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PULSE

A Monthly Update on Advances in Neuromodulation

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Cognitive and Emotional Effects of Bilateral Prefrontal Anodal tDCS and High-Frequency tRNS in Schizophrenia: A Randomized Sham-Controlled Study

Clara D. T. Nguyen, MD, MPH reviewing Jafari et al., Schizophrenia, 2026 Jan.

In this sham-controlled crossover study of adult males with schizophrenia, anodal tDCS and high-frequency transcranial random noise stimulation (tRNS) showed improvement in planning performance, increased positive affect, and reduced negative affect. Both interventions demonstrated promising results as adjuncts to schizophrenia treatment, particularly for cognitive deficits, when compared to sham.

Cognitive deficits are among the most impairing symptoms of schizophrenia, affecting daily function and quality of life while showing minimal response to antipsychotic treatment. Non-

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Glossary

invasive neuromodulation approaches, such as tDCS and tRNS, have shown promise as adjunctive treatments across psychiatric disorders. However, recent meta-analyses have reported inconsistent evidence for their efficacy in improving negative symptoms and cognition in schizophrenia, highlighting the need to optimize stimulation parameters. Using these treatment approaches, the authors examined whether bilateral stimulation of the DLPFC, a region implicated in working memory and executive function, could improve cognitive and emotional outcomes in schizophrenia.

The study enrolled 36 male patients (mean age 46 years) from inpatient psychiatric wards in the Daroshafa Hospital for Psychiatric and Chronic Diseases in Iran. Eligible participants met DSM-5 criteria for schizophrenia, were on a stable dose of antipsychotics, met safety guidelines for tDCS and tRNS interventions, and had no history of alcohol or substance dependence. All participants completed three counterbalanced stimulation sessions separated by one-week washout periods: (1) anodal tDCS, (2) high-frequency tRNS, and (3) sham stimulation. Each session targeted the bilateral DLPFC (F3-F4 electrode positions) for 20 minutes. The tDCS condition used 2 mA anodal stimulation with return electrodes positioned on the shoulders, whereas the tRNS condition used 2 mA high-frequency random noise stimulation (100-640 Hz). The sham stimulation used the same electrode configuration, but the device was inactive except for 30-s ramp-up and ramp-down periods at the beginning and end of the session. Working memory, spatial planning, and emotional state were assessed using the Spatial Working Memory task, Stockings of Cambridge task, and Positive and Negative Affect Schedule (PANAS), respectively.

Both the tDCS and tRNS improved spatial planning relative to sham stimulation, as reflected by a greater number of problems solved ($F_{2,70} = 34.3$, $p \leq 0.001$) and fewer moves required ($F_{2,70} = 29.9$, $p \leq 0.001$) on the Spatial Working Memory Task. Both treatment protocols significantly reduced negative affect when compared to sham (tDCS: $p < 0.001$, tRNS: $p < 0.001$), but only tRNS increased positive affect (tDCS: $p = 0.108$, tRNS: $p < 0.001$). Side effects were minimal in both treatments.

Impact: This study demonstrates treatment with tDCS and tRNS may confer both cognitive and emotional benefits in patients with schizophrenia. tRNS may be particularly helpful in working memory and enhancement of positive emotions, potentially due to its ability to increase prefrontal excitability and synchronize neural activity through the application of random oscillatory currents. The study was limited by the lack of neuroimaging and neurophysiological data to support the impact of the neuromodulation interventions. The use of male participants only may also impact the generalizability of results. Nevertheless, as non-invasive interventions, these neuromodulation approaches may represent useful adjuncts to antipsychotic treatment for cognitive and affective symptoms that are often inadequately addressed by medication alone.

Jafari, E., Moghadamzadeh, A., Vaziri, Z. et al. Cognitive and emotional effects of bilateral prefrontal anodal tDCS and high-frequency tRNS in schizophrenia: a randomized sham-controlled study. Schizophr 12, 28 (2026). https://doi.org/10.1038/s41537-025-00720-z

Assessing tDCS Efficacy in Reducing Negative Symptoms in Schizophrenia Spectrum Disorders: A Systematic Review and Meta-Analysis

Melvin Rico, MD, MPH, reviewing Guiomar et al. Brain Stimul. 2025

This systematic review and meta-analysis evaluated 18 RCTs examining the effects of tDCS on negative symptoms in schizophrenia spectrum disorders (SSDs). This study supports that tDCS is a promising add-on intervention to standard medication treatment for reducing negative symptoms in patients with SSDs.

tDCS has shown promise in the treatment of positive symptoms in patients with SSDs, especially auditory hallucinations. However, its efficacy to treat negative symptoms, which affect approximately 60% of patients with SSDs, remains unclear. Worse, these symptoms often do not respond to antipsychotic medications, highlighting the need for the need for novel treatment approaches. To address this, the authors conducted a meta-analysis of RCTs examining the effects of tDCS on negative symptoms in patients taking medications for SSDs.

