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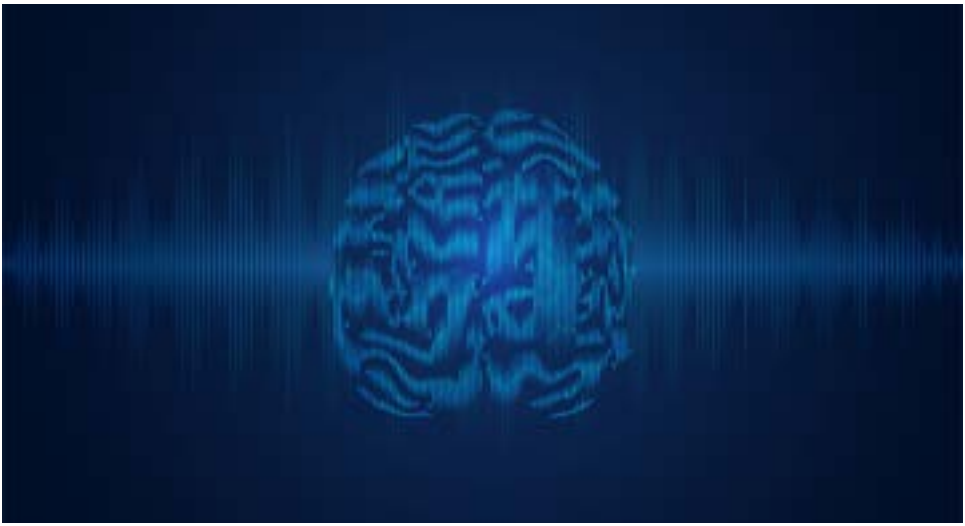
PULSE

A Monthly Update on Advances in Neuromodulation



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tFUS Demonstrates Capacity for Modulation of the Amygdala and Promising Transdiagnostic Benefits in Mood, Anxiety, and Trauma-Related Disorders (MATRDs)

Praveen P. Rajaguru MD, MPH reviewing Barksdale et al., Molecular Psychiatry, 2025 Apr

In this study, MRI-guided low-intensity transcranial focused ultrasound (tFUS) was administered to the left amygdala during fMRI in a double-blind, within-subject, sham-controlled design in patients with mood, anxiety, and trauma-related disorders (MATRDs) and healthy controls. tFUS produced significant reductions in both amygdala BOLD activation and the Mood and Anxiety Symptom Questionnaire General Distress (MASQ-GD) subscale relative to sham. Following this, the MATRD group completed a 3-week daily (15 sessions), unblinded, single-arm, repetitive

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tFUS (rtFUS) treatment trial with further significant reductions in MASQ-GD and amygdala activation. Findings provide preliminary evidence that tFUS can modulate amygdala function, demonstrate the safety and feasibility of real-time tFUS in MATRDs, and support the need for double-blind randomized controlled trials to assess clinical efficacy.

Heightened emotional reactivity is a common feature across MATRDs and is associated with hyperactivity of the amygdala, with clinical associations stronger with the left amygdala. However, the amygdala is a subcortical structure that cannot be directly modulated by cortical neuromodulation such as TMS. Low-intensity tFUS can utilize high-frequency sound waves to precisely target and inhibit subcortical structures. This study sought to explore whether tFUS can engage/inhibit the amygdala in humans and whether it may produce clinical benefit in MATRD patients.

