



A Monthly Update on Advances in Neuromodulation



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5x5 Accelerated rTMS Produces Comparable Depression Improvement to Conventional Daily Treatment, with Unique Delayed Response Patterns

Praveen P. Rajaguru MD, MPH reviewing Apostol et al., *Journal of Affective Disorders*, 2026

In this retrospective comparative study, a 5x5 accelerated rTMS protocol consisting of five treatment sessions per day for five consecutive days produced similar overall improvement in depressive symptoms compared with conventional once-daily rTMS administered five days per week for six weeks. About half of the accelerated-treatment group demonstrated limited improvement immediately after treatment but subsequently showed significant symptom improvement over the following 2–4 weeks, suggesting that conventional post-treatment assessment may underestimate the efficacy of accelerated rTMS.

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Glossary

Accelerated rTMS protocols can substantially reduce the duration of treatment by administering multiple stimulation sessions per day. The FDA-cleared accelerated protocol uses 10 sessions of prolonged intermittent theta-burst stimulation (piTBS) per day for five days. However, the optimal number of daily sessions and total number of pulses remains uncertain; more intensive or frequent stimulation is not necessarily associated with greater clinical benefit, and the relationship between treatment dose, speed of improvement, and durability remains incompletely understood. This study retrospectively compared responses to a 5×5 accelerated protocol with conventional once-daily rTMS with a 4-week follow-up to assess whether clinical response continues to evolve after the final treatment session.

This retrospective analysis examined clinical data from 175 patients with major depressive disorder diagnosed by structured interview and treated at a UCLA rTMS clinical service. Conventional rTMS treatment consisted of either 3000 pulses 10 Hz rTMS (n=132) or 1800 pulses iTBS (n=3) administered to L-DLPFC with intensity increased to 120% RMT; these participants received one rTMS session per day, five days per week, for six weeks (at least 30 total sessions). The accelerated group (N = 40) received five rTMS sessions per day for five consecutive days (25 total sessions) consisting of 1800 pulses of piTBS (n=25) or 3000 pulses of individualized EEG-based resonant-frequency (RF) rTMS (n=15) at 120% RMT. RF-rTMS uses TMS-EEG frequency mapping to identify each patient's individualized resonant frequency (3–20 Hz) based on stimulation-induced

changes in EEG connectivity. Depression severity was assessed using the PHQ-9, with response defined as $\geq 50\%$ improvement, and remission as $\text{PHQ-9} \leq 4$ at treatment completion. Accelerated-treatment participants had additional follow-up and evaluation for 2-4 weeks after completion. Mixed-effects linear models were used to compare symptom changes across approaches and protocols.

Both conventional and accelerated rTMS produced significant reductions in depressive symptoms over the treatment period. Improvement in PHQ-9 scores was numerically greater for the conventional group (pre-rTMS PHQ-9 mean = 17.83 ± 4.44 ; post-rTMS PHQ-9 mean = 8.97 ± 5.79) when compared to the accelerated group (pre-rTMS PHQ-9 mean = 17.68 ± 5.47 ; post-rTMS PHQ-9 mean = 10.98 ± 7.68), although this difference was not statistically significant following multiple comparison correction (Bonferroni-corrected $p = 0.07$). The response rates at treatment completion for the conventional versus accelerated groups were 58.5% and 37.5%, respectively, while the remission rates for the conventional versus accelerated groups were 24% and 22.5%, respectively. There was no significant difference between piTBS and RF stimulation ($p > 0.05$). The accelerated patients seemed to have a more rapid rate of response between treatment days 1–5, relative to a more gradual improvement in the conventional group. At treatment completion, a median split showed that “top-half” subjects in both groups showed similarly substantial improvement (74.7% conventional and 68.7% accelerated). “Bottom-half” subjects in the conventional group were partial responders (27.6%), while those in the accelerated group

showed minimal response (7.93%). However, from treatment completion to follow-up, only the accelerated “bottom-half” subjects showed a statistically significant improvement (36%; $V = 0$, $p = 0.001$). At four-week follow-up, the conventional group had a greater improvement relative to the two-to-four-week follow-ups for the accelerated group (56.95% vs 45.75%; $W = 1933.5$, $p = 0.015$).

