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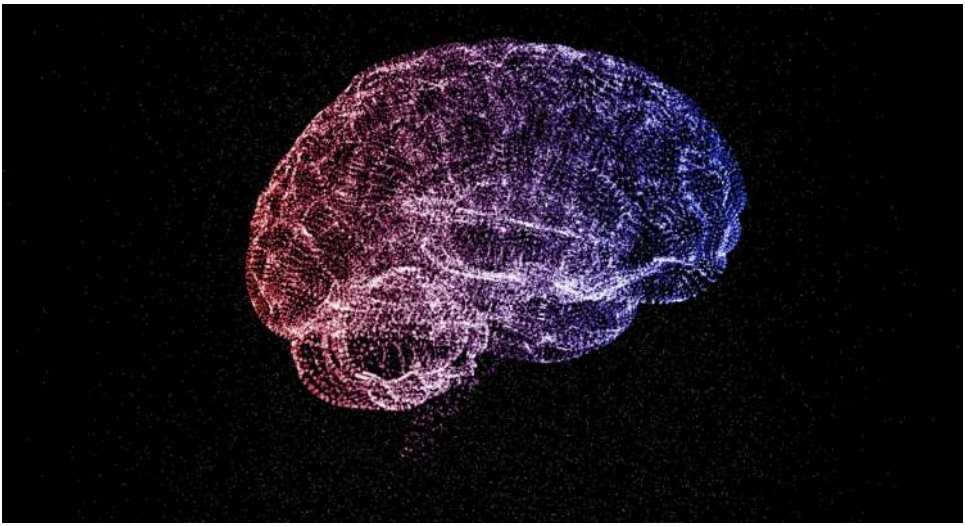
PULSE

A Monthly Update on Advances in Neuromodulation



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Prefrontal Transcranial Pulse Stimulation for Major Depressive Disorder: A Randomized Clinical Trial

Clara D. T. Nguyen, MD, MPH reviewing Qin et al., JAMA Network Open, 2026 July.

In this 2-arm, parallel-design, double-blind, and sham-controlled randomized controlled trial of adults with MDD, active transcranial pulse stimulation (TPC) of the LDLPFC showed significant improvements in MADRS scores when compared to the sham group. TPC was also associated with increased resting-state functional connectivity between the LDLPFC and multiple cortical brain regions implicated in MDD.

While TMS has been shown to be safe and efficacious for the treatment of MDD, evidence supporting TPS remains limited, particularly from RCTs. Whereas TMS typically employs alternating magnetic pulses via electromagnetism, TPS utilizes an extremely short ~3μs single high-pressure ultrasound shock wave via mechanotransduction. This mechanism promotes

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angiogenesis and neurogenesis through the upregulation of brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). TPS is also theorized to stimulate the brain deeper than TMS, reaching up to 8cm into subcortical structures like the thalamus. Given its novel mechanism of action, there is growing interest in evaluating its efficacy in treating psychiatric disorders.

Between June 2023 and October 2025, researchers at the Hong Kong Polytechnic University recruited 80 participants aged 18-65 years via convenience sampling. To be eligible, patients were required to have a diagnosis of MDD confirmed by a psychiatrist or Mini International Neuropsychiatric Interview and score of 14 or greater on the HAM-D. In addition, participants needed to be treatment-naïve or on a stable antidepressant medication regimen for at least 4 weeks. Participants completed pre- and post-intervention fMRI for resting state functional connectivity analyses. Utilizing a fixed block design, participants were randomized 1:1 to the TPS or sham arm. All patients received 12 sessions of TPS, 3 days per week for 4 weeks. Guided by fMRI neuronavigation, each session delivered 1000 pulses to the LDLPFC at a frequency of 4Hz and energy flux densities 0.2mJ/mm2 for the first 6 sessions and 0.25mJ/mm2 for the latter 6 sessions, consistent with previously published protocols. While TPS participants had a 6.6mm gel cushion placed on their scalp to ensure proper penetration, the sham participants received an air cushion, significantly attenuating ultrasound penetration. The primary outcome was MADRS score after completion of 12 sessions.

