UCLA Semel Institute

MAY 2025 / ISSUE 50

PULSE

A Monthly Update on Advances in Neuromodulation

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VNS Provides Sustained Symptom Relief in Largest Trial for TRD

Meghan Y. Reddy, MD reviewing Conway et al. Brain Stimul., 2024 Dec

In this multi-site, double-blind, sham-controlled RCT, there was no significant difference between active and sham vagus nerve stimulation (VNS) on the primary outcome of percent time in response on the MADRS. However, active VNS was associated with significantly greater percent time in response on secondary measures including the CGI, QIDS-Self Report (QIDS-SR) and QIDS–Clinician (QIDS-C).

VNS delivers intermittent electrical stimulation to the left cervical vagus nerve via a surgically implanted pulse generator. While traditionally used to treat epilepsy, studies have shown that long-term VNS has been associated with improvement in depressive symptoms and quality of life. Initially approved by the FDA for TRD based on open-label data, its adoption was limited after the Centers for Medicare & Medicaid Services (CMS) deemed the evidence insufficient. This trial was the first large-scale, sham-controlled RCT of VNS for TRD and aimed to address these gaps in evidence by analyzing efficacy and safety over 12 months.

This study—the RECOVER trial—included 493 participants with TRD, defined by ≥4 failed adequate antidepressant treatments and a baseline MADRS ≥22. Participants were randomized to receive adjunctive VNS plus treatment as usual (TAU) or sham VNS with TAU. Sham participants received no electrical stimulation. Active VNS was delivered at 20 Hz, with a pulse width of 250 μs, on time of 30 seconds, off time of 5 minutes, and current starting at 1.0 mA which was titrated to the highest tolerable level. Depression severity and treatment response were assessed using the MADRS, QIDS-C, QIDS-SR, and CGI-Improvement (CGI-I). The primary outcome was percent time in MADRS response (≥50% reduction from baseline), while secondary outcomes included time to first response and maximum duration of response, as well as percent time in partial response. Wilcoxon rank-sum test was used for comparing the effectiveness of VNS relative to sham treatment.

There was no significant difference in the primary outcome, with 18.9 ± 28.8% time in MADRS response with active VNS versus 16.3 ± 27.4 % with sham ($p = 0.137$). However, active VNS was associated with significantly greater percent time in response and partial response across multiple secondary outcomes. On the CGI-I, active VNS showed more time in response (26.7 ± 33.2% vs. 18.2 ± 28.9%; $p = 0.004$) and partial response (scores of 1-3; $p < 0.001$). Similarly, on the QIDS-SR there was significantly more time spent in response for active VNS (25.2 ± 32.3% vs. 19.8 ± 28.9%; $p = 0.049$), while percent time spent in partial response was greater for active VNS on the QIDS-C (39.6 ± 34.9% vs. 30.7 ± 32.3%; $p = 0.006$). All other measured outcomes, including remission rates, time to first response, maximum duration of response, and sustained response, did not significantly differ between groups. The treatment was generally well-tolerated, with no significant differences in serious adverse events or discontinuations between groups. Common side effects included worsening depression, dysphonia, suicidal ideation, implant site pain, and COVID-19. Dyspnea occurred more frequently in the active group ($p = 0.035$), consistent with known VNS side effects. Blinding was only partially maintained: 67.5% of participants in the VNS group correctly guessed their assignment compared to 53.3% in the sham group ($\chi^2(1) = 10.4$; $p = 0.001$).

Impact: This large, multi-site, sham-controlled RCT of VNS for TRD found no significant difference on the primary endpoint (percent time in MADRS response). However, secondary endpoints revealed meaningful therapeutic antidepressant effects with active VNS. Generalizability may be limited by recruitment challenges inherent to a 12-month sham-controlled design, which may have selected for a particularly treatment-resistant population, and by partial unblinding. Additionally, a 12-month duration may underestimate VNS efficacy, as prior studies suggest benefits often emerge or strengthen beyond the first year. Despite these challenges, the scale and rigor of the study may influence clinical practice guidelines and support broader insurance coverage for VNS in this population.

