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## A case study of the feasibility of weekly tACS for the treatment of auditory hallucinations in schizophrenia

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### Dear Editor,

In a previous double-blind placebo-controlled clinical trial for the treatment of auditory hallucinations in patients with schizophrenia, we administered five consecutive days of transcranial alternating current stimulation (tACS) targeted to increase network synchronization between the prefrontal cortex and auditory cortex [1]. Our initial study found that tACS restored impaired alpha oscillations and that this increase correlated with clinical benefit. These findings suggest that tACS may be of future therapeutic value, and weekly tACS may be a means of increasing the durability of clinical benefit [2]. However, the feasibility of weekly tACS sessions for the treatment of auditory hallucinations is

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Author contributions

LFJ and FF designed the experiment. RBF, JR, LFJ, and FF wrote the letter.

Declaration of competing interest

FF is the lead inventor of IP filed by UNC. FF is founder, shareholder, and chief scientific officer of Pulvinar Neuro, which did not play any role in the writing of this article. FF has received honoraria from the following entities in the last twelve months: Sage Therapeutics, Academic Press, Insel Spital, and Strategic Innovation. RBF, JR, and LFJ have no conflict of interest.

currently unknown. To address this question, we recruited a single patient from those who completed an ongoing randomized, clinical trial of tACS to participate in an exploratory open-label study of weekly tACS. In this letter, we report on the successful completion of 20 weekly 40-min tACS sessions and a shift in the sense of controllability captured by the auditory hallucination rating scale (AHRS) and a personal log provided by the patient after study completion. Our study supports the feasibility and safety of prolonged, weekly tACS paradigms in patients with schizophrenia. However, due to the exploratory, open-label nature of this study, no conclusions can be drawn about the efficacy of weekly tACS.

The patient was a 35-year-old woman diagnosed with schizophrenia at least 10 years prior to study enrollment who was stabilized on lurasidone 80 mg per day before enrolling in the study. The patient is a single female in a long-term relationship and a successful entrepreneur. Her primary complaint was the frequency, duration, and hostile content of her auditory hallucinations and the adverse impact these symptoms had on her ability to run her business. Prior to enrolling in this open-label feasibility study, the patient completed [NCT#03221270](#). As the trial is ongoing, her group assignment in the clinical trial remains undisclosed to the authors. Each week, the patient rested quietly with her eyes open while receiving alpha-frequency tACS for 40 minutes. Stimulation was delivered at 10 Hz with 1 mA zero-to-peak amplitude in-phase to left dorsolateral prefrontal cortex (between F3 and Fp1) and temporal parietal junction (between T3 and P3) with 5 × 5 cm electrodes (see Ref. [1]). A 5 × 7 cm return electrode was centered on Cz. Side effects were quantified using a systematic assessment, and all side effects of stimulation reported were expected and determined to be mild [3]. There were no serious adverse events and side effects were well tolerated. The patient demonstrated 100% attendance with all 20 study visits. The only side effects consistently reported were transient scalp pain (60% of sessions), tingling (60%), and burning sensation (55%) at the electrode sites.

After each session, the Auditory Hallucinations Rating Scale (AHRS), a subscale of the Psychotic Symptoms Rating Scale (PSYRATS) [4,5], was administered and rated by trained research personnel. The Hamilton Program for Schizophrenia Voices Questionnaire (HPSVQ) was also completed at the end of each session by self-report [6]. Of note, the AHRS is rated by the clinician and the HPSVQ is self-report. Both scales measure the experience of auditory hallucinations, but the AHRS includes questions regarding volitional control over hallucinations absent in the HPSVQ. The HPSVQ also assesses the form and content of the voices in addition to severity. Furthermore, the patient maintained a journal throughout the study that she shared with investigators upon early termination of the study due to COVID-19 after 20 sessions (originally planned: 24).

The AHRS consists of 11 questions concerning the experience of auditory hallucinations over the course of the previous week and is rated on a five-point scale (0–4) such that higher values indicate increased severity of symptoms (total score range: 0–44). Over the course of 20 weeks of stimulation, the cumulative score of the patient did not substantially change (average in first month: 33.75, last week: 30, mean: 32.4, standard deviation: 1.76) (Fig. 1A). Of note, there was a consistent decrease that started at the 9th week of stimulation and was driven by a decrease in the duration (first month average: 4, last week: 2) and an increase in the controllability (first month average: 4, last week: 2) of auditory hallucinations

as assessed by the AHRS (Fig. 1B). In contrast, the HPSVQ scores failed to capture this sustained improvement, likely because the HPSVQ does not assess controllability. The failure of many assessments to capture perceived controllability was recently noted as this dimension is significantly implicated in predicting the level of distress from auditory hallucination [7].