Following completion of 12 sessions of TPS, MADRS showed a significantly greater reduction with a mean difference of -4.19 points (95% CI, -8.33 to -0.04, p = 0.048, Hedge's g = 0.45). Secondary outcomes analysis showed no group difference in HAM-D (active: difference, 7.25; 95% CI, 5.57-8.94; P <0 .001; sham: difference, 5.74; 95% CI, 4.01-7.47; P <0 .001) or PHQ-9 (active: difference, 5.30; 95% CI, 3.50-7.10; P < 0.001; sham: difference, 4.43; 95% CI, 2.59-6.28; P <0 .001), where both groups showed significant improvements from the pre-treatment baseline. For resting state functional connectivity, the active group showed significantly increased connectivity between the LDLPFC and two clusters encompassing (1) the bilateral precuneus, calcarine cortex, and left posterior cingulate cortex (estimate, 0.08; 95% CI, 0.01-0.16; P =0 .02) and (2) the left orbitofrontal, superior medial prefrontal, and pregenual anterior cingulate cortices (estimate, 0.11; 95% CI, 0.05-0.17; P <0 .001).

The active group also showed enhanced functional connectivity within left DLPFC (estimate, 0.11; 95% CI, 0.03-0.19; P = 0.009). While there were no significant adverse events, mild to moderate adverse events were more frequent in the active TPS group (n = 37 of 40) than the sham group (n = 22 of 40; OR, 10.09; 95% CI, 2.67-38.20; P <0 .001), with the most common symptoms being tingling and pain in the treatment area which self-resolved within 24 hours.

Impact: This study demonstrates that LDLPFC TPS can be safe and efficacious in the treatment of depression. However, its comparative efficacy against TMS remains an open question, especially since the current study only demonstrated a significant difference between the active and sham groups in MADRS, but not HAM-D or PHQ-9. Also, this study provides no insight into the durability of the benefits in question. Although TPS is far from FDA clearance for treatment-resistant depression, it is a cautiously optimistic option due to its favorable side effect profile and fewer required sessions.

Qin PP, Jin M, Kan RL, et al. Prefrontal Transcranial Pulse Stimulation for Major Depressive Disorder: A Randomized Clinical Trial. JAMA Netw Open. 2026;9(7):e2621592. doi:10.1001/jamanetworkopen.2026.21592

Once Daily iTBS Provides Short-Term Improvement in Clinician-Rated Depression Scales but Lacks Sustained Benefit at Four Weeks

Meghan Y. Reddy, MD reviewing Ørbo et al., JAMA Network Open, July 2026

This double-blind RCT found that a 10-session course of once daily iTBS significantly reduced clinician-rated depressive symptoms in adults with MDD. However, the therapeutic advantage over sham was not sustained at a 4-week follow-up, as both groups showed continued improvement over time.

While iTBS is established as an efficient alternative to traditional rTMS, sham-controlled evidence for once-daily protocols remains limited. Most existing evidence for iTBS efficacy stems from active comparator trials, which may not fully account for the contextual and nonspecific factors, such as patient expectancy, motivation, and therapeutic engagement, or for neuromodulatory effects that

accumulate across repeated treatment sessions. By employing a brief, sham-controlled treatment window, this study aims to isolate the effects of active iTBS while minimizing the duration for which participants are withheld from active treatment.

In this double-blind trial, researchers in Norway enrolled 83 patients with MDD to receive 10 daily sessions of iTBS over 2 weeks. Of the 83 patients 73 completed baseline assessment. Participants were randomized to receive either active iTBS of 600 pulses at 120% of RMT or sham stimulation to the LDLPFC using MRI-guided neuronavigation. Sham stimulation was delivered using a coil with an altered winding configuration (i.e., with 1 loop reversed) that produced a magnetic field insufficient for cortical stimulation while preserving auditory and scalp sensations. Following the blinded phase, participants in the sham group were offered a crossover to 10 sessions of active iTBS. The study's primary outcomes were clinician-rated MADRS and self-reported BDI-II on day 10. Secondary outcomes included MADRS scores at day 5, MADRS and BDI-II measures at a 4-week follow-up, and categorical response (≧ 50% reduction in MADRAS) and remission (MADRS ≦ 10) rates. Continuous variables were analyzed using linear mixed models and binary variables were examined using logistic regression.

