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PULSE

A Monthly Update on Advances in Neuromodulation

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Neuro-Cardiac–Guided TMS Demonstrates Target-Specific and Replicable Heart–Brain Coupling Effects with Stimulation of the DLPFC

Praveen P. Rajaguru MD, MPH reviewing Feng et al., Translational Psychiatry, 2026

In this exploratory study, neuro-cardiac-guided TMS (NCG-TMS) demonstrated target-specific and intensity-dependent modulation of heart-brain coupling after neuronavigated targeting of subregions within the dorsolateral prefrontal cortex (DLPFC). Across 19 healthy participants undergoing three repeated stimulation sessions, lateral and posterior F3 targets produced the strongest increases in heart–brain coupling relative to sham stimulation, with the lateral F3 target demonstrating the most robust repeatability and the only consistent stimulation-induced heart rate reduction.

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The frontal-vagal network model of MDD proposes that interactions among the DLPFC, subgenual ACC (sgACC), and vagus nerve contribute importantly to the pathophysiology of depression. Consistent with this framework, neuro-cardiac-guided TMS (NCG-TMS) seeks to modulate autonomic cardiac activity through cortical stimulation, with the goal of leveraging heart-brain interactions to identify physiological biomarkers, such as heart rate changes, that could help individualize and optimize rTMS treatment. This study investigated (1) whether NCG-TMS could reliably modulate heart rate, (2) whether these effects were reproducible and generalizable across cohorts, and (3) which stimulation target produced the strongest heart-brain coupling effects.

Nineteen healthy adults participated in the study. Following an initial preparatory session to determine the RMT and localize anatomical targets using MRI-guided neuronavigation, participants completed three experimental sessions separated by at least one week. During each session, participants received 15 blocks of modified 10-Hz “dash” rTMS trains (5 s stimulation, 11 s inter-train interval). Stimulation intensity started at 28% below the total machine output corresponding to 120% RMT and was progressively increased by 2% per block up to the machine output corresponding to 120% RMT for each participant. Stimulation was delivered to six distinct left DLPFC targets: the standard EEG-based Beam F3 location, a traditional 5-cm target positioned anterior to the motor cortex, and four additional targets systematically displaced relative to Beam F3 along anterior, posterior, medial, and lateral axes to sample neighboring DLPFC subregions. One of the six target locations was additionally assigned to sham stimulation for each participant using a MagVenture sham coil. Stimulation side effects were monitored by a checklist of 20 symptoms. Using continuous ECG recordings, heart–brain coupling was quantified as spectral power at 0.0625 Hz, corresponding to the frequency of the dash rTMS cycle (one cycle every 16 s), thereby indexing stimulation-induced modulation of heart rate dynamics. Because the relationship between stimulation intensity and heart–brain coupling was nonlinear, the authors used generalized additive mixed-effects models to evaluate the effects of target location, stimulation intensity, pain, and side effects on heart–brain coupling. Intraclass correlation coefficients (ICC) assessed repeatability across sessions.

Heart-brain coupling modulation varied significantly by stimulation target and intensity in a nonlinear fashion. Relative to sham stimulation, the strongest increases in heart-brain coupling occurred at the F3 lateral ($\beta = 1.46$, $p < 0.001$), and F3 posterior ($\beta = 1.18$, $p = 0.033$) targets. Significantly increased heart-brain coupling was observed for F3 and all surrounding targets when averaging across stimulation intensities (all $p<0.05$), with the strongest increase relative to sham in the posterior, medial, and lateral F3. These effects were intensity-dependent; at 100% RMT, several F3 targets demonstrated marked increases in heart-brain coupling relative to sham, whereas no significant differences were observed at 60% RMT. Importantly, pain and stimulation-related side effects were included as covariates in the mixed-effects models, suggesting that discomfort during treatment was not the primary driver of heart rate changes. Repeatability analyses demonstrated moderate-to-high ICC for anterior and lateral F3 targets, particularly during sessions 2 and 3 at higher stimulation intensities.