Conway CR, Aaronson ST, Sackeim HA, et al. Vagus nerve stimulation in treatment-resistant depression: A one-year, randomized, sham-controlled trial. Brain Stimul. Published online December 18, 2024. doi:10.1016/j.brs.2024.12.1191

Transcranial Focused Ultrasound Targeting the Default Mode Network Reduces Repeated Negative Thought Patterns in Depression

Leela Rao reviewing Schachtner et al., Front. Psychiatry., 2025 April

In a series of open-label treatment trials, adults with MDD received transcranial focused ultrasound targeting the antero-medial prefrontal cortex, a node within the DMN. After up to three weeks of treatment, 45%-60% of patients met response criteria and 35% met remission criteria.

Traditional MDD interventions are often lengthy and do not effectively remediate repetitive negative thought (RNT) patterns, highlighting the need for more targeted treatment. The default mode network (DMN), particularly the anterior medial prefrontal cortex (amPFC), exhibits hyperconnectivity in MDD and contributes to RNT. This study evaluated the effectiveness of transcranial focused ultrasound (tFUS) targeting the DMN in patients with MDD and significant RNT. Twenty patients aged 18-50 with MDD and significant RNT were enrolled following diagnostic confirmation using the Structured Clinical Interview for the DSM-5 (SCID-5) and Perseverative Thinking Questionnaire (PTQ).

Exclusion criteria included neurological disorders, mania, psychosis, history of head injury, metal facial implants, or active suicidal ideation. Each participant underwent a structural MRI to localize the anterior medial prefrontal cortex (amPFC), which served as the stimulation target. Personalized targeting was guided by K-Wave, a MATLAB-based acoustic simulation toolbox, to model ultrasound propagation and calibrate a five-foci phased array transducer for precise convergence on the amPFC. Participants received 5-11 sessions of tFUS, each lasting 10 minutes, then sat quietly for 20 minutes. The BDI-II and PTQ were administered at baseline and after each session, alongside visual analog ratings of treatment-related sensations (e.g., itching/tingling, pain, or heat/burning). Other assessments, including the HDRS, World Health Organization Quality of Life Survey (WHOQOL-BREF), and Colombia Suicide Severity Rating Scale (CSSRS), were only administered at baseline and post-treatment. If participants did not reach early remission criteria (BDI ≤ 12, HDRS ≤ 7) after five treatments, they continued with two additional weeks of treatment (3 sessions each). Two participants who did not see symptom improvement dropped out of the study after the first week due to time constraints and were excluded from further analyses. Paired t-tests assessed changes in clinical outcomes, while multilevel modeling and regression analyses examined symptom trajectories and associations between depression and RNT reduction. Susceptibility-weighted imaging (SWI) scans were acquired at baseline and post-treatment to monitor for potential microhemorrhages.

At study completion, 60% of participants met response criteria on the BDI-II and 45% on the HDRS, while 35% met remission criteria on both measures. Depression severity significantly declined on both scales (BDI-II = -10.9, $p < 0.001$; HDRS = -4.2, $p < 0.001$). PTQ scores also decreased (-8.4, $p < 0.001$), suggesting a reduction in RNT. Regression analyses showed that improvement in depressive symptoms significantly predicted reductions in RNT (BDI-II: $R^2 = 0.67$, $p < 0.001$; HDRS: $R^2 = 0.48$, $p = 0.001$). Post-study WHOQOL-BREF results indicated improvements in physical and psychological wellbeing and environmental satisfaction, but not improved satisfaction with social support. Though some participants reported discomfort from the headset, mean side effect sensation intensities for the actual ultrasound were 0 for all categories. No serious adverse events were reported, and no microhemorrhages were observed on SWI scans.

Impact: In this small open-label study of tFUS for MDD with prominent RNT, the novel neuromodulation intervention was well-tolerated and produced rapid antidepressant effects. Furthermore, reductions in RNT closely tracked improvements in depression severity, supporting the hypothesis that precisely targeting the amPFC—thereby decreasing DMN hyperconnectivity—can alleviate negative thought patterns and enhance quality of life. These findings warrant validation in larger, controlled trials designed to test efficacy and clarify mechanisms of action.

Schachtner JN, Dahill-Fuchel JF, Allen KE, et al. Transcranial focused ultrasound targeting the default mode network for the treatment of depression. Front Psychiatry. 2025;16:1451828. Published 2025 Apr 4. doi:10.3389/fpsyt.2025.1451828

"Online" HD-tDCS to DLPFC Reduces Negative Symptoms in Schizophrenia

Mohamad Shamas, PhD, reviewing Yeh TC et al. Psychiatry Clin Neurosci. 2024 Sep

In this double-blind RCT, "online" high-definition transcranial direct current stimulation (HD-tDCS) targeting the left DLPFC significantly improved negative symptoms in patients with schizophrenia. These benefits persisted for at least one month and were accompanied by changes in EEG functional connectivity.