The active iTBS group demonstrated significantly greater reductions in MADRS compared to the sham group by day 10 (mean difference, 3.57 [95% CI, 0.79-6.35]; Hedges g = 0.61; P = 0 .01). Although both groups improved significantly from baseline, the mean reduction in MADRS score was greater with active iTBS (−9.89) than with sham (−4.85). This significant difference was observable as early as day 5, with the iTBS group showing a 2.89 advantage over sham (p = 0.04). However, self-reported measures (i.e., BDI-II) did not show a significant group difference on day 10 (p = 0.30). Furthermore, the treatment response and remission rates did not show statistically significant differences between the two groups at day 10 (p = 0.14 and p = 0.29, respectively). At the 4-week follow-up, the outcomes for both groups converged resulting in no sustained advantage for active stimulation as the sham group continued to show improvement. Specifically, the mean difference on MADRS was 1.58 (p = 0.27) and BDI-II was 1.63 (p = 0.59). Treatment resistance, as quantified using the Maudsley Staging Method, did not significantly influence the improvements in MADRS or BDI-II scores.

Impact: Findings from this double-blinded RCT suggest that while a fixed, short course of once-daily iTBS can result in rapid clinical improvement, 10 sessions may be insufficient to stabilize treatment effects. The divergence between clinician-rated and self-reported outcomes highlights the importance of multimodal assessment and suggests that clinician ratings may be more sensitive to early changes. The substantial improvement in the sham group underscores that nonspecific factors significantly shape response in neuromodulation. It also highlights the importance of considering the potentially therapeutic effects of theoretically inert sham stimulation protocols (e.g., altered coil configurations [as is the case here], electrical stimulation). The study was limited by a small sample size and a course of 10 treatment sessions. Future studies are needed to expand on sustained benefits from iTBS in longer treatment schedules.

Ørbo MC, Grønli OK, Brochs MS, et al. Intermittent theta-burst stimulation and depressive symptoms in major depressive disorder: A randomized clinical trial. JAMA Netw Open. 2026;9(7):e2621262. doi:10.1001/jamanetworkopen.2026.21262

Connectivity- vs Scalp-Based Targeting of Accelerated TMS for Depression

Nisha C. Choothakan, MD MPH, reviewing Taylor, J. et al., JAMA Psychiatry. August 2026.

In this RCT, investigators compared the efficacy of accelerated TMS (aTMS) for treatment-resistant depression using connectivity- versus scalp-based targeting. Results demonstrated greater improvement in clinician-rated depression at 1 month with connectivity-based targeting when compared to a standard scalp-based method.

Although TMS is FDA-cleared for treatment-resistant depression, treatment targets largely continue to be selected using scalp landmarks rather than neuroimaging. aTMS combines an accelerated dosing schedule (e.g., 10 treatments per day for 5 days) with personalized imaging-based targeting. Though prior retrospective studies suggest scalp-based TMS targets located closer to predicted connectivity-based targets are associated with improved clinical outcomes, prospective head-to-head

evidence have been limited. This study aimed to isolate the effect of connectivity-based targeting, hypothesizing that connectivity-targeted aTMS would produce greater antidepressant effects than scalp-targeting aTMS at 1 month.