Impact: These findings extend prior evidence that rTMS targeting of the DLPFC can modulate cardiac activity, demonstrating that these effects are both target-specific and intensity-dependent within the DLPFC. Lateral and posterior F3 targets produced the most robust physiologic effects, with lateral F3 stimulation showing the strongest repeatability and autonomic modulation. The persistence of these effects after accounting for pain and side effects supports a direct physiologic influence of TMS on the heart–brain axis, rather than purely nonspecific sensory activation. These results provide preliminary support for heart-brain axis biomarkers as a signal for individualized TMS target optimization in MDD and psychiatric disorders involving autonomic dysregulation. Future randomized controlled trials in clinical populations are needed to determine the clinical relevance and therapeutic utility of these biomarkers.

Feng ZJ, Martin S, Numssen O, et al. Target-Specificity and repeatability in neuro-cardiac-guided TMS for heart-brain coupling. Transl Psychiatry. 2026;16(1):79. Published 2026 Feb 7. doi:10.1038/s41398-026-03879-w

Personalized Continuation Therapy with SAINT for Maintaining Remission in Treatment-Resistant Depression

Nisha C. Choothakan, MD MPH, reviewing Stimpson, K.H.. et al., Transcranial Magnetic Stimulation, 100203, March 2026.

An open-label feasibility trial was conducted to evaluate whether personalized continuation therapy (PCT) with SAINT (Stanford Accelerated Intelligent Neuromodulation Therapy) could be used to treat severe treatment-resistant depression (TRD) as well as maintain long-term remission.

SAINT is a 5-day course of fMRI-guided intermittent theta-burst stimulation that has shown robust efficacy in the treatment of MDD and TRD. In general, TRD treatments have been limited by difficulties in daily symptom monitoring, lack of approved interventions for rapidly correcting disease course prior to relapse, and concerns regarding tolerance. To address this, this study evaluated a personalized continuation therapy approach that combined longitudinal symptom monitoring with individualized SAINT re-treatment schedules aimed at maintaining long-term remission.

Participants were adults with TRD who had previously undergone an acute course of SAINT and achieved clinical remission. Of the 48 participants initially treated, 21 met eligibility criteria and were subsequently enrolled in the personalized continuation therapy phase. During this phase, participants provided daily subjective mood ratings and wore a wrist-worn wearable device that recorded multimodal data including electrodermal activity and heart rate. They also completed biweekly clinician-administered MADRS assessments. These longitudinal behavioral and wearable data were used by a machine learning algorithm to predict daily MADRS scores. When the predicted MADRS exceeded 11 for two consecutive days, participants completed a clinician-administered MADRS assessment. Participants with a confirmed MADRS score greater than 11 received daily SAINT treatment sessions until symptoms returned to their baseline MADRS achieved after the acute course of SAINT. Primary outcome measured was mean MADRS scores over 12 months, measured as the area under the curve (AUC) for MADRS versus time.

In total, 21 participants completed the study. Participants demonstrated moderate treatment resistance with an average Maudsley Staging Method (MSM) score of 8.6 (SD = 1.9) and had previously tried an averaged of 5.7 antidepressants (SD = 3.1). Average MADRS AUC during continuation therapy was 8.0 (SD = 4.2) which was 21.6 points lower (8.0 vs 29.5) compared to baseline prior to SAINT (95% CI [-24.7, -18.4], $p < 0.001$; Cohen's $dz=3.13$, 95% CI [-3.56,-2.70]), demonstrating a sustained reduction following SAINT with PCT. MADRS-24hr scores were used to compare symptom improvement following the initial acute SAINT course versus completion of personalized continuation therapy (PCT). MADRS-24hr scores were 2.90 (SD = 1.3) points lower after a course of PCT with SAINT compared to the initial 5-day course of SAINT. Over the 12-month continuation period, participants remained in remission an average of 85.9% of the time and in response 95.3% of the time. Participants received an average of 14.6 treatment days (SD=13.8, median=11) over 6.4 PCT courses (SD=5.2) during the continuation period. The average time from the SAINT protocol to the first PCT course was 80.5 days (SD=104.0, median=37 days).

