



A Monthly Update on Advances in Neuromodulation



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Long-term DBS of the Amygdala Reduces Symptoms in Treatment-Resistant Combat PTSD

Amanda Mengotto, MD reviewing Koek RJ et al. *J Psychiatr Res.* 2024 May

This prospective longitudinal study reports four-year outcomes of DBS targeting the basolateral amygdala in two combat veterans with treatment-resistant PTSD (TR-PTSD). Both patients experienced significant symptom reduction over four years, and no serious stimulation-related adverse effects were observed.

Combat-related PTSD is often treatment resistant, with about half of patients failing to respond to psychotherapy or medication. PTSD symptoms, particularly hyperarousal and re-experiencing, are thought to arise from overactivity in the amygdala due to poor ventromedial prefrontal cortex control (vmPFC). This study explores whether DBS targeting the amygdala can help restore balance to this circuit and alleviate symptoms in TR-PTSD.

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Glossary

Two veterans with TR-PTSD were implanted with bilateral quadripolar electrodes (with four separate contacts) targeting the basolateral amygdala. High-frequency DBS starting at 160 Hz was administered, with adjustments made based on PTSD severity as measured by the Clinician-Administered PTSD Scale (CAPS-IV). Stimulation parameters included a pulse width of 60 μ s, except for a brief trial period using 90 μ s. Monopolar stimulation was used, with the case (+) serving as the return electrode. Intensity adjustments were made according to individual patient responses, with safety ensured through EEG telemetry during initial stimulation mapping. Neuroimaging scans, including CT and FDG-PET, were completed pre- and post-operatively to assess network engagement. Volume of tissue activated (VTA) modeling was conducted post-implantation using CT scans, revealing that the stimulation primarily targeted the basal and medial lateral segments of the basolateral amygdala (BLA). These

regions are functionally connected to circuits involved in PTSD, such as the ventromedial prefrontal cortex and hippocampus. The study used a staggered, randomized double-blind phase where active and sham DBS treatments were alternated for several months. A battery of neuropsychological assessments were conducted monthly for 15 months, and then quarterly for 33 months.

Both participants showed marked improvements in PTSD symptoms based on CAPS-IV score changes, from 119 at baseline to 53 four years later (55% improvement) in one participant, and from 68 to 38 (44% improvement) in the other participant. Functional and symptomatic improvements continued in the following years without severe side effects. Improvements in nightmares, dissociation, and impulsive aggression were reported by the participants. Neuroimaging results were inconclusive regarding the exact mechanism of symptom improvement, as FDG-PET showed no significant pre-post DBS

changes in provocation-related activation in the amygdala or insula. There was variability among participants in the optimal treatment protocol, as participant 1 responded best to unilateral stimulation while participant 2 responded best to bilateral stimulation.

Impact: This prospective pilot study suggests that long-term DBS to bilateral amygdala may significantly reduce severe TR-PTSD symptoms. The study reinforces the safety of basolateral amygdala DBS and demonstrates the potential for long-term sustained clinical improvement in the TR-PTSD patient population. The findings highlight the need for further studies to confirm DBS efficacy and to better understand the underlying neurobiological mechanisms.

Koek RJ, Avcillas-Chasin J, Krahl SE, et al. Deep brain stimulation of the amygdala for treatment-resistant combat post-traumatic stress disorder: Long-term results. *J Psychiatr Res.* 2024;175:131-139.

Positive Treatment Expectations Improve Outcomes in rTMS for TRD

Amanda Mengotto, MD reviewing Mollica A et al. *Brain Stimul* 2024 Aug

This retrospective chart review explored how treatment expectations influence clinical outcomes following rTMS for TRD. Patients with higher positive expectations had significantly better remission rates and symptom improvement, while negative expectations did not significantly affect outcomes.

rTMS is a well-established treatment for TRD, but its efficacy can vary significantly depending on various patient- and treatment-specific factors. Emerging evidence suggests that patient expectations may influence treatment outcomes, similar to placebo and nocebo effects seen in other medical treatments. This raises the question: Do treatment expectations affect the therapeutic effects of rTMS for TRD?

This study retrospectively reviewed

the charts of 208 patients with TRD treated with rTMS at a single center. Patients' expectations were assessed using the Stanford Expectancy of Treatment Scale (SETS) before treatment. Patients received a course of 20 daily rTMS sessions over 4 weeks at an intensity of 120% rMT. Patients had a choice of stimulation parameter: either deep TMS (using an H1 coil delivering 1980 pulses at 18 Hz) or iTBS (using a figure-8 coil delivering 600 pulses as 50 Hz bursts at a frequency of 5 Hz). All

treatments involved coil placement over the left DLPFC. The primary outcome was remission as defined as a score <8 on the HAM-D. Premature discontinuation of the 4-week treatment course was analyzed as an additional primary outcome. Secondary outcomes included changes in HAM-D scores from baseline to weeks 2, 4, and 6.