Forty adults, aged 22 to 80, with moderate-to-severe MDD and moderate-to-severe treatment resistance participated in this RCT between July 2023 and March 2025. Participants were excluded for contraindications to TMS or magnetic resonance imaging, primary psychiatric diagnosis aside from MDD or anxiety, recent rapid-acting antidepressant treatments and significant neurological or substance use disorders. All participants underwent a 41-minute multi-echo resting-state functional connectivity prior to aTMS, then randomized to receive aTMS with connectivity- vs scalp-based targeting. The connectivity-based target was defined as the LDLPFC region with the greatest resting state functional connectivity to a published convergent depression circuit, which is freely available in the public domain (https://neurovault.org/images/787859/). This circuit includes a negative correlation to the subgenual cingulate cortex, which has been recently identified as a potential biomarker for TMS efficacy in depression. The scalp-based target was identified with the Beam F3 method. The primary outcome was baseline-adjusted MADRS score at 1-month post-treatment, with follow-up every 3 months for 1 year. Secondary analysis included response (≥ 50% MADRS score reduction) and remission (MADRS score ≤ 10).

Of the 40 participants, 22 were female, with mean age 45.7. At 1-month post-treatment, the median (IQR) reduction in MADRS score was greater with connectivity-based than scalp-based targeting: 24 (19–28) vs 18 (10–23) points, respectively ($p < 0.05$; Cohen d analog, 0.80; 95% CI, 0.26–1.54; number needed to scan = 5). No significant differences in MADRS scores were observed at interim assessments (5 days, 7 days) preceding the 1-month primary end point. In the connectivity-based group, 16/20 (80%) and 13/20 (65%) met response and remission criteria, respectively, compared with 12/20 (60%) and 13/20 (65%), respectively, in the scalp-based group. BDI and BAI scores did not differ significantly between groups. Connectivity- and scalp-based targets also differed spatially, with median MNI coordinates of (-46, 41, 23) and (-39.7, 46.1, 29.5), respectively, including significant differences in the x- and y-dimensions (adjusted $p < 0.01$). Notably, differences in MADRS score remained significant after adjusting for target coordinates with no significant association between stimulation coordinates and antidepressant response. There was no observed correlation between a participant's scalp-based target and their individualized connectivity-based target in the x-, y-, or z- dimensions. Finally, split-half analysis demonstrated lower variability within participants (4.47mm split-half distance) than across participants (12.97mm, $p < 0.001$) for the connectivity-based targets, supporting the reliability and individual specificity of connectivity-based targeting.

Impact: Overall, this study suggests that connectivity-based targeting of the convergent depression circuit may enhance antidepressant effects of aTMS when compared to conventional scalp-based targeting, highlighting the potential for neuroimaging to inform and optimize therapeutic interventions. Moreover, individualized connectivity-based targets demonstrated high within-participant reliability while remaining distinct across participants, supporting its reproducibility and significant personalization with this approach. As the first published prospective head-to-head trial comparing connectivity- and scalp-based targeting, this study provides preliminary evidence that target selection may independently influence aTMS outcomes. Larger, multisite trials are needed to further establish treatment efficacy, generalizability, and durability.

Taylor JJ, Kare MR, Haj-Darwish D, et al. Connectivity- vs Scalp-Based Targeting of Accelerated Transcranial Magnetic Stimulation for Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2026;83(8):807–817. doi:10.1001/jamapsychiatry.2026.1100

Efficacy of tDCS to the DLPFC on Alcohol Consumption in AUD: A Multisite Randomized Sham-Controlled Trial

Sheyna M. Nathwani, MD, reviewing Trojak et al., Addiction 2026 Aug.

In this triple-blind, sham-controlled RCT, a five-day course of bilateral DLPFC tDCS significantly reduced heavy drinking days (HDD), but not total alcohol consumption (TAC), over 24 weeks in patients with AUD. Reductions in craving and carbohydrate-deficient transferrin (CDT) levels in the active-tDCS group provide preliminary biological and clinical support, though participant attrition and incomplete diary data limit the certainty of these findings.

