JANUARY 2026 / ISSUE 55

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 | AIJang@mednet.ucla.edu
Aaron Slan, MD, Editor-in-Chief | aslan@mednet.ucla.edu

Efficacy of rTMS in Parkinson's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Nisha C. Choothakan, MD MPH, reviewing Zhang, W. et al., EClinicalMedicine, Oct 2022.

In this systematic review and meta-analysis, RCTs were analyzed to evaluate the efficacy of rTMS intervention in motor and non-motor symptoms in Parkinson's disease (PD). The findings suggest the possibility of rTMS as an adjuvant therapy to treat motor symptoms and depression in patients with PD.

Parkinson's disease (PD) is a neurodegenerative disease characterized by progressive loss of dopaminergic neurons which can manifest as motor (bradykinesia, tremor, hypertonia) or non-motor (cognitive impairment, emotional dysregulation) symptoms. Current pharmacological therapies are effective,

though they have limitations. rTMS is a non-invasive form of brain stimulation that has been used to regulate the motor and non-motor symptoms of PD. Though previous systematic reviews suggested some benefits, very few have restricted their analyses to RCTs. To address this gap, the authors conducted a meta-analysis by including RCTs exclusively to evaluate the efficacy of rTMS in PD.

This study was conducted following PRISMA guidelines and analyzed published articles from PubMed, MEDLINE, and Web of Science from 1988 to 2022 for RCTs. Included studies were sham-controlled RCTs that used rTMS for motor or non-motor symptoms in adults with PD and reported outcomes using validated scales. Summary data was extracted from RCTs by 2 investigators independently. Random effects meta-analysis was performed using the standardized mean difference (SMD). Heterogeneity was analyzed via Cochran's statistics and I^2 index. Risk of bias was assessed with the Cochrane risk-of-bias tool. Outcomes measured were motor and non-motor exam scales used in PD, such as the Movement Disorders Society

Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

Of the 2,760 studies screened, 14 sham-controlled RCTs were included (n = 469), with 381 patients in motor analysis and 202 in non-motor analysis. Participants were predominantly older adults (mean age >60 years) with moderate disease duration (>6 years) on stable PD medications and received rTMS across various targets (M1, DLPFC, SMA, and cerebellum). Overall, rTMS significantly improvement motor outcomes when compared to sham stimulation, with a pooled SMD of 0.51 (95% CI, 0.30 to 0.71) and low heterogeneity (I^2 = 29%). Subgroup analysis showed significant results with high-frequency stimulation ($\geq$ 5Hz; SMD = 0.56; 95% CI, 0.34 to 0.77) but not with low-frequency stimulation ($\leq$ 1Hz; SMD = 0.10; 95% CI, -0.44 to 0.64). rTMS efficacy did not significantly differ by PD medication status ("ON": SMD = 0.58; 95% CI, 0.31 to 0.85; "OFF": SMD = 0.37; 95% CI, 0.05 to 0.69). Subgroup analyses by number of rTMS sessions indicated significant benefits for protocols involving fewer than five sessions (0.66, 95% CI, 0.28 to 1.03) and for 5-10 sessions (0.66 95% CI, 0.05 to 0.64), but not for

protocols exceeding 10 sessions (0.28, 95% CI, -0.21 to 0.76). However, no subgroup differences reached statistical significance. When looking at antidepressant effects, rTMS demonstrated a modest significant effect on depressive scales (SMD = 0.42; 95% CI, 0.13 to 0.70; I^2 = 25%). In contrast, rTMS intervention did not show significant effects on cognitive scale scores (SMD = -0.11; 95% CI, -0.57 to 0.35).

> **Impact: Overall, this meta-analysis demonstrates that rTMS is associated with improvements in motor function and depressive symptoms in those with PD, supporting its potential role as an adjuvant therapy alongside traditional pharmacologic treatment. In order to establish the ideal protocols for treatment of PD with rTMS, future directions should include prospective comparisons of different stimulation sites, device parameters, and treatment schedules.**

Zhang W, Muñoz-López A, Zhang X, et al. Efficacy of repetitive transcranial magnetic stimulation in patients with Parkinson disease: a systematic review and meta-analysis of randomized controlled trials. EClinicalMedicine. 2022;55:101740. doi:10.1016/j.eclinm.2022.101740 ([The Lancet])

TMS for Posttraumatic Stress Disorder: A Multisite, Propensity-Matched Cohort Study of Treatment Parameters

Sarah Matsunaga, MD reviewing Berlow et al., Brain Stimulation, 2025 Nov.

