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# PULSE

## A Monthly Update on Advances in Neuroscience

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## Superior Temporal Gyrus Functional Connectivity Predicts Response to tDCS for Auditory Hallucinations in Schizophrenia

*Tashalee R Brown MD, PhD reviewing Paul et al. Frontiers in Psychiatry 2022 Aug*

***A machine learning model using resting state functional connectivity was able to classify tDCS responders and non-responders in a population of patients with schizophrenia and persistent auditory verbal hallucinations***

Neuromodulation techniques could be promising adjunctive therapies for treatment refractory auditory verbal hallucinations (AVH) in schizophrenia (SZ). While tDCS has been shown to reduce AVH, there is significant inter-individual variability in treatment response. Data-driven approaches, such as machine learning, may enhance response rates by predicting which patients are likely to benefit.

## IN THIS ISSUE:

This retrospective analysis included 39 patients with SZ aged 18-48 years who had participated in prior tDCS studies (open label, n=16; double-blind RCT, n=23) for persistent AVH (defined as resistance to 1+ antipsychotic at an adequate dose for ≥3 months). tDCS treatment consisted of 10 sessions administered twice daily, separated by three hours, over five days of either conventional (n=31) or high-definition tDCS (HD-tDCS, n=8). Conventional tDCS was administered with 2 mA current strength, for 20 minutes duration with ramp-up and ramp-down time of 20 seconds each. The anode targeted the left DLPFC and the cathode targeted the left temporoparietal junction. HD-tDCS was performed with a 4x1 electrode ring with the central/anode electrode over the centro-parietal region and 0.5 mA delivered through each electrode pair. Each HD-tDCS session was 20 minutes with a ramp-up and ramp-down of 30 seconds.

Structural and functional MRIs were acquired prior to tDCS treatment. After preprocessing, 5 patients were excluded from the final analysis due to poor fMRI data quality. The final study sample contained 17 responders (change in Psychotic Symptom Rating Scales-AH score ≥ 25%) and 17 non-responders, with no demographic differences between groups but significantly higher positive and negative symptom scores in responders compared to non-responders. For the machine learning analysis, features were extracted using seed-based functional connectivity with the left superior temporal gyrus (LSTG). An L1 regularized logistic regression algorithm was used to train a classifier (responder vs. non-responder) and accuracy, specificity, sensitivity, and precision were evaluated using 10-fold cross-validation. Results from AVH subjects were compared with those from a classic convolutional neural network (CNN) analysis of an independent dataset of several cohorts including 186 healthy controls, 44 patients with SZ, 149 patients with OCD, and 62 unaffected first-degree relatives of patients with SZ, with CGI scores used to label fMRI signals associated with psychiatric pathology. CNN analyses were performed with and without transfer learning (Pre-trained CNN).

The L1-regularized logistic regression model yielded superior performance (accuracy = 72.5%) when compared to the classic CNN model (accuracy = 59.4%; paired t-test, p = 0.003) but not the pre-trained CNN model (accuracy = 68.8%; paired t-test, p = 0.47). The LSTG had the largest contribution in tDCS response prediction, consistent with prior studies. Left insular cortex, a brain region involved in the pathophysiology of AVH, showed the second highest contribution; there was minimal contribution of the right inferior frontal gyrus despite it being implicated in AVH pathophysiology.

**Impact: This retrospective analysis of pooled resting state fMRI data showed that a machine learning model based on functional connectivity predicted which patients would respond to tDCS therapy with 72.5% accuracy. Of concern is the small sample size, heterogeneity in methodology of tDCS treatment and fMRI data acquisition, and absence of a sham treatment group. These preliminary results are encouraging in that they suggest a possible imaging-based treatment target for AVH using tDCS. Prospective validation of these results in a larger controlled study is necessary.**

*Paul AK, Bose A, Kalmady SV, et al. Superior temporal gyrus functional connectivity predicts transcranial direct current stimulation response in Schizophrenia: A machine learning study. Front Psychiatry. 2022;13:923938. Published 2022 Aug 5. doi:10.3389/fpsyt.2022.923938*

## Excitatory Non-Invasive Stimulation of Left DLPFC Shows Promise for Treating Negative Symptoms in Patients with Schizophrenia

*Nicole Wong reviewing Tseng et al. JAMA Psychiatry 2022 Aug*

***A network meta-analysis of 48 RCTs suggests that excitatory noninvasive brain stimulation over the left dorsolateral prefrontal cortex is associated with significant improvements in negative symptoms in patients with schizophrenia***

Meta-analyses of randomized clinical trials using non-invasive brain stimulation (NIBS) in patients with schizophrenia have shown mixed results for the treatment of negative symptoms. These meta-analyses have been limited by lack of comparison of different NIBS protocols. This study reported results of a network meta-analysis comparing efficacy and acceptability of various NIBS protocols for negative symptoms in schizophrenia.