Intriguingly, the increase in controllability of hallucinations temporally aligned with the notes provided by the patient. After 9 weeks of stimulation, the patient wrote in her journal that her perception of whether she could influence the voices changed, *“I rethought about my response to one of the research study questions of whether or not I have any control over bringing the voices on at will or dismissing them. Previously, I have answered “no,” but I realize now when I talk internally/telepathically or am thinking of something that’s of interest to the voices, they often respond and comment back. Sometimes when I have asked them to be quiet they are, but other times they just ignore me and keep talking. This may be a place where I can learn more control over the voices.”* This improved controllability might explain the reduction in duration of the daytime voices that was sustained for the remainder of the study. As she notes, *“There have been a number of days in the past few weeks in which the voices have been dramatically quiet.... Since the last couple of weeks, the episodes have been only 2–4 times a week. Compared to 5–7 times a week, it’s a vast improvement.”*

Auditory hallucinations in patients with schizophrenia are theorized to arise from a deficit in top-down control signal from the prefrontal cortex to the primary auditory cortex [8,9]. One manifestation of reduced top-down control is a reduction in network-scale functional connectivity between prefrontal and sensory regions [10,11]. The tACS montage for this case study was designed to enhance network-connectivity in the alpha frequency band in order to increase prefrontal control signals for the suppression of spontaneous activity in auditory cortex. Thus, the effect of stimulation to increase controllability may be indicative of an improvement in cognitive control. In agreement with this theory, the journal of the patient repeatedly addressed her sense of increased organization and orderliness, *“I’m so grateful my mind feels organized and that I’m able to be productive in accomplishing and achieving. To me, this is confirmation that the TACS treatment has a decidedly positive cognitive effect.”* Future studies will thus benefit from directly assessing cognitive control to investigate its relationship with controllability of hallucinations and the potentially shared underlying functional network substrate.

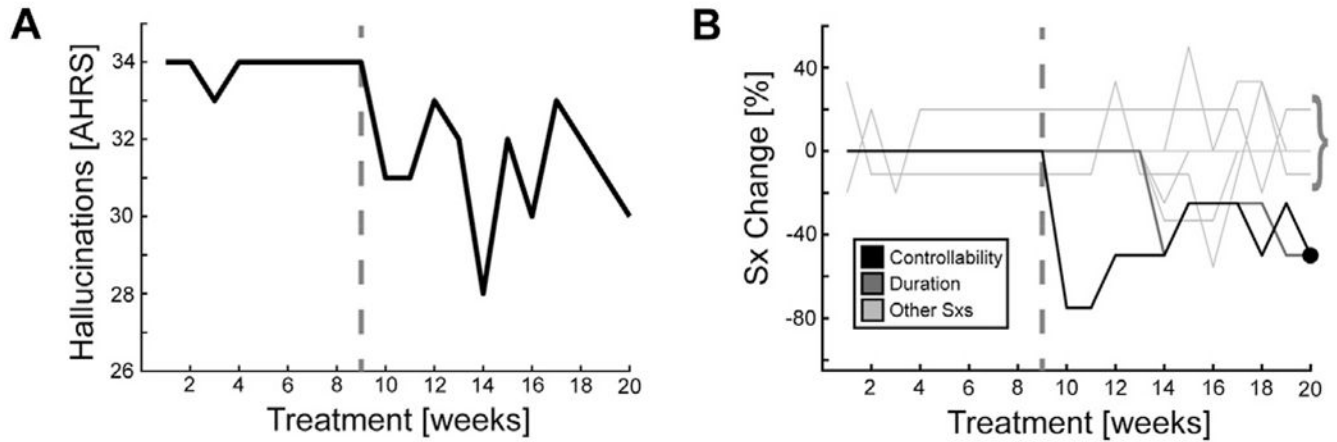
We propose that this feasibility study represents an important step towards tailoring tACS to address specific brain-behavior mechanisms that underly auditory hallucinations. Further double-blind placebo-controlled studies are needed to better understand the range of potential benefits of tACS in schizophrenia.

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**Fig. 1. Impact of alpha-frequency transcranial alternating current stimulation (tACS) on symptoms of auditory hallucinations.**

Alpha-frequency tACS was administered in-phase to left prefrontal and left auditory cortex for 40-minutes. The Auditory Hallucination Rating Scale (AHRS) is a clinician-rated survey of the severity of hallucinations (range 0–44) that was administered after stimulation on every session. (A) The cumulative AHRS score is depicted for each of the 20 weeks of stimulation. The dashed line denotes the onset of a sustained reduction in the cumulative AHRS score. (B) Individual symptoms (Sxs) on the AHRS are plotted over the course of the experiment. Scores are normalized to percent reduction from the average of the first month. In black, lack of controllability showed a notable decrease (corresponding to an increase in controllability) after the 9th week (dashed line). At the end of the experiment, both controllability and duration (in dark grey) show a notable decrease (black dot), whereas the other symptoms (in light grey) do not (grey bracket).