Analysis from a retrospective comparative effectiveness cohort study of 756 veterans with comorbid PTSD and MDD who underwent TMS treatment for MDD via either HFL, iTBS, or dTMS protocols demonstrated notable reductions in PTSD symptoms. iTBS and dTMS protocols were found to be noninferior to the HFL protocol, without statistically significant differences in PTSD outcome measures.

rTMS is noninvasive neuromodulation treatment modality whose efficacy has been well established in many conditions, particularly MDD. In light of the high prevalence of refractory PTSD,

rTMS has been increasingly studied for use in this condition. While many studies have shown benefit, it remains unclear whether any specific TMS protocol offers a therapeutic advantage for PTSD

symptoms. To address this gap, the authors analyzed data from the VA Clinical TMS Program, examining veterans with comorbid PTSD who were treated for MDD to compare the efficacy of three

commonly used TMS protocols (HFL, iTBS, and dTMS) on PTSD symptoms.

The authors conducted a retrospective comparative effectiveness study using data from over 30 hospitals across the VA Clinical TMS program. Veterans included in the study had concomitant MDD and PTSD and received TMS via HFL, iTBS (to the left DLPFC), or dTMS (delivered with the BrainsWay H1 coil). Most patients completed 20-30 sessions over a six-week course. Veterans in the iTBS or dTMS protocols were compared to those in the HFL protocol using propensity score matching based on demographic characteristics and pretreatment symptom burden reflected on the PCL-5 and PHQ-9. The authors tested their hypothesis that the TMS protocols would demonstrate equivalent clinical outcomes in the treatment of PTSD using noninferiority and equivalence testing using the two one-sided test (TOST) and conventional two-sided null hypothesis significance test. The primary outcome was defined as PTSD response via >10 point reduction in the PCL-5 and remission with PCL-5 < 33 points. The team also analyzed depression response by a 50% or more

reduction on the PHQ-9, and remission by PHQ-9 < 5.

A total of 658 veterans were included in the analysis, the majority of whom received HFL (n = 526), with smaller subsets treated with iTBS (n = 71) or dTMS (n = 61). Baseline differences were observed across treatment groups, with the dTMS group being significantly younger, more likely to be employed, comprising a higher proportion of women, and exhibiting significantly higher pretreatment PCL-5 scores. To address these imbalances, the authors applied propensity score matching, resulting in final matched sample sizes of 140 versus 70 for the HFL versus iTBS comparison, and 118 versus 59 for the HFL versus dTMS comparison. In the matched HFL versus iTBS analysis, PTSD remission rates were 43.6%, and 48.6%, respectively, while PTSD response was 58.6% and 65.7%, respectively. There were no significant differences on any PTSD measures between the two groups (all p > 0.1). In the matched HFL versus dTMS analysis, PTSD remission occurred in 43.2% and 49.2% of patients, respectively, with response rates of 67.8% and 78%, respectively. Similarly, the dTMS and HFL protocols were not

significantly different in any PTSD outcomes (all p > 0.1). Both iTBS and dTMS were noninferior to HFL across all PTSD outcome measures (all p < 0.05); however, equivalence to HFL was not demonstrated for either protocol (all TOST p > 0.05). Data from PHQ-9 surveys did not show statistically significant differences when comparing dTMS or iTBS to HFL.

> **Impact: Using a large-scale database of veterans with MDD and comorbid PTSD undergoing rTMS treatment, the authors demonstrate that rTMS is efficacious for PTSD and that newer rTMS protocols, including iTBS and dTMS, are noninferior to HFL in reducing PTSD symptoms. This study supports the growing body of work that rTMS is an effective treatment for PTSD, although future prospective studies in a more diverse treatment population, and in patients without psychiatric comorbidities, are warranted to provide more clear-cut and generalizable results.**

Berlow YA, Cilli SL, Kozel FA, et al. Effectiveness of transcranial magnetic stimulation for posttraumatic stress disorder: A multisite, propensity-matched cohort study of treatment parameters. Brain Stimul. Published online November 13, 2025. doi:10.1016/j.brs.2025.11.007

Broad-Spectrum Effects of Left DLPFC rTMS Across Psychiatric Disorders

Preston K. Igwe, MD, reviewing Kan et al., Lancet Psychiatry, 2023 Apr

In this cross-diagnostic meta-analysis, rTMS targeting the left DLPFC was associated with improvements across multiple symptom domains including substance cravings, pain, and memory, in addition to depression and anxiety, suggesting this commonly used stimulation site may exert broad, transdiagnostic therapeutic effects.

