

Targeting Impaired Neural Oscillations in Patients with Schizophrenia by Transcranial Alternating Current Stimulation for the Treatment of Auditory Hallucinations

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Neural oscillations are a fundamental mechanism in large-scale brain dynamics and many psychiatric disorders have been associated impaired neural oscillations. In particular, patients with schizophrenia exhibit impaired alpha oscillations and functional connectivity, thus targeting and modulating these dysfunctions may represent a novel target-specific therapeutic approach for schizophrenia. Transcranial alternating current stimulation (tACS) is a non-invasive brain stimulation modality that applies oscillating currents to the brain via scalp electrodes. A single session of tACS modulates posterior alpha oscillations in healthy humans but it has remained unknown if this strategy can modulate impaired neural oscillations in patients with schizophrenia. In this study, we performed a randomized, double-blind, sham-controlled clinical trial for evaluating target engagement and therapeutic efficacy of twice-daily 10Hz-tACS for five consecutive days for auditory hallucinations in schizophrenia. We added transcranial direct current stimulation (tDCS) and sham stimulation as control conditions. Twenty-two patients with schizophrenia who experience auditory hallucinations were recruited and high-density electroencephalography (EEG) data were recorded. We found that 10Hz-tACS enhanced alpha oscillations ($F_{6,57}=3.49$, $p=0.005$) on day 5 of stimulation and modulated the strength of global functional connectivity to 10Hz. In addition, 10Hz-tACS enhanced the 40Hz auditory steady-state response (ASSR, $F_{6,57}=4.20$, $p=0.001$), which is considered a hallmark of schizophrenia. Importantly, clinical improvement of auditory hallucinations assessed by the auditory hallucinations rating scale correlated with enhancement of alpha oscillations and the 40Hz-ASSR. Our findings suggest that a target-specific approach using 10Hz-tACS has the potential to reduce symptoms by modulating impaired neural oscillations in patients with schizophrenia.

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Muting the voices with brain stimulation

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Auditory verbal hallucinations (AVH) affect 70% of patients with schizophrenia and are often resistant to antipsychotic medications. While transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have shown some promising treatment results, no study has investigated their effects independently of potentially influencing effects of antipsychotics. Here, we investigate rTMS and tDCS for AVH in medication-free patients. Due to the challenges that come with medication-free patients, we additionally investigate an accelerated protocol of four rTMS sessions within one day. The few studies that implemented such a protocol used high-frequency rTMS and found it to be equally effective and safe. A total of 160 patients within the schizophrenia spectrum and AVH will be recruited from the University Hospital of Psychiatry and Psychotherapy, Bern, Switzerland, and the Zucker Hillside Hospital at Northwell Health, NYC, and randomly assigned to either the classic 10 days rTMS, the accelerated rTMS, or tDCS protocol. Preliminary data of a non-medicated patient receiving tDCS show reduced AVH severity (Auditory Hallucination Rating Scale: pre = 28, post = 22) and increased normalized regional cerebral blood flow in the left Broca's area (pre = 0.90, post = 1.07), right Heschl's gyrus (pre = 1.03, post = 1.30), and bilateral superior temporal gyrus, posterior part (left: pre = 1.05, post = 1.18; right = 1.02, post = 1.18). Understanding the effects of brain stimulation on a physiological and subjective level is crucial to assess its potential as treatment alternative.

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Transcranial Direct Current Stimulation for Auditory Verbal Hallucinations in Schizophrenia

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Auditory verbal hallucinations (AVH) involve the perception of voices in the absence of auditory stimuli, and occur in >70% of schizophrenia patients (SZ). AVH remain resistant to pharmacological treatment in 25-30% of SZ, driving development of neuromodulatory interventions for AVH treatment. A recent meta-analysis reported a 30% reduction in overall SZ AVH severity with tDCS (Lee et al., 2017; $d=1.2$). However, none of the trials investigated neural mechanisms of tDCS effects, and there was considerable unexplained variability in treatment response. To address this, finite element modeling (FEM) was used to compute tDCS current delivery in inferior prefrontal cortex (iPFC) and temporoparietal junction (TPJ) in SZ with frequent, treatment-resistant AVH (N=6). AVH severity was assessed with the Psychotic Symptom Rating scales (PSYRATS), and fMRI and magnetoencephalography (MEG) were used to measure resting iPFC and TPJ activation pre- and post-treatment. Five-day tDCS treatment resulted in 26% reduction in AVH (sd=7.6). FEM modeling indicated significant current delivery to left iPFC and TPJ for 5/6 participants ($p<.05$). MEG and fMRI analyses revealed significant reduction in resting left TPJ activation ($p<.05$). FEM-assessed current at TPJ (but not iPFC) predicted change in AVH severity scores. These results support the hyperexcitation model of schizophrenia AVH and the primacy of temporoparietal language regions in the genesis of AVH. They further suggest that neuromodulatory reduction of left TPJ hyperexcitation is critical for reducing the severity of AVH in schizophrenia. Lastly, results suggest that it may be possible to improve the effectiveness using individualized FEMs to target TPJ hyperexcitation.

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Schizophrenia Treatment with Single-Session tDCS and Cognitive Remediation Training: Preliminary Findings

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Perceptual models of auditory verbal hallucinations (AVH) in schizophrenia (Sz) include hyper-excitability of auditory/verbal perception (in left temporoparietal junction; l-TPJ), and hypo-excitability of cognitive control which normally inhibits or reattributes perceptual misrepresentations (in right ventrolateral prefrontal cortex; r-VLPFC). We examined a single-session treatment to enhance cognitive control with Cognitive Remediation Training (CRT) plus anodal tDCS applied to r-VLPFC, and to reduce AVH with cathodal tDCS applied to l-TPJ. Participants were 12 Sz with persistent daily AVH despite stable antipsychotic medication for >2 months. tDCS (2mA, n=7) or sham (0.1mA, n=5) was delivered during CRT. We assessed AVH at baseline and 1-week later. Participants also completed the AX-CPT during electroencephalography (EEG) testing at baseline and immediately after CRT+tDCS. We analyzed beta-band event-related desynchronization (ERD) during the cue evaluation period (200-400ms after 'A' stimulus onset) in left central electrodes, which has been linked to cognitive control of attention, and accuracy and RT. AVH was reduced by CRT+tDCS (36% reduction) compared to CRT+sham (18% reduction; $d=0.82$). In the AX-CPT, RT improvement was greater for CRT+tDCS ($\Delta RT=73ms$) than CRT+sham ($\Delta RT=21ms$; $d=0.80$). Beta ERD in the evaluation period was increased more for CRT+tDCS ($\Delta ERD=0.49\mu V^2$) than CRT+sham ($\Delta ERD=0.00\mu V^2$; $d=0.89$). Accuracy did not change for either group. These preliminary results suggest that a single session of CRT+tDCS may reduce AVH severity and enhance cognitive control in treatment-refractory schizophrenia patients. These findings could lead to a new adjunct biomedical treatment for improving cognition and reducing auditory verbal hallucinations in schizophrenia.