A total of 47 participants (25 MATRD, 22 controls) completed the target-engagement phase, which involved a double-blind, sham-controlled application of the tFUS protocol during fMRI. This was followed by a single-arm repetitive tFUS (rtFUS) intervention in the 20 MATRD participants. MATRD participants were included based on a MASQ-GD subscale score of ≥19 and meeting DSM-5 criteria for MDD, Bipolar Disorder, GAD, Social Anxiety Disorder (SAD), Panic Disorder (PD), and/or PTSD. During the target-engagement phase, tFUS targeted the left amygdala using MRI and neuronavigation techniques, and effects of tFUS were measured using task-based fMRI to assess BOLD change based on an emotional face task. Stimulation parameters were chosen based on animal data and unpublished pilot data. Briefly, tFUS was delivered with a 10 Hz pulse repetition frequency with 5ms pulse width (resulting in a 5% duty cycle, or the percentage of active ultrasound during treatment), and intensity metrics consistent with those from previously published work (derated spatial peak pulse average intensity of 14.4 watts/cm^2, derated spatial peak temporal average intensity of 719.91 milliwatts/cm^2, and derated instantaneous peak pressure of 0.64 megapascals). Treatment was delivered over 10 minutes in 10 sets of 30 s on/off blocks. For sham tFUS, the same protocol was delivered over a tFUS-blocking pad, providing a visual and tactile experience comparable to active stimulation. Active and sham sessions were separated by one week and delivered in a counterbalanced sequence across participants. Following the target-engagement phase, the MATRD patients completed rtFUS treatment for 3 weeks (once daily, Mon-Fri, for a total of 15 sessions) using the same stimulation parameters. Primary outcomes were change in BOLD signal, MASQ-GD, and rates of adverse effects.

For the MATRD group, diagnoses included MDD (N = 16), bipolar I disorder (N = 4), bipolar II disorder (N = 6), GAD (N = 16), PTSD (N = 10), SAD (N = 7), and PD (N = 2). Active vs sham tFUS produced significant attenuation of left amygdala BOLD ($p<0.05$) as hypothesized with no significant differences between MATRD and control groups; both groups also demonstrated modulation of the right middle insula and the control group showed modulation of the anterior hippocampus. After completion of the rtFUS treatment trial for the MATRD group, MASQ-GD scores decreased from 26.79 ± 6.41 to 21.10 ± 7.02 (Cohen's d = 0.77), and 55% of participants (11/20) achieved clinically significant change. Authors also observed significant attenuation in amygdala activation during the emotional face task after rtFUS ($p < 0.001$). There were no serious adverse effects; AEs were transient (total incidents n=24, n=22 occurring in-scanner) with all except for 3 (n= 2 headaches, n=1 irritability) resolving by the next study visit, and none required medical intervention.

Impact: These results suggest that MRI-guided low-intensity tFUS can safely and directly modulate the amygdala, and that rtFUS to the left amygdala may be a promising transdiagnostic MATRD intervention. Notable limitations include utilization of a non-traditional primary outcome measure (MASQ-GD) that limits comparison with other published data; limited sample size; diagnostic heterogeneity within the MATRD group; clinical single-arm design for rtFUS without sham or control for placebo effects; short follow-up, and lack of acoustic modeling to allow for more precise individualized targeting. However, this study provides an initial starting point for more rigorous exploration of this promising intervention.

Barksdale BR, Enten L, DeMarco A, et al. Low-intensity transcranial focused ultrasound amygdala neuromodulation: a double-blind sham-controlled target engagement study and unblinded single-arm clinical trial. Mol Psychiatry. 2025;30(10):4497-4511. doi:10.1038/s41380-025-03033-w

Biomarker Predicts DBS Clinical Response in OCD Patients

Zack Blumenfeld reviewing Provenza et al., Nat. Medicine, 2024 July

In this exploratory study, twelve adults with OCD received DBS implants in the bilateral ventral striatum. In the first five patients, pre-stimulation data showed a narrow 9-Hz band with circadian variation which correlated with clinical symptoms, while in the larger cohort, loss of that variation predicted clinical response.

Deep brain stimulation (DBS) of the ventral striatum is an established treatment for individuals with severe, treatment-resistant obsessive-compulsive disorder (OCD), although clinicians currently lack reliable neurophysiological markers to guide early programming decisions. Modern DBS devices can now record neural activity from implanted electrodes, creating a unique opportunity to link real-world brain dynamics with clinical outcomes. In this study, Provenza and colleagues analyzed intracranial recordings from the ventral striatum of individuals undergoing DBS for OCD to determine whether features of the brain's natural daily rhythms could serve as a biomarker of treatment response. By quantifying circadian periodicity and signal predictability across days, and relating these patterns to symptom improvement, the authors sought to identify objective markers that distinguish patients who ultimately benefit from DBS from those who do not. This work aims to advance a much-needed, physiology-informed framework for optimizing psychiatric neuromodulation.