Using the procedure for network meta-analysis outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, the researchers identified RCTs that compared the efficacy of NIBS interventions primarily targeting the DLPFC. RCTs were only included if they measured change in negative symptoms as a primary or secondary outcome. The NIBS techniques surveyed in the meta-analysis included transcranial random noise stimulation (tRNS), transcutaneous vagus nerve stimulation (tVNS), tACS, tDCS, 10 Hz rTMS, and iTBS. Most studies other than those using tVNS involved stimulating the left DLPFC, with the cathode over right DLPFC in tACS and tDCS studies, though other stimulation sites included the temporoparietal junction and cerebellum. The authors summarized the reduction of negative symptoms and the acceptability (based on dropout rates) in each NIBS protocol by calculating standardized mean differences with 95% confidence intervals. All included RCTs allowed for patients to continue their antipsychotic treatment during the study period. Most of the included studies had small sample sizes with <20 participants per arm.

The authors included 48 RCTs involving 2211 participants (mean age: 38.7 years; mean proportion of female patients: 30.6%), with a mean study duration of 9 weeks (range: 1-32). The stimulation paradigm ranked highest in terms of alleviating negative symptoms was tRNS (SMD = −2.19 [95% CI: −3.36 to −1.02]), followed by left DLPFC iTBS (SMD = −1.32 [95% CI, −1.88 to −0.76]) and bimodal tDCS with anodes over left DLPFC and frontal pole and cathodes over right DLPFC and frontal pole (SMD = −1.29 [95% CI, −2.27 to −0.31]). There was no difference in acceptability among treatment strategies. A test of the transitivity assumption (i.e., that treatment A could be compared to C through shared comparisons with treatment B) revealed a significant placebo response to sham iTBS and tDCS, though this response was still significantly less than that observed in active treatment.

**Impact: This meta-analysis of 48 RCTs examining the comparative effects of NIBS protocols for the treatment of negative symptoms in schizophrenia found that excitatory stimulation at the left DLPFC produced significantly greater reductions in negative symptoms than sham treatments, without differences in acceptability among protocols. tRNS, iTBS, and tDCS protocols were found to be the most effective. Limitations of this study include the small sample sizes of most of the included studies and concerns based on the significant placebo response in some studies. Additional well-designed, large-scale RCTs are warranted to expand on these promising results.**

*Tseng PT, Zeng BS, Hung CM, Liang CS, Stubbs B, Carvalho AF, Brunoni AR, Su KP, Tu YK, Wu YC, Chen TY, Li DJ, Lin PY, Hsu CW, Chen YW, Suen MW, Satogami K, Takahashi S, Wu CK, Yang WC, Shiue YL, Huang TL, Li CT. Assessment of Noninvasive Brain Stimulation Interventions for Negative Symptoms of Schizophrenia: A Systematic Review and Network Meta-analysis. JAMA Psychiatry. 2022 Aug 1;79(8):770-779. doi: 10.1001/jamapsychiatry.2022.1513.*

## Low-Frequency rTMS Improves Auditory Hallucinations in Schizophrenia and Normalizes Aberrant Measures of Nucleus Accumbens Functional Connectivity

*Collin M Price, MD reviewing Xie et al., Front. Psychiatry, 2022 Sept*

***1 Hz rTMS delivered to the temporoparietal junction daily for four weeks in an open-label trial was found to improve positive and cognitive symptoms in patients with schizophrenia. Abnormalities in resting-state fMRI functional connectivity between the nucleus accumbens and multiple brain loci normalized after rTMS in patients compared to healthy controls, and normalization correlated with symptom improvement***

The dopaminergic system is implicated in the pathophysiology of schizophrenia (SZ). A central component of this system is the nucleus accumbens (NAcc), which has been implicated in auditory verbal hallucinations (AVH) via structural, functional, and biochemical investigation. Prior work has suggested 1 Hz rTMS to the temporoparietal junction (TPJ) may reduce the severity of AVH. This study examined whether 1 Hz rTMS alters activity of the NAcc in patients with SZ.

