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PULSE

A Monthly Update on Advances in Neuromodulation

Produced by the Neuromodulation Division of the Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA

Anthony Jang, MD, Managing Editor | AlJang@mednet.ucla.edu
Aaron Slan, MD, Editor-in-Chief | aslan@mednet.ucla.edu

TMS, tDCS, and DBS Yield Possible Benefits for Adults with Substance Use Disorders as Shown in a Systematic Review and Limited Meta-Analysis

Praveen P. Rajaguru MD, MPH reviewing Mehta et al., Neuropsychopharmacology, 2023 Dec

Although limited by the heterogeneity of available data, this study suggests that neuromodulation therapies, particularly rTMS and tDCS targeting the DLPFC for alcohol and tobacco use disorders, may represent effective options in need of further exploration for reducing craving and consumption in adults with SUDs.

Substance use disorders (SUDs) account for up to 500,000 deaths each year in the US alone, despite available treatments. Given that neuroanatomical loci including the mesocorticolimbic circuit have been implicated in SUD pathophysiology, neuromodulatory

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interventions such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS) may prove beneficial. This study sought to summarize available evidence on the efficacy of neuromodulatory interventions for SUDs.

This systematic review and meta-analysis included studies published through October 2023. Eligible studies had participants 18+ years of age with diagnoses of SUD involving alcohol, nicotine, cocaine, cannabis, methamphetamines or opioids; utilized rTMS, tDCS, or DBS; and had control groups (aside from DBS studies given ethical constraints). Outcomes included consumption and craving, using validated measurement tools. 94 studies with 4,036 participants met inclusion criteria. A random-effects meta-analysis was conducted on rTMS and tDCS studies exploring alcohol and tobacco use disorders, and outcomes were reported as standardized mean differences (SMD) and 95% confidence intervals.

Of 94 studies (4,036 participants), 51 investigated rTMS (n=2,406), 36 tDCS (n=1,582), and 7 DBS (n=48). **Regarding rTMS**, the primary targets were the DLPFC, mPFC, or insula across substances. Regarding alcohol use, 11/16 trials used multiple sessions, with 7/11 showing reduced craving/consumption; 3/7 effective studies used deep TMS. Meta-analysis confirmed efficacy for craving (SMD −1.25, 95% CI −2.34 to −0.15, p=0.02, I^2=95.8%) and consumption (SMD −1.39, 95% CI −2.37 to −0.41, p<0.01, I^2=86.2%). Single-session studies were ineffective. For tobacco use, 14/16 trials reported reductions in craving and/or cigarette use, with stronger evidence for deep TMS (H4 coil). Meta-analysis found significant effects on cigarette consumption (SMD −1.65, 95% CI −3.00 to −0.30, p=0.01, I^2=95.1%), but not craving. Evidence for other substances was limited, though some benefit was seen for methamphetamine and opioid use disorders. **Regarding tDCS**, the primary target was the DLPFC across substances. In alcohol use disorder (9/14) and tobacco use disorder (7/11), the majority of trials showed benefit, but meta-analysis did not confirm significance. Limited evidence supported use for methamphetamine and opioid use, and there was minimal to no evidence for cannabis or cocaine use. **Regarding DBS**, the primary target was the nucleus accumbens across substances. All trials reported efficacy in cessation and craving reduction: 4/4 in alcohol, 1/1 in tobacco, and 2/2 in opioid use disorders.

Impact: This study provides an initial summary of the efficacy of neuromodulatory interventions in SUDs. rTMS was most supported by the evidence as indicated by medium to large effect sizes (Hedge's g > 0.5), with results most promising with protocols using multiple sessions and targeting the left DLPFC. tDCS also produced medium effect sizes for substance use and craving particularly with alcohol and tobacco, with protocols using right anodal DLPFC stimulation. DBS studies were small and uncontrolled but showed potential across substances. Future studies may further explore the mechanisms by which these treatments are effective in SUD, study longer term treatment durations and outcomes, and fill evidence gaps regarding optimal stimulation protocols and predictors of success. Importantly, future large-scale RCTs are needed to clarify the role of neuromodulation in SUD management.