Impact: Overall, this study suggests that PCT with SAINT may serve as a feasible strategy for maintaining long-term remission in individuals with TRD. Moreover, these findings may support a shift from reactive treatment of TRD toward a proactive and personalized approach that integrates symptom monitoring, wearable technology, and rapid neuromodulation interventions. However, this study is limited by the small sample size and an open-label design with the lack of a control group. Therefore, additional large-scale randomized controlled trials are needed to further evaluate the efficacy, generalizability, and long-term maintenance protocols of PCT with SAINT.

Katy H. Stimpson, Michael T. Feyder, Adi Maron-Katz, Eren Kiris, T.J. Ford, David M. Carreon, Danielle D. DeSouza, Eleanor J. Cole, Nathan F. Meng, Nolan R. Williams, Brandon S. Bentzley, Personalized continuation therapy with SAINT for maintaining remission in treatment-resistant depression, Transcranial Magnetic Stimulation, Volume 6, 2026, 100203, ISSN 3050-5291, https://doi.org/10.1016/j.transm.2025.100203.

Repetitive Peripheral Magnetic Stimulation (rPMS) Reduces Pain and Improves Function in Chronic Musculoskeletal Pain in a Systematic Review and Meta Analysis

Sheyna M. Nathwani, MD, reviewing Pan et al., European Journal of Physical and Rehabilitation Medicine 2025 Jun.

This systematic review and meta-analysis demonstrates that rPMS yields significant improvements in pain and disability, but not kinesiophobia, in chronic musculoskeletal pain (CMP). These findings highlight rPMS as a promising non-pharmacologic modality and potential rehabilitative adjunct for symptom and function improvement, with early evidence of meaningful clinical benefit.

Chronic musculoskeletal pain (CMP), defined as pain originating from the musculoskeletal system, remains one of the most disabling global health burdens, contributing to substantial functional impairment, psychological distress, and kinesiophobia (the fear of movement or re-injury). Despite widespread use of pharmacologic and rehabilitative strategies, many patients experience persistent symptoms, highlighting the need for novel mechanistically grounded interventions. Repetitive peripheral magnetic stimulation (rPMS) is a non-invasive, painless neuromodulation technique that delivers high-intensity magnetic pulses to peripheral structures. rPMS is proposed to address CMP through multiple mechanisms: both locally, by improving circulation and breaking the pathological cycle of CMP, and centrally, by driving cortical neuroplasticity to normalize maladaptive brain changes associated with chronic pain and kinesiophobia. This systematic review and meta-analysis evaluates the effectiveness of rPMS in treating CMP, with specific attention to pain intensity, disability, and kinesiophobia.

This review followed PRISMA guidelines for systematic evidence synthesis. Investigators searched major databases (Web of Science, Embase, PubMed, PEDro, and Cochrane) through 2023 for RCTs evaluating rPMS in adults with chronic musculoskeletal pain. Methodological quality was assessed using the Cochrane RoB 2.0 tool. Certainty of evidence for each outcome was evaluated using the GRADE framework, which rates evidence quality on scale of very low to high. Pain, disability, and kinesiophobia outcomes were extracted using validated instruments. The cumulative effects of available data were synthesized using RevMan software random-effects meta-analysis, and statistical heterogeneity across studies was assessed using the I^2 statistic. Of the retrieved 1801 studies during initial search, a total of 8 RCTs comprising 177 participants met the inclusion criteria.