Psychiatric disorders such as MDD, GAD, PTSD, OCD, and SUD often share overlapping symptom dimensions rooted in common neural circuit dysfunction. Because these syndromes frequently co-occur and respond variably to available treatments, there is

increasing interest in understanding whether neuromodulation, specifically rTMS of the left DLPFC, may improve symptoms beyond disorder-specific targets. Kan and colleagues conducted one of the first systematic reviews and cross-

diagnostic meta-analyses to examine whether stimulating this region reliably improves shared symptom domains across conditions.

The authors performed a systematic search of randomized

and sham-controlled trials using left DLPFC rTMS across a range of psychiatric disorders. Eligible studies were required to report validated symptom measures and deliver high (≥5 Hz) and/or low (<5 Hz) frequency stimulation to the left DLPFC. The investigators extracted outcomes across transdiagnostic symptom categories such as depression, anxiety, substance cravings, attention, and pain. Standardized mean differences were calculated for each domain, and the authors conducted a series of cross-diagnostic meta-analyses to evaluate whether left DLPFC rTMS exerted consistent therapeutic effects regardless of primary diagnosis. Heterogeneity was evaluated using Higgins' I^2 statistic and publication bias was assessed with Egger's test.

Of the 9,056 studies identified, 2,970 were screened, and 174 met eligibility criteria for inclusion. A majority of the included studies (n = 167) used high-frequency stimulation (≥5 Hz), whereas only two used low-frequency stimulation (<5 Hz), and three used both frequencies. Left DLPFC rTMS demonstrated significant reductions in depressive symptoms (Hedges' g -0.725 [95% CI -0.889 to -0.561]; p<0.0001) with effect sizes in line with those observed in meta-analyses focused solely on major depression, although there was evidence of heterogeneity (I^2=85.66%) and publication bias (p=0.00047). The analysis also showed improvements in anxiety symptoms with a smaller effect size (-0.385 [-0.575 to -0.194]; p<0.0001). Other domains which showed improvement include craving (-0.803 [-1.099 to -0.507], p<0.0001), pain (-0.491 [-0.758 to -0.224], p<0.0001), OCD (-0.473 [-0.921 to -0.025], p=0.039), upper limb motor coordination (-0.479 [-0.909 to -0.050], p=0.029), global cognition (-0.437 [-0.735 to -0.138]; p=0.0040), declarative memory (-0.321 [-0.483 to -0.158], p<0.0001), and working memory (-0.198 [-0.392 to -0.004], p=0.045). No effects were observed for domains of suicidal ideation, attention, language, walking ability, fatigue, and sleep (p > 0.05). The authors noted that effect sizes were generally comparable across diagnostic categories, supporting a transdiagnostic model in which left DLPFC stimulation modulates neural circuits relevant to mood regulation, threat processing, and cognitive control. Limitations include heterogeneity across studies in stimulation protocols, coil positioning, sample sizes, and symptom measurement, as well as the predominance of studies focused on adult patients with depression, limiting conclusions about diagnosis-specific strengths or weaknesses.

Impact: This meta-analysis supports the view of left DLPFC rTMS as a transdiagnostic neuromodulation strategy capable of improving multiple symptom domains that cut across psychiatric diagnoses. By demonstrating consistent effects on depression, anxiety, and cognition, the findings underscore the potential of circuit-based treatments to address shared neurobiological dysfunctions rather than disorder labels alone. Similar cross-diagnostic meta-analytic inquiries into other prominent stimulation sites, especially the often-employed right DLPFC, are warranted to expand upon this study's results.