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not respond to antipsychotic medications, highlighting the need for the need for novel treatment approaches. To address this, the authors conducted a meta-analysis of RCTs examining the effects of tDCS on negative symptoms in patients taking medications for SSDs.

Authors followed PRISMA and Cochrane Collaboration methodology guidelines for systematic reviews and searched for major databases for RCTs published up to May 2024. Of the 156 screened studies, 18 met the inclusion criteria, for a total of 709 study participants (361 active, 348 sham). SMD for changes in negative symptom severity was the primary outcome. Negative symptoms were measured using the PANSS and the Scale for the Assessment of Negative Symptoms (SANS). Cochran's Q-test and the I^2 index were used to calculate study heterogeneity. Subgroup analyses looked at the effects of relevant variables such as specific diagnosis, stimulation site, and number of sessions.

Active tDCS outperformed sham in reducing negative symptoms, with a moderate effect size (pooled SMD = -0.41, 95% CI: -0.66 to -0.15). Subgroup analyses showed consistent effects when negative symptoms were the primary outcome (SMD = -0.80, 95% CI: -1.08 to -0.53, I^2 = 16.5%) and when studies were limited to patients with schizophrenia (SMD = -0.51, 95% CI: -0.84 to -0.17, $p < 0.01$). Targeting the left DLPFC was also associated with a significant reduction in negative symptoms (SMD = -0.30, 95% CI: -0.57 to -0.03). These results suggest that tDCS is a safe adjunct to medication treatment for this patient population. However, the therapeutic benefit of tDCS was not sustained at follow-up (2 weeks to 3 months), with an SMD of -0.32 (95% CI: -0.67 to 0.03, $p = 0.069$), possibly indicating the need for maintenance sessions to sustain initial treatment benefits.

Impact: This study strengthens the evidence supporting tDCS as a safe adjunctive intervention for reducing negative symptoms in patients receiving medication treatment for SSDs. The main study limitations include the moderate methodological heterogeneity across trials and the limited data on specific negative symptom subdomains (e.g., expressive versus volitional deficits). Although antipsychotic dosage was not a significant moderator, future studies could explore the effect of antipsychotic medications on tDCS outcomes.

Guiomar R, Sobral M, Vanden Berghe L, et al. Assessing tDCS efficacy in reducing negative symptoms in schizophrenia spectrum disorders: A systematic review and meta-analysis. Brain Stimul. 2025;18(6):1794-1806. doi:10.1016/j.brs.2025.09.011

Long-Term Outcomes Following Randomized rTMS or Antidepressant Treatment: A Twelve-Month Naturalistic Follow-Up

Zack Blumenfeld, MD, PhD, reviewing Dalhuisen et al., Transcranial Magnetic Stimulation, 2026 Mar

In this naturalistic follow-up study, patients with unipolar depression and moderate treatment resistance (≥2 treatment trials) who had recently been enrolled in an eight-week open-label RCT comparing rTMS plus psychotherapy to pharmacotherapy plus psychotherapy were assessed for treatment response up to 12 months onward. Both response and remission rates remained largely stable for the rTMS cohort, while both response and remission rates increased in the pharmacotherapy cohort after 4 months before stabilizing for the remainder of the study.

While many studies have investigated the acute and short-term effects of rTMS on unipolar depression, few have examined the long-term effects on clinical response and remission rates. Evidence in previous naturalistic studies suggests that patients with depression treated with rTMS may experience sustained effects up to 12 months, while similar studies investigating the long-term effects of acute treatment with antidepressants or psychotherapy have shown significant drop-offs in response and remission. This study sought to compare the long-term effects of rTMS plus psychotherapy to the long-term effects of pharmacotherapy (wherein the antidepressant regimen was either augmented with a second agent or switched out for an alternative) plus psychotherapy in a population which had recently undergone an RCT comparing the short-term effects of these treatments.