Negative symptoms of schizophrenia, such as avolition and anhedonia, are a significant source of disability and are poorly addressed by current treatments. These symptoms have been linked to dysfunction in the prefrontal cortex, and noninvasive brain stimulation techniques like high-definition transcranial direct current stimulation (HD-tDCS) have shown promise in alleviating them. Resting-state EEG studies suggest that changes in connectivity between the default mode and executive networks may underlie these symptoms. This study aimed to evaluate the immediate and long-term effects of "online" HD-tDCS–administered during a working memory task–on negative symptoms and functional brain connectivity in patients with schizophrenia.

This double-blind, sham-controlled, randomized trial included participants (N=60; mean age: 43.4 years; 50.8% female) at a single hospital in Taiwan with DSM-5-defined schizophrenia or schizoaffective disorder. Inclusion criteria included clinical stability on consistent antipsychotic treatment for at least 8 weeks, a PANSS > 70, and predominant negative symptoms. Participants were randomized 1:1 to receive either active or sham HD-tDCS to the left

DLPFC, twice daily for five days. Stimulation (2 mA for 20 minutes) was delivered using a NeuroConn DC Stimulator Plus via a 4x1 ring montage with the anode over F3 and four surrounding cathodes (Fp1, Fz, C3, F7), guided by computational models to optimize current flow. During each session, participants performed a 2-back working memory task with the goal of engaging the left DLPFC target region–a procedure referred to as "online" stimulation. Sham stimulation mimicked all procedures except stimulation was turned off after a brief ramp-up period to mimic the sensation of active treatment without delivering current. Blinded psychiatrists and psychologists assessed participants at baseline, post-treatment, and at 1-week and 1-month follow-ups. The primary outcome was the change in PANSS Factor Score for Negative Symptoms (PANSS-FSNS). EEG functional connectivity between regions of the default mode and frontoparietal networks was assessed using lagged phase synchronization (LPS) across six frequency bands.

Active HD-tDCS significantly outperformed sham in reducing negative symptoms on the PANSS-FSNS at the end-of-treatment (difference = 2.34 points; Cohen's d = 1.15), 1-week (4.28 points; d = 1.66), and 1-month follow-up (4.91 points; d = 1.58; all $p < 0.01$),with a significant group-by-time interaction ($F = 26.38$, $p < 0.001$). Response rates (≥20% reduction in PANSS-FSNS) were higher in the active group at all time points: 30.0% vs. 0% at end-of-treatment ($p < 0.01$), 53.3% vs. 3.4% at 1 week ($p < 0.001$), and 60.0% vs. 6.9% at 1 month ($p < 0.001$). Significant group-by-time interactions were also found for PANSS total and subscales for negative, excitement, disorganization, and emotional distress domains (all $p < 0.05$, d = 0.74 – 1.39), while positive symptoms, neurocognitive performance, and adverse events showed no significant differences between groups. EEG functional connectivity analyses revealed a significant reduction in delta-band LPS in the active group compared to sham ($p < 0.05$), specifically between the posterior cingulate cortex and medial frontal gyrus. No serious adverse events occurred in either group; mild tingling was more commonly reported in the active group (63.3% vs. 10.3%).

Impact: This double-blind RCT provides compelling evidence that online HD-tDCS targeting the left DLPFC is a safe and effective adjunctive treatment for reducing negative symptoms in schizophrenia, with large effect sizes and associated changes in EEG connectivity. These findings highlight the therapeutic potential of activity-synchronized HD-tDCS and hint at neurophysiological mechanisms. However, the study's relatively short follow-up period, modest sample size, and single-site design may limit generalizability. Future trials should compare electrode montages and explore cognitive and functional outcomes more broadly.

Yeh TC, Lin YY, Tzeng NS, et al. Effects of online high-definition transcranial direct current stimulation over left dorsolateral prefrontal cortex on predominant negative symptoms and EEG functional connectivity in patients with schizophrenia: a randomized, double-blind, controlled trial. Psychiatry Clin Neurosci. 2025;79(1):2-11. doi:10.1111/pcn.13745.