Thirty-two patients with SZ and AVH were recruited along with 35 demographics-matched healthy controls (HC) for comparison of resting-state functional connectivity (FC). Patients were included if they had persistent AVH after trying ≥2 antipsychotic medications, as well as ≥5 episodes of AVH per day over the prior month and no neurological diseases, substance use disorders, or MRI contraindications. Patients received 1 Hz rTMS delivered at 110% MT to the left TPJ for 15 minutes a day over 15 consecutive days. Structural and functional MRI scans were obtained once for HCs and before and after treatment for the patients. FC data were calculated using bilateral NAcc seeds correlated to a whole brain map, and gray matter volumes (GMV) of left and right NAcc were extracted. Clinical measurements included the PANSS, the auditory hallucination rating scale (AHRS), and the Chinese version of the MATRICS Consensus Cognitive Battery (MCCB).

Patients showed significant improvements after treatment in overall PANSS score ($t=4.18$, $p<0.001$), PANSS positive symptoms ($t=4.32$, $p<0.001$), AHRS ($t=6.54$, $p<0.001$), and two domains of the MCCB (verbal memory: $t=2.60$, $p=0.047$ | visual memory: $t=2.91$, $p=0.042$). At baseline, comparisons of NAcc FC between patients and HC revealed significantly increased FC in patients between bilateral NAcc and 1) left inferior/middle temporal gyrus and 2) right fusiform gyrus. Bilateral NAcc FC was found to be decreased with the 1) right superior/inferior frontal gyrus and 2) left anterior cingulate gyrus (voxel- and cluster-level p<0.05, clusters >30 voxels). Patients were also found to have decreased GMV compared to controls, though only in the left NAcc (t=2.18, p=0.038). After treatment, the abnormal FC patterns observed at baseline were reversed between the NAcc and the 1) left inferior temporal gyrus (t=2.72, p=0.11) and 2) right inferior frontal gyrus (t=2.65, p=0.013). The change in left NAcc FC with the left inferior temporal gyrus was further correlated with the change in positive symptom PANSS score (r= -0.54, p=0.024), while the change in right NAcc FC with the right inferior frontal gyrus was correlated with change in verbal memory score (r=0.53, p=0.016)

**Impact: This four-week course of 1 Hz rTMS to left TPJ to treat AVH in patients with SZ revealed significant clinical benefits of treatment that were correlated with resolution or reversal of NAcc FC differences between patients and HC. A significant limitation of this study was a lack of a sham control group, which makes it challenging to interpret the clinical changes observed after rTMS. Nevertheless, the FC changes seen following treatment represent a putative biomarker of response that should be examined in future studies.**

*Su X, Zhao L, Shang Y et al. Repetitive transcranial magnetic stimulation for psychiatric symptoms in long-term hospitalized veterans with schizophrenia: A randomized double-blind controlled trial. Front Psychiatry. 2022;13. doi:10.3389/fpsyt.2022.873057*

## HFL rTMS Yields Modest Benefits for Positive Symptoms in Long-Term-Hospitalized Veterans with Schizophrenia

*Collin M Price reviewing Su et al., Front. Psychiatry, 2022 September*

***In a small double-blind, sham-controlled RCT, military veterans with schizophrenia admitted to long-term psychiatric hospitalization received 20 sessions of neuronavigation-guided HFL rTMS. Although some improvements in positive symptoms were noted, modest effect sizes leave open the question of whether this treatment is useful in schizophrenia***

Previous work has suggested rTMS improves multiple symptom domains of schizophrenia (SZ) and represents a promising treatment adjunct to antipsychotics, though these findings have not been consistently replicated. Military veterans have an increased prevalence of SZ over the general population, and this study sought to assess the efficacy of rTMS in a population of veterans with SZ admitted for long-term psychiatric hospitalization.