Seventy-six patients completed the preceding eight-week open-label RCT for which they were randomized to either the rTMS or pharmacotherapy treatment groups. Patients were selected on the basis of a clinical diagnosis of unipolar depression without psychotic features, all with moderate to severe depression, measured as scores > 16 on the

HDRS-17 and with diagnoses confirmed using the Structured Clinical Interview for DSM-V Disorders (SCID). Additional inclusion criteria were failure of two or more treatment trials which could include either antidepressants or psychotherapy, as well as a current depressive episode lasting less than two years. Exclusion criteria included diagnosis of other significant mental illness or contraindications to rTMS including epilepsy or history of seizures. For the rTMS group, patients underwent twenty-five sessions of 10 Hz stimulation (3000 pulses, 120% of the RMT) to the left DLPFC; while for the pharmacotherapy group, patients were either given medication augmentation (current antidepressant plus an additional agent) or an alternative antidepressant, both of which were based on current Dutch guidelines for treatment-resistant unipolar depression. Both groups received equivalent psychotherapy throughout. After completing the initial open-label RCT, patients were interviewed by clinicians at baseline and at the four-, six-, nine-, and twelve-month mark post-RCT, during which time HDRS-17 scores were assessed, with response measured by a >50% score decrease and remission measured by a score <8. Additional questionnaires were also administered at baseline and at the six- and twelve-month mark to investigate specific symptoms, including the State/Trait Anxiety Inventory (STAI) to measure anxiety, the Snaith-Hamilton Pleasure Scale (SHAPS) to measure anhedonia, and the Perseverative Thinking Questionnaire (PTQ) to measure rumination.

At the end of the open-label RCT, there were forty-four patients in the rTMS cohort and thirty-two patients in the pharmacotherapy cohort. Over the course of the twelve-month period, patient attrition rates were comparable for each group, with the rTMS group reduced by 43.2% and the pharmacotherapy group reduced by 50%. In the rTMS group, the response rate at baseline was 40.9% which remained stable throughout the twelve months (40.5% at 4 months, 45.5% at 6 months, 44.8% at 9 months, 36% at 12 months), while remission rates likewise remained unchanged (29.5% at baseline, 32.4% at 4 months, 30.3% at 6 months, 34.5% at 9 months, 32% at 12 months). In the pharmacotherapy group, both the response and remission rates increased significantly between baseline and 4 months (18.8% to 33.3% for response rate and 6.3% to 20% for remission). Of note, out of the six patients in the pharmacotherapy group who showed an increase in response rate, four had received rTMS during the twelve-month naturalistic period. Among the time points for which STAI, SHAPS, and PTQ data were available, while there were some trends towards decreased scores in the rTMS group, no significant differences were found between time points.

Impact: In this study assessing the long-term effects of rTMS compared to guideline-directed medical therapy in patients with treatment-resistant unipolar depression, both response and remission rates in the rTMS group were stable over the course of the twelve-month study period. While there was a significant increase in response and remission rates in the pharmacotherapy group, this may be attributable to patients receiving rTMS during that same period. Taken together, these findings reinforce the durable benefits of rTMS. Of additional note is the fact that the rTMS arm received only 25 sessions, which is below the conventional treatment count of those receiving daily rTMS in the community (usually 36). Therefore, response and remission rates may be relatively modest in this study.

Dalhuisen I, van Oostrom I, Spijker J, et al. Long-term outcomes following randomized rTMS or antidepressant treatment: A twelve-month naturalistic follow-up. Transcranial Magnetic Stimulation. 2026;7:100212. doi:https://doi.org/10.1016/j.transm.2026.100212

Targeted TMS Can Modulate Default Mode Network Connectivity and Reduce Nicotine Cravings in Psychosis

Sheyna M. Nathwani, MD, reviewing Ward et al., Brain Stimulation 2026 Feb.

In this multi-part translational study, current tobacco use was associated with lower default mode network (DMN) connectivity in psychosis, and DMN-targeted TMS altered both craving and network connectivity in mechanistic follow up studies. Together, these findings identify a potential neural mechanism for nicotine use in psychosis and highlight DMN-focused TMS as a candidate non-pharmacologic intervention.

Tobacco use remains the leading preventable cause of early mortality in schizophrenia, overall contributing to a 20-year reduction in life expectancy. Additionally, prevalence of tobacco use in this group is triple that of the general population. Despite significant research into the reward-based mechanisms of addiction, proposed cessation strategies are markedly less effective in schizophrenia, suggesting that additional neurobiological drivers may be involved. Previous studies have shown that individuals with schizophrenia who smoke heavily demonstrate pathological DMN expansion, and emerging evidence indicates that nicotine may normalize DMN hyperconnectivity in a dose-dependent manner. Building on these observations, this study evaluates whether DMN connectivity is systematically related to tobacco use in a large psychosis-spectrum cohort and whether targeted modulation of this network using TMS can influence nicotine cravings in schizophrenia.