AUD remains a significant clinical challenge characterized by high relapse rates and a limited pharmacotherapeutic arsenal. tDCS has emerged as a candidate adjunctive treatment, given the DLPFC's role in craving regulation, executive control, and reward processing. While earlier studies have explored the use of tDCS in AUD, they have been constrained by small sample sizes, brief follow-up periods, and heterogeneous stimulation protocols, limiting definitive conclusions. The REDSTIM trial was designed to address these methodological gaps by conducting the largest sham-controlled, triple-blind, randomized trial of tDCS in AUD to date, with the primary aim of evaluating its efficacy in reducing alcohol consumption.

This RCT used a triple-blind, sham-controlled, parallel-group design across 14 clinical sites. Of 356 adults screened, the trial enrolled 337 outpatients with mild to severe AUD per DSM-5 criteria, each having undergone at least one prior standard treatment attempt. Participants were randomized 1:1 to active-tDCS or sham-tDCS. The intervention consisted of two daily stimulation sessions, separated by a 20-minute interval, over five consecutive days (10 total sessions). Active-tDCS delivered 2 mA using a bilateral DLPFC montage with the anode at F4 (right DLPFC) and cathode at F3 (left DLPFC). The sham protocol mimicked the initial sensory experience — a brief ramp-up to 2 mA followed by a rapid ramp-down — to maintain participant and investigator blinding. Co-primary endpoints were change in HDD, defined as daily consumption exceeding 60g (men) or 40g (women) of pure alcohol daily, and change in daily TAC. These were assessed using self-reported alcohol diaries over a 24-week follow-up period, with visits at 4-week intervals. Secondary outcomes included craving severity, biochemical alcohol consumption markers, quality of life, mood, and cognitive and safety assessments.

For the first co-primary endpoint, active-tDCS produced a significantly greater reduction in HDD than sham, with a between-group difference of −2.45 HDD per 4-week period (97.5% CI: −4.86 to −0.05, P = 0.022). This between-group difference reflected the averaged treatment effect modeled across the 24-week follow-up period. On the second co-primary outcome, active-tDCS was associated with a numerically greater reduction in TAC compared to sham (−5.96 g/day; 97.5% CI: −15.18 to 3.26), though this difference did not reach statistical significance (p = 0.147). Analysis of secondary outcomes showed that at the 24-week time point, current craving was significantly reduced with active tDCS relative to sham (standardized effect size −0.36; 95% CI: −0.65 to −0.07; p = 0.016), but not other craving measures like maximal craving for the past 28 days or craving measured by the Obsessive-Compulsive Drinking Scale (OCDS). There were no group differences for the remaining clinical assessments (clinical global impression, mood, cognitive assessment and quality of life). Among the biochemical markers of alcohol consumption, CDT was significantly lower in the active group (−0.33; 95% CI: −0.65 to −0.01; p = 0.045), suggesting a potential biological correlate of reduced drinking. Adverse events, most commonly paresthesia, headache, and asthenia, occurred in 41.1% of the active-tDCS group vs. 36.7% of the sham-tDCS group. Nine (5.3%) participants dropped out from the sham group, compared to only three (1.8%) in the active group, due to adverse events.

Impact: The REDSTIM trial demonstrates that a brief course of bilateral DLPFC tDCS can produce a modest but statistically significant reduction in HDD over 24 weeks in outpatients with mild-to-severe AUD who had previously failed standard treatment. The findings also point to potential secondary benefits, including reduced craving and a lower objective biomarker of consumption, while demonstrating a safety and tolerability profile comparable to sham. However, the absence of a significant effect on TAC, combined with substantial missing data from incomplete alcohol diaries and high dropout rates, warrants cautious interpretation of these findings. Larger trials with longer follow-up, maintenance-stimulation protocols, and prespecified strategies to address the durability of effect are warranted to establish whether tDCS offers a reproducible, clinically meaningful benefit in AUD.

Trojak B, Sauvaget A, El Hage W, Wallenhorst T, Rolland B, Nubukpo P, et al. Efficacy and safety of transcranial direct current stimulation in alcohol use disorder: A randomized controlled triple-blind trial. Addiction. 2026; 121(8): 2141–2153. https://doi.org/10.1111/add.70461

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)