Forty-seven veterans with SZ admitted to a long-term psychiatric hospital in China were recruited to participate in a double-blind sham-controlled RCT. Inclusion criteria included male gender and stable antipsychotic regimen for ≥6 months, while exclusion criteria included ECT treatment in the prior six months, history of suicide attempts, additional mental illness diagnoses, and major brain or other physical diseases. After randomization to active (n=27) or sham (n=20) groups, patients received rTMS delivered at 10 Hz, 110% MT, targeted to the left DLPFC once a day, five days a week, for four weeks. Neuronavigation based on a 0.3T structural MRI was used to target Brodmann area 46, and a sham coil was used to mimic the real treatment sound and sensation. The primary outcome was change in PANSS scores from baseline to four-week follow-up, assessed using a repeated-measures ANOVA. Peripheral blood was also collected for routine inpatient biomarkers, and these 15 assays were correlated with symptom changes.

There were no significant differences at baseline between the two groups on demographic variables or PANSS scores. After four weeks of treatment, the active group was found to have lower scores on the positive symptom factors of the PANSS as compared to sham with a significant group x time interaction (F = 4.3, p = 0.04, d = 0.08). However, there was no significant main effect or interaction effect of time or group on the total PANSS or the four other factors (negative symptoms, excitement, depressive symptoms, and disorganization). In the biomarker assessment, the only significant association was between white blood cell (WBC) count and improvement on the positive symptom factor (r= −0.42, p = 0.03), and a regression analysis showed that WBC count was predictive of positive symptom improvements. Notably, the authors do not comment on whether results were corrected for multiple comparisons.

**Impact: In this double-blind sham-controlled RCT, HFL rTMS in patients with SZ admitted to long-term hospitalizations yielded significantly greater improvements in positive symptoms than sham, and these improvements were associated with baseline WBC counts. However, the effect size of this change was low, and there were no other significant benefits associated with treatment. This may reflect an issue with statistical power given the small sample size. Further work is needed to assess the potential for benefit of the use of rTMS for symptoms of SZ.**

*Su X, Zhao L, Shang Y et al. Repetitive transcranial magnetic stimulation for psychiatric symptoms in long-term hospitalized veterans with schizophrenia: A randomized double-blind controlled trial. Front Psychiatry. 2022;13. doi:10.3389/fpsyt.2022.873057*

# Abbrevations

*cTBS (continuous theta burst stimulation)*
*DBS (deep brain stimulation)*
*dTMS (deep transcranial magnetic stimulation)*
*HFL (high frequency left, 10 Hz stimulation to left DLPFC)*
*HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)*
*iTBS (intermittent theta burst stimulation)*
*TENS (transcutaneous electrical nerve stimulation)*
*rTMS (repetitive transcranial magnetic stimulation)*
*tDCS (transcranial direct current stimulation)*
*tACS (transcranial alternating current stimulation)*

*BOLD (blood oxygen level dependent)*
*DTI (diffusion tensor imaging)*
*EEG (electroencephalography)*
*EMG (electromyography)*
*fMRI (functional magnetic resonance imaging)*
*MRI (magnetic resonance imaging)*
*MT (motor threshold)*

*ADHD (attention-deficit/hyperactivity disorder)*
*AUD (alcohol use disorder)*
*GAD (generalized anxiety disorder)*
*MDD (major depressive disorder)*
*OCD (obsessive compulsive disorder)*
*SUD (substance use disorder)*
*TRD (treatment resistant depression)*

*BAI (Beck Anxiety Inventory)*
*BDI (Beck Depression Inventory)*
*CGI (clinical global impression scale)*
*HAM-A (Hamilton Anxiety Rating Scale)*
*HAM-D / HDRS (Hamilton Depression Rating Scale)*
*MADRS (Montgomery-Asberg Depression Rating Scale)*
*PANSS (Positive and Negative Symptom Scale)*
*YBOCS (Yale-Brown Obsessive Compulsive Scale)*

*ANOVA (analysis of variance)*
*AUC (area under the curve)*
*CI (confidence interval)*
*FDA (United States Food and Drug Administration)*
*ICA (independent component analysis)*
*ITT (intention to treat)*
*RCT (randomized controlled trial)*
*ROC (receiver operating characteristic)*
*SMD (standard mean difference)*

*DLPFC (dorsolateral prefrontal cortex)*
*DMPFC (dorsomedial prefrontal cortex)*
*M1 (primary motor cortex)*
*OFC (orbitofrontal cortex)*
*SMA (supplementary motor area)*