Impact: This study suggests that a 5×5 accelerated rTMS regimen, regardless of modality, may achieve antidepressant efficacy comparable to conventional once-daily treatment while significantly compressing the active treatment period. Of note, a distinct delayed-response pattern was observed following accelerated treatment where early nonresponders continued to improve after stimulation had concluded, whereas responders had a non-significant but numerical reduction in benefit. These points suggest that evaluating response immediately following an accelerated course may inaccurately estimate treatment efficacy and inappropriately affect treatment decisions; longer follow-up evaluations may best guide further treatment decisions. Future studies may build upon this study and address its limitations by using a prospective, randomized, controlled, and adequately powered design; avoiding aggregating different modalities of 5x5 accelerated treatment; and utilizing standard follow-up intervals across groups.

Repetitive Transcranial Magnetic Stimulation for Autism Spectrum Disorder: A Systematic Review and Meta-Analysis of Treatment Regimens, Efficacy, and Safety

Clara D. T. Nguyen, MD, MPH reviewing Mei et al., *Psychiatry Research*, 2026 August.

In this systematic review and meta-analysis of 53 RCTs, researchers sought to evaluate utility of rTMS in patients with autism spectrum disorder (ASD). They found rTMS yielded statistically significant improvement in several symptom scales including the Aberrant Behavior Checklist (ABC), Childhood Autism Rating Scale (CARS), Autism Treatment Evaluation Checklist (ATEC), Social Responsiveness Scale (SRS) and Repetitive Behavior Scale-Revised (RBS-R).

ASD is a multifaceted neurodevelopmental disorder that is marked by a range of symptoms including differences in social communication, restricted and repetitive behaviors, and delays in developmental markers. While pharmacologic intervention can be employed to help with behavioral symptom management, there are not yet medications approved to treat core symptoms. Therefore, researchers aimed to study the efficacy and safety of rTMS as a noninvasive neuromodulation intervention that could possibly address excitatory and inhibitory pathways that are associated with ASD.

Researchers compiled information from RCTs from PubMed and the China National Knowledge Infrastructure for work published through May 2026. To meet criteria, RCTs needed to compare individuals with ASD of any demographic receiving rTMS versus sham or non-rTMS controls. Because of expected heterogeneity between studies, researchers utilized a random-effects model to account for differences in treatment protocols. The primary effect metric was recorded with the standardized mean difference (SMD), the between-group difference in mean outcome divided by the pooled standard deviation. This allowed for the paper to pool analysis, weighing smaller studies more than larger ones that could result in more conservative confidence intervals, despite use of varying scales to measure change in core symptoms.

All core ASD symptom measures favored rTMS over control conditions to varying degrees, including the ABC (SMD = -1.48, 95% CI: -1.84 to -1.12, $P < 0.001$), $I^2 = 93\%$), CARS (SMD = -0.95, 95% CI: -1.15 to -0.75, $P < 0.001$, $I^2 = 77\%$), ATEC (SMD = -1.83, 95% CI: -2.33 to -1.33, $P < 0.001$, $I^2 = 91\%$), SRS (SMD = -0.25, 95% CI: -0.48 to -0.02, $P = 0.03$, $I^2 = 48\%$), and RBS-R (SMD = -0.40, 95% CI: -0.65 to -0.14, $P = 0.002$, $I^2 = 46\%$). Improvements were also observed in measures of comorbid symptoms, including the Children's Sleep Habits Questionnaire (CSHQ; SMD = -0.96, 95% CI: -1.26 to -0.67, $P < 0.001$) and Child Behavior Checklist (CBCL; SMD = -0.39, 95% CI: -0.58 to -0.20, $P < 0.001$). However, when analyses were restricted to double-blind RCTs, effects were no longer significant for either the SRS (SMD = -0.14, 95% CI: -0.35 to 0.07, $P = 0.20$, $I^2 = 22\%$) or RBS-R (SMD = -0.07, 95% CI: -0.31 to 0.17, $P = 0.55$, $I^2 = 0\%$). Evidence for improvements in executive function was also insufficient. Subgroup analyses based on CARS outcomes found no significant differences between low-frequency (<5 Hz) and high-frequency (5–20 Hz) stimulation ($P = 0.82$) or across stimulation targets ($P = 0.31$), which included the left and/or right DLPFC, left Broca's area, posterior superior temporal sulcus (pSTS), and EEG-defined frontal and parietal sites. Despite the overall direction of findings favoring rTMS, GRADE indicated low to very low certainty of evidence due to