Citation: Mehta DD, Praecht A, Ward HB, et al. A systematic review and meta-analysis of neuromodulation therapies for substance use disorders. Neuropsychopharmacology. 2024;49(4):649-680. doi:10.1038/s41386-023-01776-0

cTBS Yields Significant Benefits for Auditory Verbal Hallucinations in Adults with Schizophrenia Spectrum Disorders

Praveen P. Rajaguru MD, MPH reviewing Plewnia et al., Lancet Psychiatry, 2025 Sept

In this triple-blind, sham-controlled, multicenter RCT, cTBS to the temporo-parietal cortex demonstrated a 22% reduction in auditory verbal hallucinations in adults with schizophrenia spectrum disorder, with minimal adverse effects and an effect size of -0.45, comparable to that of CBT or antipsychotics.

Auditory verbal hallucinations occur in ~60% of patients with schizophrenia spectrum disorder. Although antipsychotics are first-line treatment, they have notable adverse effect profiles, and symptoms persist in 25-30% of cases. Evidence exists for the use of neuromodulatory approaches for auditory hallucinations, with pilot studies suggesting that inhibitory continuous theta-burst stimulation (cTBS) to the left or bilateral temporo-parietal cortex has efficacy, with a minimal adverse effect profile. This study sought to compare the efficacy and safety of cTBS in adults with auditory verbal hallucinations versus sham cTBS.

This triple-blind, sham-controlled, multicenter, phase 3 clinical RCT studied patients aged 18-65 years, with persistent auditory verbal hallucinations (at least once weekly for at least 3 months), insufficient response to at least 1 antipsychotic, and scoring 3 points or more on item P3 (evaluating hallucinations) of the Positive Scale of the Positive and Negative Syndrome Scale (PANSS). Eligible participants (n=138) were randomized to active (n=70) or sham cTBS (n=68), administered sequentially as 600 pulses to the left and 600 pulses to the right temporo-parietal cortex at 80% RMT with 15 treatments conducted in a 3-week period. An intention-to-treat (ITT) analysis was used and all participants who received at least one session were included in the final analysis. The primary outcome was the change from baseline at the 3-week timepoint in the auditory hallucinations subscale of the Psychotic Symptom Rating Scales (PSYRATS-AH). Adverse effects were also assessed.

130 patients were included in the final ITT analysis (n=66 active group, n=64 sham group). The baseline PSYRATS-scores in the ITT analysis did not vary across treatment groups. Regarding primary outcome, the active group had a significantly greater reduction in PSYRATS-AH score after treatment (–2.36 ([95% CI –4.71 to –0.01]; p=0.042, effect size -0.448). Regarding secondary outcomes, the active cTBS group had a significantly greater reduction in PANSS positive score (−1.33 ([95% CI –2.51 to –0.15]; p=0.027, effect size -0.291) and PANNS item 3 representing hallucinatory behavior (−0.47 ([95% CI –0.84 to –0.10]; p=0.012, effect size -0.548). Analysis of PSYRATS-AH individual items found significant differences between groups regarding the frequency, duration, and loudness of hallucinations. 85 adverse events (n=43 active group; n=42 sham group) were reported in 22/66 (33%) patients in the active group and 21/64 (33%) in the sham group; headache was the most common adverse event across groups. One serious adverse event (suicide attempt) occurred in the active group.

Impact: This triple-blind, sham-controlled, multicenter RCT suggests that sequential bilateral temporo-parietal cTBS over 3 weeks may be a safe and effective option in reducing auditory verbal hallucinations in adults with schizophrenia spectrum disorder. Roughly half of the improvement in this study was attributable to effects beyond sham response. The pooled effect size of –0.45 on primary outcome in this study is comparable with that of CBT for auditory verbal hallucinations and antipsychotic medication for positive symptoms in acute schizophrenia. The 3-week adherence rate was 85% with a low rate of adverse effects, which suggests cTBS is well tolerated by patients. Preliminary analysis at follow-up intervals suggested that the effects of TBS may persist up to 6 months; however, increasing attrition (22% at 1 month, 39% at 3 months, and 62% at 6 months) prevents definitive conclusions. Further research may explore the duration of these effects, predictors of these effects, optimal treatment targets, the role of maintenance treatment, and the extent of dose-dependent response based on different stimulation protocols.

Plewnia C, Brendel B, Schwippel T, et al. Theta burst stimulation of temporo-parietal cortex regions for the treatment of persistent auditory hallucinations: a multicentre, randomised, sham-controlled, triple-blind phase 3 trial in Germany. Lancet Psychiatry. 2025;12(9):638-649. doi:10.1016/S2215-0366(25)00202-0

Subgenual Cingulate Connectivity as a Conditional, Not Universal, Predictor of TMS Response: a prospective, multisite cohort study

Mohamad Shamas, PhD, reviewing Khosravani S et al. Mol Psychiatry 2025

This prospective, multisite observational study found that TMS site connectivity to the subgenual cingulate cortex (SGC) was not a significant standalone predictor of antidepressant response in a diverse clinical population with MDD. However, the expected relationship between SGC connectivity and antidepressant response emerged when accounting for various clinical covariates or when restricting the analysis to a highly selected patient subgroup matching the strict criteria of prior research.