HD-tACS to Sensorimotor Cortex Outperforms Transcranial Temporal Interference Stimulation to Thalamus for Acute Pain

Kaleab Tessema, MD, PhD reviewing Jia et al. Brain Stimul. 2025 Mar

In a double-blind, sham-controlled, crossover experiment in healthy volunteers, high-definition tACS (HD-tACS) targeting the primary sensorimotor cortex (SM1) demonstrated significant analgesic effect in the post-stimulation period, while transcranial temporal interference stimulation (tTIS) targeting the ventral posterolateral nucleus of the thalamus (VPL) did not.

DBS targeting the VPL has demonstrated potent analgesic effects, but its invasiveness limits widespread clinical use. There is some evidence suggesting that HD-tACS targeting SM1 can improve chronic pain, possibly by targeting pain perception via thalamocortical rhythmic entrainment. Another emerging non-invasive approach is tTIS, which theoretically enables deep brain modulation via interference-induced electric fields, potentially allowing targeted stimulation of thalamic structures like the VPL. The authors aimed to compare these two approaches in terms of analgesic effect in healthy humans.

In this double-blind, sham-controlled, crossover experiment, 63 healthy participants attended two separate sessions 10 days apart, one with active stimulation (either HD-tACS targeting SM1 [n=33] or tTIS targeting VPL [n=30]) and one with sham stimulation. After exposure to 0.5 mL of capsaicin cream to the left forearm to induce pain, participants received 30 minutes of stimulation. HD-tACS was delivered to the right SM1 using a NeuStim 4x1 electrode montage centered over C4, employing a 10 Hz alternating current at 1.5 mA, while sham stimulation included brief ramping (30 seconds each) at session start and end to mimic active stimulation. tTIS was delivered to the VPL using the NervioX-H0800 system, with personalized targeting based on structural MRI. Active tTIS applied two high-frequency sine-wave currents (e.g., 2000 Hz and 2010 Hz) to generate a 10 Hz amplitude-modulated envelope at the VPL with an estimated field intensity of 1 mA. Sham stimulation followed the same ramping protocol as the HD-tACS condition. Participants were asked to rate their pain using a 0-10 numeric rating scale (NRS) every 2 minutes during the 30-minute stimulation period and an additional 30-minute post-stimulation period. Primary outcomes were the difference in NRS scores between active and sham conditions for each stimulation type. Secondary outcomes included AUC analyses for the full session (0–60 minutes), stimulation phase (0–30 minutes), and post-stimulation phase (30–60 minutes). Statistical analyses included repeated-measures ANOVA and false discovery rate (FDR)–corrected t-tests.

In the HD-tACS group, active stimulation significantly reduced pain scores compared to sham during the post-stimulation period (34-60 minutes post-capsaicin; corrected $p < 0.05$). In the tTIS group, no significant differences were observed at any time point. The active-sham differences were significantly larger in the HD-tACS group than the tTIS group at 28-40 minutes and 46-58 minutes post-capsaicin (corrected $p<0.05$). Repeated-measures ANOVA revealed a significant time-by-stimulation interaction ($p < 0.0001$) and main effect of time ($p < 0.0001$).Comparing the AUC for pain scores revealed that active HD-tACS demonstrated significant improvement over sham HD-tACS for the entire session (0-60 minutes; $p = 0.0013$) and the post-stimulation period (30-60 minutes; $p = 0.001$), but not during the stimulation period (0-30 minutes). By contrast, the tTIS group did not show any significant AUC differences between active and sham in any of the session periods.

Impact: This double-blind crossover study in healthy volunteers suggests that HD-tACS targeting SM1 could be an effective strategy for relief of acute pain, with effects primarily emerging in the post-stimulation period. In contrast, the tTIS protocol targeting VPL does not appear to be effective. Additional investigation is warranted to more robustly assess stimulation parameters (e.g., intensity, duration) and anatomical variation in VPL location, as both may influence whether tTIS can effectively engage VPL neurons. Further research can also address effectiveness compared to DBS and variability across pain modalities.

Jia T, Xia J, Zhang C, et al. Comparing analgesic effects of temporal interference stimulation on ventral posterolateral thalamus and high-definition transcranial alternating current stimulation on sensorimotor cortex during sustained experimental pain. Brain Stimulation. 2025;18(3):701-703. doi:10.1016/j.brs.2025.03.013

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)