Twelve patients (eight females) aged 20–55 with treatment-resistant OCD were enrolled in this study. Treatment resistance was defined by a diagnosis of OCD for more than five years, failure of adequate trials of both SSRIs and clomipramine, and failure of Exposure and Response Prevention (ERP) therapy. Patients received clinical ratings using the Y-BOCS I and II, both before and during the postoperative DBS treatment period. This was supplemented by observations from patients' family members and caregivers, which helped classify patient status into responder (≥35% improvement per Y-BOCS or increased level of functioning) or non-responder (a return to baseline OCD symptom severity during the postoperative state). All patients had implantation of DBS leads in the bilateral ventral striatum with electrodes in bipolar configuration. While the DBS records data at 250 Hz, the device was configured to produce the signal's power at 9Hz, sampled every 10 minutes throughout the day, yielding a total of 144 samples per day. To quantify how periodic, and therefore predictable, the neural data is, they used linear and nonlinear autoregressive models and compared the models' goodness of fit (R^2) between the pre- and post-DBS states using a two-tailed Welch's t-test. They also used sample entropy, which quantifies the regularity of time-series data, and compared its value between the pre- and post-DBS states. Data from these output measures were then used to train a machine learning classifier (i.e., logistic regression model) to test whether they can be used to predict responders vs. non-responders to DBS treatment using a leave-one-patient-out cross validation. It is important to note that given the exploratory nature of the study, statistics were reported for each participant separately, often separating results from the right and left hemispheres.

When analyzing the 9 Hz neural data from the initial five patients, where several months of data were collected before activating DBS, the authors observed significant circadian (24-hour) periodicity. This was suggested by significant differences in the autoregressive model fit and sample entropy between the pre- and post-DBS activity in at least one brain hemisphere (autoregressive model: 4 out of 5 participants, sample entropy: 3 out of 5 participants, $p < 0.05$). To test whether these metrics generalize to a larger sample, the authors applied the same analysis after adding seven additional patients who had less data. Both the autoregressive model and sample entropy were still successful in distinguishing pre- versus post-DBS in both the left ($P < 10^{-15}$) and right ($P < 10^{-5}$) hemispheres. Using the autoregressive model metrics to train a logistic regression model demonstrated an accuracy of 82% in predicting whether a participant was a responder or non-responder, suggesting these features could help identify when a patient is improving, perhaps sooner than traditional symptom scales.

Impact: In this exploratory study examining intracranial EEG local field potentials collected before and during DBS for treatment-resistant OCD, investigators identified a 9 Hz ventral striatal signal that tracked patients' clinical state. Greater periodicity of this rhythm correlated with sustained symptom severity, whereas reductions in these features predicted clinical improvement. These findings highlight a promising biomarker for future adaptive, closed-loop DBS systems in which a "smart" neurostimulator monitors neurophysiological activity in real time and delivers stimulation contingent on changes in the 9 Hz signal. Such approaches may

ultimately enhance therapeutic outcomes for individuals with treatment-resistant OCD. While compelling, these results should be interpreted cautiously given the exploratory nature of the work, and additional studies in larger, well-controlled cohorts will be necessary to validate the biomarker and strengthen these initial conclusions.

Provenza, N.R., Reddy, S., Allam, A.K. et al. Disruption of neural periodicity predicts clinical response after deep brain stimulation for obsessive-compulsive disorder. Nat Med 30, 3004–3014 (2024). https://doi.org/10.1038/s41591-024-03125-0

Sex- and Age-Based Differences in Clinical Efficacy of iTBS and 10 Hz rTMS in Patients with MDD

Kaleab Tessema, MD PhD, reviewing Slan et al., J. Affect. Disorders, 2024 Aug

In a retrospective study of MDD patients who were treated with 30 sessions of rTMS, treatment outcomes varied depending on age, sex assigned at birth, and protocol (10 Hz or iTBS). iTBS demonstrated greater efficacy in male patients than female patients, and rTMS overall demonstrated greater efficacy in patients over 50 years old, especially in female patients.