Kan RLD, Padberg F, Giron CG, et al. Effects of repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex on symptom domains in neuropsychiatric disorders: a systematic review and cross-diagnostic meta-analysis. 2023;10(4):252-259. doi:https://doi.org/10.1016/s2215-0366(23)00026-3

Effects of Transcranial Magnetic Stimulation on the Human Brain Recorded with Intracranial EEG

Clara D. T. Nguyen, MD, MPH reviewing Wang et al., Molecular Psychiatry, 2024 Feb.

In this study of neurosurgical epilepsy patients with implanted electrodes, combined TMS and intracranial EEG (iEEG) evoked strong local neural responses at DLPFC and downstream activation in salience network nodes including the ACC and insula in 8 participants. These findings further clarify the mechanisms underlying TMS and support the feasibility of future studies combining TMS with iEEG to investigate its neural effects.

TMS is a widely used noninvasive neuromodulation technique in both research and clinical settings, yet its underlying mechanisms are not well understood. Neurosurgical patients with medication-refractory epilepsy undergoing temporary iEEG implantation offer a rare opportunity to study human neural activity, but the safety and feasibility of TMS in this cohort remain unknown. In this study, the authors aimed to establish safety parameters and characterize TMS-evoked iEEG activity both locally and in.

downstream brain regions

In this experimental, within-subject, non-randomized, unblinded study, data from iEEG electrodes was collected from eight participants who received temporary implantation of iEEG electrodes for seizure mapping (total of 1414 electrodes). First, safety of combining TMS with iEEG was validated through a gel-based phantom brain model under different conditions to test for electrode heating, electrode displacement, induced currents, and artifact levels. After establishing safety parameters, in vivo stimulation was performed 12–13 days after electrode implantation surgery and after the patients restarted seizure medications. TMS pulses were delivered to the left DLPFC at 0.5 Hz at 120% MT. Sham stimulation was delivered using the MagVenture Active/Placebo coil achieved by flipping the TMS coil. To determine whether an iEEG channel exhibited a TMS-specific neural response (intracranial TMS evoked potential; iTEP), the authors assessed whether the iEEG signal (1) differed significantly from both baseline and

sham conditions, (2) exceeded an amplitude threshold of 10 μV, and (3) showed no significant difference between sham and baseline conditions. The sham versus baseline comparison was included since there were iEEG contacts where sham and TMS both elicited significant responses but at different amplitudes. In six participants, researchers compared the TMS-evoked activity to direct electrical stimulation at the DLPFC to compare its effects.

TMS pulses delivered to a custom-made gel phantom brain containing iEEG electrodes did not result in significant heating or electrode displacement. TMS delivered to the DLPFC elicited iTEPs in 8.7% of all iEEG contacts, with a significantly higher proportion of contacts within 30mm of the stimulation site (19%; p = 0.02, 2-proportion z-test). In contrast, 5.8% of contacts responded to both TMS and sham stimulation and were predominantly located in auditory processing regions, including the transverse temporal cortex. iTEPs were also identified in the dorsal ACC and insula by comparing the mean evoked potentials following DLPFC

stimulation when compared to sham (t(7) = −2.461, p = 0.042). Notably, iTEPs were not observed in these regions when stimulating active control sites that included the parietal lobe, superior temporal gyrus, and motor cortex. Lastly, direct electrical stimulation to the DLPFC using the iEEG electrodes also showed a robust qualitative response in not only the DLPFC, but also the dorsal ACC and insular regions, further strengthening the hypothesis that DLPFC stimulation leads to downstream activation of these regions. Limitations to this study included a small sample size and variability in electrode implantation and coverage based on participants' anatomy and individualized needs. No adverse effects occurred in any of the 8 patients.

Impact: This study demonstrates the safety, feasibility, and potential utility of combined TMS-iEEG in studying the neural mechanisms of TMS. Moreover, the findings suggest that therapeutic TMS protocols may act through the modulation of downstream regions, including the ACC.

Wang, J.B., Hassan, U., Bruss, J.E. et al. Effects of transcranial magnetic stimulation on the human brain recorded with intracranial electrocorticography. Mol Psychiatry 29, 1228-1240 (2024). https://doi.org/10.1038/s41380-024-02405-y

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)

UCLA NEUROMODULATION

To refer a patient or learn more about our program, please call or visit us online.

310-825-7471   **tms.ucla.edu**   6