This investigation comprised three parts: 1) a validation study using a large psychosis-spectrum sample from the Bipolar-Schizophrenia Network on Intermediate Phenotypes 2 (B-SNIP2); 2) a Single-Session DMN-targeted TMS study; and 3) Accelerated Multi-Session DMN-targeted cTBS study. In the B-SNIP2 component, investigators analyzed 596 participants (320 psychosis-spectrum; 276 controls) from B-SNIP2 using resting-state fMRI, with primary outcome measuring DMN connectivity. In the TMS protocols, the target of TMS was localized by generating a participant-specific DMN map and placing the coil over the left posterior inferior parietal lobule node showing the strongest DMN connectivity.In the Single-Session DMN-targeted TMS study, 10 individuals aged 18-65 with schizophrenia or schizoaffective disorder and daily nicotine use completed a randomized, sham-controlled, crossover study. Each participant received one session of iTBS (600 pulses, 100% active motor threshold; AMT), cTBS (600 pulses, 80% AMT), and sham stimulation (coil was flipped 180 degrees) targeted to an individualized left parietal DMN node, as well as pre-/post-TMS neuroimaging. In the Accelerated Multi-Session DMN-targeted cTBS study, 12 individuals with similar inclusion parameters received 5 cTBS sessions (600 pulses, 100% AMT) with pre-/post-neuroimaging. Primary outcomes for the TMS studies were nicotine craving assessments and DMN connectivity via neuroimaging.

In B-SNIP2, DMN connectivity differed significantly by smoking status. Current smokers demonstrated lower DMN connectivity compared to former smokers (p=0.017) and never smokers (p=0.021). When restricted to participants with psychotic disorders specifically, the pattern persisted: current smokers had lower DMN connectivity than former smokers (p=0.044) and never smokers (p=0.011). A dose-response relationship was also observed between cigarettes/day and reduced DMN connectivity in the psychosis group (Spearman r = −0.22; p=0.013) but was notably nonsignificant in controls. In Single-Session TMS, there was a significant treatment × time interaction (X^2=5.41, p =0.02), where iTBS significantly increased craving compared to cTBS ($p_{adjusted}$=0.018). No significant changes in DMN connectivity were detected after single sessions (X^2=1.47, p =.48). In Accelerated Multi-Session cTBS, nicotine craving was reduced after each of the 5 sessions, with significant effects of time (X^2=14.67, p =.0001) and TMS session number (X^2=19.80, p =.0005). Additionally, DMN connectivity was significantly reduced following completion of treatment (p=0.047). Overall, TMS was well-tolerated and there were no reported serious adverse events.

Impact: This multi-part translational study identifies a potential neural mechanism underlying nicotine use in psychosis and provides initial evidence that DMN-targeted TMS can reduce nicotine craving in individuals with psychotic disorders. This suggests that the DMN may serve as a viable neuromodulation target for smoking cessation interventions in this population with high morbidity and limited treatment response. Despite promising findings, the study was substantially limited by its small sample size. Larger, multisite studies with long-term follow-up will be essential to determine durability, refine stimulation parameters, and clarify how network-based interventions might integrate with established cessation approaches.

Ward HB, Blyth SH, Vandekar S, Rogers BP, Yildiz G, Connolly JG, Clementz B, Gershon E, Keshavan M, McDowell J, Meda S, Pearlson G, Tamminga C, Halko MA, Brady RO. Network-targeted TMS modulates nicotine craving and default mode network connectivity in psychotic disorders. Brain Stimul. 2026 Mar-Apr;19(2):103064. doi: 10.1016/j.brs.2026.103064. Epub 2026 Feb 26. PMID: 41759716.

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
ECT (electroconvulsive therapy)
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)
MST (magnetic seizure therapy)
TBS (theta-burst stimulation; TMS delivered as triplet burst pulses at 50 Hz, repeated at 5 Hz)
TENS (transcutaneous electrical nerve stimulation)
TMS (transcranial magnetic stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tDCS (transcranial direct current stimulation)
tACS (transcranial alternating current stimulation)
TPS (transcranial pulse 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)
RMT (resting MT)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
PTSD (post-traumatic stress 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)
MoCA (Montreal Cognitive Assessment)
PANSS (Positive and Negative Symptom Scale)
QIDS (Quick Inventory of Depressive Symptomatology)
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)
OR (odds ratio)
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)
SMD (standard mean difference)

BA (Brodmann area)
DLPFC (dorsolateral prefrontal cortex)
DMPFC (dorsomedial prefrontal cortex)
M1 (primary motor cortex)
mPFC (medial prefrontal cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)