The study found that patients with higher positive pre-treatment

expectations were significantly more likely to achieve remission (OR = 1.5, 95% CI: 1.15, 2.07, $p = 0.004$) and had greater reductions in depressive symptoms (HAMD-17: $\beta = 1.30$, $p = 0.005$). Patients with a higher positivity bias (difference between positive and negative expectancy) were more likely to achieve remission (OR = 1.25, 95% CI: 1.05, 1.49, $p = 0.014$). Negative expectations were not associated with treatment discontinuation ($p = 0.16$) or remission ($p = 0.38$). There was a small but significant positive association between patient age and positivity bias scores ($\beta = 0.02$, $p = 0.04$).

Impact: The results from this retrospective chart review underscore the importance of psychological factors, such as expectations, in determining rTMS efficacy. Enhancing positive treatment expectations could be a promising strategy to improve outcomes in TRD. This could open avenues for patient education and pre-treatment interventions aimed at fostering positive outlooks, such as informational sessions or even therapeutic approaches designed to shift negative expectations. Future research should explore whether these outcomes are driven by psychological mechanisms, similar to placebo effects, or reflect state-dependent changes rooted in a neurocircuitry model. Additionally, assessing these effects over a standard course of 36 treatments may help clarify whether the influence of expectations persists or diminishes, offering a more precise understanding of their significance in sustained rTMS efficacy.

Mollica A, Ng E, Burke MJ, et al. Treatment expectations and clinical outcomes following repetitive transcranial magnetic stimulation for treatment-resistant depression. *Brain Stimul.* 2024;17:752-759. doi:10.1016/j.brs.2024.06.006.

Improvements in Sleep Dysfunction Associated with Improved Outcomes in rTMS for Major Depressive Disorder

Mohamad Shamas, PhD, reviewing Norred MA et al. *J Affect Disord.* 2024 Oct 1

This retrospective cohort study is the largest to date examining the relationship between sleep dysfunction and treatment outcomes in rTMS for TRD. Results indicate that improvements in sleep dysfunction correlate with significant reductions in depression symptoms and higher remission rates.

MDD has a significant impact on the general population, with only about one-third of patients achieving remission from standard treatments like psychotherapy and psychopharmacology. Given that sleep dysfunction is common among MDD patients and is associated with poor treatment outcomes, this study sought to explore the relationship between improvements in sleep dysfunction and the effectiveness of rTMS as a treatment for TRD. Therefore, it asked the following: Could improvements in sleep dysfunction during rTMS treatment serve as a predictor for better depression outcomes?

This retrospective cohort study included 825 veterans treated for MDD under the 'VA TMS Clinical Pilot Program' from 2017 to 2020. rTMS targeted the left DLPFC with 10 Hz stimulation at 120% rMT over 30 sessions with an additional six-session taper. Sleep dysfunction was assessed using the single sleep item (#3) of the PHQ-9, and

improvements were measured at weeks 1, 3, and 6. Depression symptoms were tracked via the PHQ-8 (modified version of the PHQ-9 with the sleep item removed). Statistical analyses, including chi-square tests and univariate analysis of variance, were used to determine the relationship between sleep improvements and depression remission, with depression remission defined as a PHQ-8 score of less than 5.

Of the 825 veterans with baseline sleep data, 778 (94.3%) reported sleep dysfunction, most commonly at the highest severity level (59.5%). A significant correlation between baseline sleep dysfunction and post-treatment depression remission was observed ($\chi^2[3, N = 541] = 23.71$, $p < .001$), with those experiencing severe sleep dysfunction showing lower remission rates compared to those with less severe dysfunction. Significant improvements in sleep were observed after treatment in

37.4% of veterans by week 1, 51.8% by week 3, and 57% by week 6. Those with improved sleep had higher remission rates at weeks 1 (27.8% vs. 18.2%, $p < 0.001$), 3 (29.3% vs. 14.5%, $p < 0.001$), and 6 (31.0% vs. 9.9%, $p < 0.001$; $\chi^2 [1, N = 374] = 23.73$) compared to those without. Veterans with sleep improvements also showed greater reductions in depression symptoms, as reflected by significant decreases in PHQ-8 scores across all three time points: week 1 ($M = 2.4$, $SE = 0.6$, 95% CI [1.2, 3.6]), week 3 ($M = 3.2$, $SE = 0.6$, 95% CI [2.0, 4.3]), and week 6 ($M = 4.8$, $SE = 0.6$, 95% CI [3.4, 6.1]).

Impact: This retrospective cohort study suggests that in patients with TRD undergoing rTMS, improvements in sleep dysfunction are significantly associated with higher depression remission rates. Veterans who experienced early improvements in sleep were more likely to achieve remission from depression,

while those with persistent sleep issues had lower remission rates. Some notable limitations of this study include reliance on a single PHQ-9 sleep item, use of remission was used rather than response as the primary outcome, and the prevalence of comorbid PTSD in this study which may affect generalizability given common sleep issues in that condition. These findings highlight the potential predictive value of early sleep changes and underscore the importance of addressing sleep dysfunction to optimize TRD treatment outcomes. Future research using prospective samples could further validate these findings, ideally incorporating a more rigorous sleep battery to identify which aspects of sleep are most predictive of treatment success. Additionally, testing outcomes with both remission and response measures—more typical in TRD studies—could provide a nuanced view of rTMS efficacy. Integrating specific sleep interventions, such as cognitive behavioral therapy for insomnia (CBT-I), alongside rTMS may also enhance treatment outcomes in TRD.