Across the included RCTs, rPMS produced a significant effect on pain reduction compared with control conditions (SMD=-1.16; 95% ci: -1.56 to -0.76). Heterogeneity was low (I^2 = 21%), suggesting consistency across studies, though the evidence was graded as very low quality. In the subgroup analysis of chronic low back pain (CLBP), rPMS also showed significant pain relief (SMD = -0.92, 95% CI: -1.67 to -0.17), though with moderate heterogeneity (I^2 = 45%) and, again, very low-quality evidence.

rPMS also produced a significant improvement in disability as measured by the Oswestry Disability Index (mean difference (MD) = -6.55, 95% CI: -10.27 to -2.82). Heterogeneity was absent (I^2 = 0%), indicating highly consistent results across studies, though the evidence was rated as very low quality. In contrast to pain and disability, rPMS did not significantly reduce kinesiophobia as measured by the Tampa Scale for Kinesiophobia (MD = -1.81, 95% CI: -7.60 to 3.98). Heterogeneity was absent (I^2 = 0%), and the evidence was rated as low quality. All studies were rated as having “some concerns” on the Cochrane RoB 2.0 assessment, and GRADE evaluations indicated low to very low certainty across outcomes.

Impact: This systematic review and meta-analysis provides preliminary evidence that rPMS may offer clinically meaningful reductions in pain and disability for individuals with CMP, supporting its potential role as a non-pharmacologic adjunct within rehabilitation-focused care. However, the overall certainty of evidence remains low to very low due to small sample sizes, methodological limitations, and variability in stimulation parameters. The study highlights the need for larger, high-quality RCTs with standardized dosing, longer

follow-up, and mechanistic endpoints to meaningfully assess the efficacy of rPMS in the treatment of CMP.

Pan J, Jia Y, Li K, Liu X, Liu Z, Cui Z, Liao L, Diao Y, Liu H. Repetitive peripheral magnetic stimulation for pain, disability, and kinesiophobia in patients with chronic musculoskeletal pain: a systematic review and meta-analysis. Eur J Phys Rehabil Med. 2025 Jun;61(3):572-582. doi: 10.23736/S1973-9087.25.08442-4. Epub 2025 Jun 12. PMID: 40501206; PMCID: PMC12411938.

Focused Ultrasound Neuromodulation: Exploring a Novel Treatment for Severe Opioid Use Disorder

Zack Blumenfeld, MD, PhD, reviewing Rezai et al., Biological Psychiatry, 2025 Jul

In this prospective, single-arm, open-label feasibility study, eight patients with opioid use disorder (OUD) received 20 total minutes of focused ultrasound (FUS) of the bilateral nucleus accumbens (NAc) at sub-ablative frequency. Cravings for opioids decreased both in the acute period as well as for up to 90 days post-procedure. These clinical improvements were accompanied by reductions in the use of other substances and reduced functional connectivity between NAc and frontal lobe regions involved with reward processing.

Despite the availability of gold-standard treatments for OUD, the recurrence rate remains high, and fatalities due to opioid overdose remain at alarming levels. The nucleus accumbens (NAc) plays a central role in reward processing and addiction, with chronic exposure to addictive substances producing molecular and physiological alterations within the NAc as well as changes in its functional connectivity with higher-order cortical regions, including the prefrontal cortex. Neuromodulation of the NAc has largely been limited to invasive approaches due to its deep subcortical location. FUS is a noninvasive technique whereby ultrasonic waves are targeted at specific brain regions, typically at a high enough intensity to ablate the structure of interest. However, recent studies have explored the use of a low-intensity FUS procedure that can induce reversible neuromodulation of subcortical areas. This study sought to demonstrate the efficacy of bilateral NAc FUS neuromodulation in patients with OUD in reducing cravings both immediately after the procedure as well as up to 90 days afterward.