Differential response to psychiatric treatment is a widespread yet poorly understood phenomenon. Precision approaches to psychiatry are a prominent goal, with many recent studies establishing relationships between certain patient characteristics and treatment outcomes. In the context of MDD, past work has identified sex-related differences in risk factors, clinical characteristics, and response to antidepressants. Additionally, age has correlated with treatment response and prevalence of side effects. The combination of sex and age may also play an important role, as, for example, postmenopausal female patients have demonstrated higher MDD rates, lower response to antidepressants, and higher sensitivity to antidepressant side effects. rTMS is a non-invasive treatment option for adult patients with MDD, particularly those who have not been successfully treated with antidepressant medications. While there exists some evidence that suggests sex and age may impact 10 Hz rTMS efficacy, these relationships have thus far not been evaluated systematically, particularly in relation to other rTMS protocols, such as iTBS. Thus, the authors aimed to investigate whether there are differences in antidepressant efficacy of iTBS and 10 Hz rTMS that correlate with sex and/or age.

This retrospective study included 414 patients (212 female, based on self-report of sex assigned at birth) with moderately severe MDD based on assessment via the Mini International Neuropsychiatric Interview (MINI), Inventory of Depressive Symptomatology Self-Report (IDS-SR30), and Patient Health Questionnaire-9 (PHQ-9). Most patients were taking antidepressant medication at the time of the study. Patients received rTMS treatment through the TMS Clinical and Research Service at UCLA. 319 patients were given 10 Hz treatment (3000 pulses; 40-pulse train; and inter-train interval of 11, 16, or 26 seconds), and 95 patients were given iTBS treatment (1800, 1200, or 600 pulses; triplet 50-Hz bursts on 5-Hz carrier wave; inter-train interval of 8 seconds). After 10 treatment sessions, a small percentage of patients (10.3% for 10 Hz, 17.9% for iTBS) were treated with a modified protocol to address early limited response. Treatment outcome was assessed via IDS-SR scores at baseline, treatment 10, and treatment 30. Baseline differences between the 10 Hz and iTBS treatment groups were assessed using unpaired t-tests and the Fisher Exact test. To evaluate contributors to differential treatment outcome, a linear mixed-effects model was used, with fixed effects including biological sex, protocol, age, and time. Differences between protocols for each biological sex and differences between male and female patients for each protocol were evaluated using post-hoc t-tests.

The 10 Hz and iTBS treatment groups showed no significant differences in sex, age, depression severity at baseline (mean IDS 43.2 vs 44.1 respectively, p=0.43), or improvement in depression severity at treatments 10 (20% vs 20.6%, p=0.82) or 30 (34.9% vs 34.8%, p=0.98). While sex and protocol did not demonstrate significant interaction with time (i.e., clinical improvement over time did not vary by sex alone or by protocol alone), there was a significant sex-protocol-time interaction at treatment 10 (p=0.016) and treatment 30 (p=0.031), which reflects

differences in treatment outcome over time depending on the combination of sex and protocol. There were also significant interactions between age and time at treatments 10 (p=0.007) and 30 (0.042), and between age, sex, and time at treatment 30 (p=0.028), reflecting greater clinical improvement in patients over 50 years old and greater improvement in female patients within that group. There was no significant age-protocol-time interaction. Finally, post-hoc t-tests showed higher efficacy of iTBS in male patients than female patients at treatments 10 (Δ=9%, p=0.041) and 30 (Δ=14%, p=0.035), with no significant differences in the remaining comparisons.

Impact: This study suggests that the efficacy of 10 Hz and iTBS rTMS in treating MDD significantly differs depending on age and sex. Confirmation of these findings with future controlled trials may help to validate and expand upon these findings, and lead to precision approaches to clinical rTMS for treatment of MDD.

Slan AR, Citrenbaum C, Corlier J, et al. The role of sex and age in the differential efficacy of 10 Hz and intermittent Theta-burst (iTBS) repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder (MDD). Journal of Affective Disorders. 2024;366:106-112. doi:https://doi.org/10.1016/j.jad.2024.08.129

A Review of Dose-Response Relationships in TMS and tDCS

Melvin Rico, MD, MPH, reviewing Sabé et al. JAMA Network Open. 2024

This systematic review and dose-response meta-analysis examined 110 RCTs to identify possible relationships between the dose of rTMS or tDCS and symptom improvement across various psychiatric disorders. Significant dose-response associations were identified for schizophrenia, depression, obsessive-compulsive disorder, and substance use disorders. Most associations followed a bell-shaped curve relationship, suggesting that rTMS and tDCS have distinct near-maximal effective doses for each disorder and stimulation site, after which benefits begin to decrease. These findings provide valuable guidance to optimize rTMS and tDCS dosing protocols in clinical practice.