TMS targeting the left DLPFC is an FDA-cleared treatment for MDD, yet individual patient outcomes show considerable variability. Previous smaller, single-site studies have suggested that TMS targets demonstrating stronger negative functional connectivity (anticorrelation) to the SGC are associated with a better antidepressant response. This "anti-subgenual" targeting approach has influenced recent clinical trials and the development of scalp-based targeting algorithms. Despite these advancements, the practical relevance of this anti-subgenual finding for routine TMS clinical practice remains uncertain. Prior studies often excluded individuals with comorbid psychiatric

conditions and provided limited data on the consistency of TMS site targeting within individuals. Given the complex and heterogeneous nature of MDD, various clinical factors such as age, treatment resistance, illness duration, concurrent medications, and comorbid diagnoses are known to impact TMS response. How these numerous clinical variables interact with the connectivity between TMS sites and the SGC has largely been unexplored. Therefore, this study aimed to assess whether normative connectivity of the TMS site to the SGC robustly predicts antidepressant response in a diverse, real-world MDD patient population, and how these numerous clinical covariates influence this relationship.

This was a multisite observational study involving 66 treatment-seeking individuals diagnosed with medication-resistant MDD. Participants were recruited from TMS clinics at Butler Hospital in Providence, Rhode Island, and Beth Israel Deaconess Medical Center (BIDMC) in Boston, MA. The study's inclusion and exclusion criteria were intentionally liberal to reflect the diverse patient population typically seen in routine clinical practice, allowing for individuals with comorbid psychiatric or neurological conditions, chronic pain, previous electroconvulsive therapy (ECT), and concurrent psychotropic medications. All participants received 4–8 weeks of daily 10Hz rTMS to the left DLPFC, 3000 pulses per session, as part of their standard clinical care. The primary outcome measure was the correlation between the change in Beck Depression Inventory-II (BDI-II) scores from baseline to post-treatment and the resting-state functional connectivity of each individual's TMS site to a pre-defined SGC region of interest. This connectivity was computed using normative resting-state functional connectivity data from a database of 1000 healthy individuals. Secondary post-hoc analyses explored the impact of various clinical covariates, such as comorbid psychiatric conditions, baseline anxiety, chronic pain, and medication use, by incorporating them into a multivariate linear model. The study also assessed within- and between-individual variability of TMS site markings.

In the full cohort of 66 individuals, the primary analysis, which controlled for hospital site and baseline BDI scores, found no significant relationship between TMS site connectivity to the SGC and the change in BDI-II scores (Spearman's $r = 0.1$, $p = 0.39$). This null result remained consistent across numerous sensitivity analyses, including alternative depression measures, SGC masks, electric field models, and normative connectome datasets. However, when the dataset was aggressively pruned to match the strict inclusion/exclusion criteria of prior studies (n=14), SGC connectivity emerged as a significant predictor of TMS response in the expected direction (Spearman's $r = -0.7$, $p = 0.01$). Crucially, when the full dataset (n=66) was re-examined using a multivariate linear regression model that incorporated baseline clinical covariates (comorbidities and medications), connectivity between the TMS site and the SGC also emerged as a significant predictor of TMS response ($\beta = -0.27$, $p = 0.014$; Spearman's $r = -0.35$, $p = 0.006$). Other significant and stable clinical predictors of antidepressant response identified in the model included the presence of psychiatric comorbidities ($\beta = -0.88$, $p < 0.0001$), baseline anxiety sensitivity (ASI-3 score) ($\beta = 0.59$, $p < 0.0001$), chronic pain ($\beta = -0.25$, $p = 0.0004$), and the use of certain baseline medications (antipsychotics, stimulants, benzodiazepines), and a history of previous ECT.

Impact: These findings significantly challenge the concept of a universally effective atlas-based "anti-subgenual" TMS target for all MDD patients. The study demonstrates that the predictive value of normative SGC connectivity for TMS response is minimal when considering the diverse patient population typically encountered in routine clinical practice. Instead, its predictive utility becomes apparent only when patients are highly selected (as in previous research) or when a comprehensive range of clinical covariates, such as psychiatric comorbidities, anxiety, and medication use, are taken into account.