Sixteen patients with severe OUD were enrolled in the study. Participants were recruited while already receiving treatment in a 28-day residential SUD treatment program. Inclusion criteria required participants to be on a stable dose of medication for OUD for at least seven days before enrollment and for the duration of the study. Of note, eight participants were excluded from analysis because they did not receive bilateral NAc FUS, had a primary diagnosis other than OUD, or experienced device malfunction, resulting in a final sample of eight participants. Participants completed a single session of MRI-guided FUS delivered using a 220-kHz hemispheric helmet containing 1024 ultrasound transducers that converge on a focal target. After entering the MRI scanner, participants completed behavioral and craving assessments followed by an initial 5-minute sham condition in which zero-energy FUS was delivered. Participants then received four separate 5-minute blocks of active FUS (8 subspots, 90–100 W therapeutic energy; duty cycle = 3.3% per subspot; 100 repetitions; TR = 3 seconds; pulse duration = 100 ms) targeting the bilateral NAc, receiving up to 20 minutes of total active stimulation. Throughout the FUS procedure, participants viewed a series of substance-related cues (images of substances or paraphernalia tailored to each participant's three most used substances) via MRI-compatible goggles and rated their level of craving. Participants additionally completed self-report measures including the HAM-D, Snaith-Hamilton Pleasure Scale, and multiple Neuro-Quality of Life subscales. Cue-induced craving assessments, psychiatric questionnaires, urine toxicology, and resting-state fMRI were collected during all follow-up visits conducted at 7, 30, 60, and 90 days post-procedure. Due to the small sample size, authors utilized Bayesian statistical methods for data analysis, where evidence for treatment-related effects was quantified using Bayes factors (BF_{10}; BF_{10} = 1: ambiguous, 1 < BF_{10} < 3: weak evidence, 3 < BF_{10} < 10: moderate evidence, 10 < BF_{10} < 30: strong evidence, 30 < BF_{10} < 100: very strong evidence).

Opioid craving significantly decreased following FUS, with strong evidence for reductions from baseline to 1 day post-FUS (BF_{10} = 28.1) and stronger evidence when comparing baseline to all subsequent follow-up timepoints combined (BF_{10} =

1048.3). There was also modest evidence for reduction in depression (BF_{10} =4.2) and anxiety (BF_{10} = 2.9) throughout the study period. All participants remained substance-free through day 7 post-FUS, with 1–3 participants testing positive throughout the remainder of the study period. Functional connectivity analyses conducted among the abstinent participants (day 7 [n = 8], day 30 [n = 7], and day 90 [n = 5]) demonstrated reduced positive connectivity from the NAc to frontal cortical regions involved in reward, including the ventromedial PFC, ACC, and posterior cingulate cortex (PCC) (all $p < .05$) compared to baseline. The FUS procedure was overall safe and well tolerated, although authors noted one serious adverse event (drug overdose) deemed not to be linked to the study. Suicidality, depression, anhedonia, and ability to experience pleasure were not worsened at any point throughout the study.

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Impact: This study provides early, preliminary evidence of both safety and efficacy of low-energy FUS for neuromodulation of bilateral NAc in patients with severe OUD. Patients exhibited reduced cravings for opioids and other substances both acutely and up to 90 days after FUS. Moreover, FUS appears to modulate neural connectivity in people who remain abstinent, with decreased positive connectivity between the NAc and frontal brain regions involved in reward processing. However, interpretation of these findings is limited by the small final sample size (N = 8) and the exclusion of half of the initially enrolled participants (N = 16). Future studies should employ larger, sham-controlled, randomized designs, assess the contribution of concurrent MOUD vs. FUS alone on OUD, discern the applicability of FUS for the treatment of other substance use disorders, and determining how long the post-procedure effects last.

Rezai A, Thompson-Lake DGY, D'Haese PF, et al. Focused ultrasound neuromodulation: Exploring a novel treatment for severe opioid use disorder. Biological Psychiatry. 2025 Jul 1;98(1):56-64. doi: 10.1016/j.biopsych.2025.01.001

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)