substantial methodological heterogeneity, risk of bias related to the predominance of open-label studies (85%), and publication bias, with more than half of studies also failing to report safety data.

Impact: This study represents an important step toward evaluating TMS for ASD, but substantial methodological and clinical heterogeneity limits its conclusions. Most studies were open label (85%), protocols varied widely, and several outcomes showed high heterogeneity and publication bias. Importantly, when analyses were restricted to double-blind RCTs, the effects on the SRS and RBS-R were no longer significant, suggesting that the overall estimates may be inflated by bias in unblinded studies. Pooling distinct stimulation protocols under the broad category of "rTMS" limits the clinical and mechanistic interpretability. Nevertheless, the authors thoughtfully addressed these limitations through subgroup and sensitivity analyses, providing a valuable synthesis that highlights the need for rigorous, well-powered, double-blind trials of clearly defined TMS protocols to establish the efficacy of TMS for ASD.

Symptom Trajectories and Treatment Outcomes Following a Five-Day Accelerated iTBS Protocol for TRD: A Naturalistic Study in a Real-World Setting

Zack Blumenfeld, MD, PhD, reviewing Janssen-Aguilar et al., *Psychiatry Research*, 2026 Oct

In this retrospective study, patients with TRD underwent accelerated iTBS (aiTBS) under a modified protocol (tailored towards decreasing the daily frequency of sessions and reducing barriers to receiving stimulation) over five days to assess clinical response. While significant reductions in clinical ratings of depression and anxiety were shown on Day 5 as well as up to one month after, substantial loss of follow-up data limits the broader applicability of these results.

Stimulation of the left DLPFC with rTMS or iTBS has been shown to be efficacious in the treatment of TRD. Previous TMS protocols involved sessions spread out over weeks, but accelerated TMS (aTMS) have been developed to administer therapeutic stimulation over days by administering several sessions daily. Stanford Neuromodulation Therapy (SNT) involves ten sessions of iTBS daily given over five days and uses fMRI to identify the stimulation target, demonstrating high remission rates for TRD. However, implementing such intensive protocols reduces access for patients outside the highly controlled setting of a research study. Less intensive protocols have thus been implemented during which patients undergo 2-5 sessions for a week with results suggesting comparable rates of remission to protocols like SNT in TRD patients. Given the ongoing investigations into shorter aTMS protocols which have the potential to benefit a broader range of patients (e.g. in the community setting), this study evaluated the effects of seven sessions of aiTBS over five days in patients with TRD.

Charts were reviewed from patients referred to the Interventional Psychiatry Program at Unity Health Toronto, Canada. Patients eligible for rTMS were offered either standard daily iTBS or aiTBS, with the choice of protocol determined collaboratively by the treating psychiatrist and patient. TRD was

defined as patients with no meaningful clinical response to at least two different antidepressant trials. aiTBS sessions were conducted by clinical staff with follow-up visits at approximately two weeks and one month after the five-day protocol ended. A modified Beam F3 Measurement System was used to localize the left DLPFC in all patients. Sessions were conducted hourly and consisted of 600 pulses at 120% of RMT, balancing real-world feasibility in the outpatient clinical setting with consistency with established iTBS protocols. Baseline information about patient demographics and treatment parameters was quantified using simple statistical tests, while linear mixed-effects models were used to compare clinical scale scores from Day 5 of aiTBS as well as at the two week and one month follow-up appointments.

