SRS performed neuropsychological evaluation and wrote the manuscript. All authors contributed to the article and approved the submitted version.
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