Khosravani S, Palm ST, Drew W, et al. Predictive value of subgenual cingulate normative connectivity to TMS treatment site for antidepressant response in routine clinical practice: a prospective, multisite cohort study. Mol Psychiatry. 2025. https://doi.org/10.1038/s41380-025-03153-3.

Symptom Provocation During TMS Treatment Shows Encouraging, but Not Statistically Significant, Benefit in OCD and Nicotine Dependence

Anthony I. Jang MD reviewing Bello et al., JAMA Psychiatry, 2025 Aug

This systematic review and meta-analysis by Bello et al. investigates the effect of symptom provocation during TMS in patients with OCD and nicotine dependence. While the authors did not find a statistically significant improvement in treatment response attributable to symptom provocation, studies incorporating provocation tended to report higher effect sizes compared to those without provocation in both OCD and nicotine dependence. These findings suggest that symptom provocation may enhance the therapeutic impact of TMS, underscoring the need for larger, well-powered randomized controlled trials specifically designed to directly compare TMS with and without symptom provocation.

OCD and nicotine dependence are prevalent and debilitating conditions with significant public health impact. Neuromodulatory techniques, including TMS, have gained traction as adjunctive or alternative treatment options for these disorders. However, response rates to TMS remain variable. Symptom provocation, the deliberate elicitation of distressing symptoms immediately prior to or during TMS sessions, is hypothesized to enhance treatment effects through an interaction between external stimulation and internal brain state. While individual studies have explored this approach, results have been inconsistent, and protocols varied widely. This systematic review and meta-analysis aimed to comprehensively synthesize the evidence regarding the efficacy of symptom provocation during TMS for OCD and nicotine dependence.

The authors performed a systematic literature search from August 2023 to March 2025 that identifying 44 studies evaluating symptom provocation with TMS in OCD and 27 studies in nicotine dependence (total n = 2,998). Eligible studies included adult participants diagnosed with OCD or nicotine dependence who underwent TMS with or without symptom provocation. Outcomes assessed were changes in OCD symptom severity, primarily via the YBOCS, and smoking abstinence rates verified through standardized measures. A multilevel random-effects meta-analysis was conducted to compare outcomes between symptom provocation and standard TMS groups.

First, the authors examined the efficacy of active TMS compared to sham treatment without considering symptom provocation. Across all diagnostic groups and provocation protocols, active TMS was associated with a significantly greater clinical improvement than sham, with a standardized mean difference (SMD) of -0.37 (standard error [SE], 0.06; 95% confidence interval [CI], -0.48 to -0.26). There was no significant difference in the effect size of TMS versus sham between the diagnostic groups (SMD [SE] = 0.14 [0.13]; 95% CI, −0.12 to 0.40; P = 0.29), indicating that TMS demonstrated comparable efficacy in both OCD and nicotine dependence. Regarding symptom provocation, the authors found no statistically significant additional benefit when provocation was included across both diagnostic groups, although the results trended toward a beneficial effect (SMD [SE] = −0.23 [0.21]; 95% CI, −0.68 to 0.21; P = 0.28). Within each diagnostic group, similar non-significant trends were observed for both OCD (SMD [SE] = −0.22 [0.15]; 95% CI, −0.65 to 0.20; P = 0.22) and nicotine dependence (SMD [SE] = −0.21 [0.36]; 95% CI, −1.00 to 0.58; P = 0.57).

The authors noted considerable heterogeneity across studies, likely reflecting differences in TMS target sites, stimulation parameters, the timing of symptom provocation, and patient populations.

Impact: This meta-analysis offers promising, though not statistically significant, evidence that symptom provocation during TMS may enhance treatment outcomes in OCD and nicotine dependence. This finding is particularly relevant given that FDA-cleared TMS protocols for these conditions intentionally provoke symptomatic states prior to stimulation, aiming to prime the brain for greater responsiveness to TMS. Future research should focus on well-designed, large-scale randomized controlled trials that systematically compare TMS with and without standardized symptom provocation procedures to better assess its true impact.

Bello D, Jones M, Gadiyar I, et al. Symptom Provocation and Clinical Response to Transcranial Magnetic Stimulation. JAMA Psychiatry. Published online June 4, 2025. doi:https://doi.org/10.1001/jamapsychiatry.2025.0792

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)