Noninvasive brain stimulation (NIBS) interventions, such as rTMS and tDCS, are increasingly being used to treat various psychiatric disorders. High frequency rTMS targeting the left DLPFC and tDCS have demonstrated strong efficacy for depression. However, optimal therapeutic dosing (i.e., how much, to where, and what parameters to use) remains unclear for specific psychiatric conditions. Dose-response meta-analyses could clarify optimal dosing, but most past meta-analyses have focused on medications, not NIBS. Establishing clear dose-response relationships is essential for developing evidence-based NIBS protocols and optimizing clinical outcomes in NIBS. This systematic review followed PRISMA guidelines and updated a previously completed systematic review by searching major databases through April 30, 2023. Studies included RCTs applying rTMS (including iTBS) or tDCS provided via two or more distinct protocol paradigms for the same disorder, along with a sham control at a similar stimulation site. The total dose administered was standardized as total pulses for rTMS and total coulombs for tDCS, stratified by stimulation site and frequency (low vs. high). The primary outcome was the standardized mean difference in the core symptom reduction. Dose-response curves were generated to estimate the 95% effective dose (ED95), which represented the near-maximal effect compared to control.

A total of 110 RCTs met inclusion criteria and were incorporated in the analysis, for a total of 4,820 participants. Dose-response associations with distinct curve graphs were noted. Curves were classified as ascending, plateaued, or bell-shaped to describe the type of dose-response relationship observed. A bell-shaped curve indicated that doses above the ED95 resulted in reduced therapeutic effect. This pattern was seen with high-frequency rTMS to the left DLPFC for treatment-resistant depression (TRD) (ED95: 12,374 pulses; 95% CI: 11,185–15,026; P<0.001) and for negative symptoms in schizophrenia (ED95: 21,695 total pulses; 95% CI: 19,971–23,531; P=0.009) but not for positive symptoms. Similarly, tDCS at the left DLPFC for TRD (ED95: 48.2 C; 95% CI: 35–55 C; P<.001) and for cravings in substance use disorders (ED95: ≈9.6 C; 95% CI: 8.9–13.2; P<.001) demonstrated bell-shaped curves. In contrast, ascending dose-response curves indicate that effectiveness continues to increase with higher doses of stimulation. This relationship was observed for low-frequency (LF) rTMS targeting the

right DLPFC for depression overall (not just TRD) (ED95: 1,835 pulses; 95% CI: 1,721–1,919; P=.001) and PTSD (ED95: 17,495 pulses; 95% CI: 16,596-18,523; P<.001). Lastly, for OCD, LF TMS targeting the orbitofrontal cortex demonstrated an ascending curve that began to plateau at 13,679 pulses (95% CI: 7,117-14,734; P<.001).

Impact: This systematic review and meta-analysis enhances our understanding of dose-response relationships for TMS and tDCS in psychiatric disorders. The findings proposed near-maximal effective doses for various psychiatric conditions and provide guidance for protocol-specific dosing thresholds to optimize clinical outcomes while avoiding under- or over-dosing. The bell-shaped dose-response curves align with established pharmacologic models and support the premise that higher doses are not necessarily more effective. This is particularly relevant for clinicians prescribing TMS or tDCS for TRD and schizophrenia, where the authors observed these curves. Key limitations of this study included significant methodological heterogeneity among the evaluated RCTs and insufficient data to assess the impact of parameters such as pulse intensity and duration of trial. As suggested by the modest ED95s reported, the protocol heterogeneity may be a particularly notable shortcoming and therefore limit the applicability of these findings, as a single pulse of one protocol (e.g., 10 Hz) does not equal that of another (e.g., iTBS), with the latter, in this example, being approximately five times as efficient and therefore prone to deflating the ED95. Future research is needed to validate and refine these dose-response models and to clarify the influence of specific variables.

Sabé, M., Hyde, J., Cramer, C., et al. Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation Across Mental Disorders: A Systematic Review and Dose-Response Meta-Analysis. JAMA Network Open, 2024;7(5):e2412616. doi:10.1001/jamanetworkopen.2024.12616

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)