Norred MA, Zuschlag ZD, Madore MR, Philip NS, Kozel FA. Sleep as a predictor of improved response to transcranial magnetic stimulation for depression (SPIRiTeD). *J Affect Disord.* 2024;362:9-13. doi:10.1016/j.jad.2024.06.077

Single-pulse TMS Activates Unique Brain Rhythms in Cortical and Subcortical Regions

Mohamad Shamas, PhD reviewing Solomon EA et al. *Brain Stimulation* 2024 May 29

This prospective observational study in patients with epilepsy undergoing clinical monitoring with intracranial electrodes examined the effects of single transcranial magnetic stimulation (TMS) pulses to the DLPFC or parietal cortex on brain rhythms in cortical and subcortical regions. Single TMS pulses caused increased low-frequency theta power in frontal and limbic areas and suppressed high-frequency gamma activity in frontotemporal regions, offering new insights into how TMS affects both cortical and subcortical brain structures.

While prior research has shown that TMS alters brain circuits, understanding of its effect on deeper brain structures remains limited. This study uses intracranial EEG (iEEG) in epilepsy patients to evaluate how single-pulse TMS at the DLPFC and parietal cortex influences cortical and subcortical neural activity across frequency bands.

In a prospective observational study, 17 patients with epilepsy undergoing monitoring for seizures with implanted intracranial electrodes were recruited. Patients were monitored for 14 days after electrode implantation, with TMS administered 1-2 days before electrode removal. TMS was applied to either the left DLPFC (identified using the Beam F3 method) or left parietal cortex (identified using resting-state fMRI based on strongest connectivity to the hippocampus) using MRI-guided neuronavigation. All stimulation was performed at a rate of 0.5 Hz, allowing for analysis of iEEG spectral responses to each individual pulse. Sham trials were also conducted, with additional use

of cutaneous electrical stimulation to mimic sensory effects in 4 patients. iEEG recordings used depth and grid electrodes referenced to a midline subgaleal electrode. After excluding contaminated contacts, 3,580 were retained for analysis. Signals were analyzed by comparing active TMS to sham TMS trials in 2.5-second windows around the stimulation, measuring changes in power to avoid noise. Researchers also investigated the consistency of low-frequency brain-wave synchronization after TMS and whether certain brain regions showed increased theta power.

TMS pulses delivered to the left DLPFC resulted in significant increases in theta power (3-8 Hz) in both frontal (Wald $Z = 3.20$, $p = 0.001$) and limbic cortices (Wald $Z = 4.161$, $p < 0.001$) within the time window of 50–550 ms post-stimulation. These changes were most notable in the precentral (Wald $Z = 2.75$, $p = 0.006$), cingulate (Wald $Z = 3.01$, $p = 0.002$), and orbitofrontal (Wald $Z = 3.57$, $p < 0.001$) regions. In contrast, gamma (30–100 Hz) and high-

frequency activity (HFA, 100–400 Hz) power decreased significantly in the temporal cortex (Wald $Z = -3.81$, $p < 0.001$) during the 250–450 ms interval, indicating that DLPFC stimulation not only activates frontal regions but also modulates temporal cortex activity. TMS pulses delivered to the parietal cortex led to significant theta power increases in the medial temporal lobe (MTL; Wald $Z = 3.75$, $p < 0.001$). Following DLPFC stimulation, broadband power increases were initially recorded in both frontal and limbic regions, revealing a global response pattern preceding specific spectral changes, while gamma responses showed a significant decrease ($t = -3.86$, $p < 0.001$) from the beginning to the end of the session. These results indicate potential adaptation effects. No such global changes were observed after parietal cortex stimulation. Importantly, no significant differences in spectral responses were found between the early (first 10 trials) and late phases (last 10 trials) of the stimulation session, except for the decline in gamma responses, and

significant suppression of gamma and HFA power was specifically noted in the superior (Wald $Z = -3.45$, $p < 0.001$) and middle temporal gyri (Wald $Z = -3.12$, $p = 0.001$).

Impact: This prospective observational study of the effects of single-pulse TMS in patients with epilepsy advances our understanding of how TMS modulates neural circuits, leveraging the precision of rare intracranial recordings. Key findings include TMS' ability to influence subcortical structures and produce frequency-specific neural activity. These results may inform the development of more targeted neuromodulatory treatments for psychiatric conditions by elucidating the relationship between cortical stimulation and subcortical responses. Overall, this research underscores the potential of TMS to engage complex neural circuits and highlights the importance of precise intracranial measurements in understanding the physiological effects of brain stimulation.

Solomon EA, Wang JB, Oya H, et al. TMS provokes target-dependent intracranial rhythms across human cortical and subcortical sites. *Brain Stimul.* 2024;17:698-712. doi:10.1016/j.brs.2024.05.014.

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)