Forty-eight patients (62.5% female) met inclusion criteria for this retrospective study. Among participants, 89.6% of the patients completed all five days of aiTBS, with a total response rate of 16.67% at Day 5. There were no significant differences in demographic or baseline clinical scores between patients classified as responders vs. non-responders. While 91% of clinical rating scale data was available at Day 5, data availability declined to 35% at the two-week follow-up and 25–29% at the one-month follow-up. Compared to baseline, PHQ-9 scores were 2.97 points lower at Day 5 (LSMD =

–2.97, 95% CI: –4.58, –1.36, $p < 0.001$), 6.81 points lower at two weeks (LSMD = –6.81, 95% CI: –9.20, –4.42, $p < 0.001$), and 6.50 points lower at one month (LSMD = –6.50, 95% CI: –9.09, –3.90, $p < 0.001$). Similarly for GAD-7 scores, compared to baseline, scores were 2.27 points lower at Day 5 (LSMD = –2.27, 95% CI: –3.68, –0.86, $p = 0.006$), 4.53 points lower at two weeks (LSMD = –4.53, 95% CI: –6.59, –2.48; $p < 0.001$), and 5.41 points lower at one month (LSMD = –5.41, 95% CI: –7.78, –3.04, $p < 0.001$).

Impact: In this naturalistic study of patients with TRD treated in a real-world outpatient setting, a modified iTBS protocol was associated with significant reductions in depression and anxiety symptoms, with clinical improvements persisting for up to one month. However, compared to more rigorously implemented five-day iTBS protocols, a smaller percentage of patients achieved clinical response by treatment day 5, and a majority of participants were lost to follow-up, demonstrating both the preliminary nature of the findings as well as the limitations of interpreting the feasibility and efficacy of studies performed outside the clinical trial setting.

Personalized Connectivity-Guided Approaches in iTBS May Accelerate Antidepressant Outcomes Compared with Conventional 5-cm Targeting

Praveen P. Rajaguru MD, MPH reviewing Li et al., *American Journal of Psychiatry*, 2026

In this randomized, double-blind, three arm study, individualized structural- and functional-connectivity-guided targeting of iTBS produced significantly greater reductions in depressive symptoms compared with conventional 5-cm targeting in adults with major depressive disorder or bipolar II depression in the short term, although no between-group differences were observed by week 12.

Conventional TMS targeting of the left DLPFC using scalp-based guidance rules does not account for interindividual differences in cortical anatomy and functional connectivity. Individualized targeting approaches attempt to account for these differences. One category consists of functional-connectivity (FC) approaches that target specific areas of the DLPFC connected to other relevant regions such as the subgenual anterior cingulate cortex (sgACC), for which a negative functional connectivity has been associated with greater antidepressant effect. Another category consists of structural-connectivity (SC) approaches that use tract-based anatomy to identify targets. This study directly compared conventional scalp-based targeting with these two individualized approaches: FC-guided targeting based on negative resting-state connectivity with the sgACC and SC-guided targeting based on structural pathways connecting the DLPFC with the sgACC.

This randomized, double-blind, parallel-design trial enrolled adults aged 18–65 years with major depressive disorder or bipolar II depression, scoring ≥ 18 on the HAM-D, and at least one prior antidepressant treatment failure. Participants were randomized to one of three targeting strategies: conventional 5-cm targeting, FC-guided targeting, or SC-guided targeting. Robotic neuronavigation was used to deliver 20 iTBS sessions delivered over 2 weeks, with two sessions per day spaced 2

hours apart. Each treatment consisted of 1800 pulses at 90% RMT. FC-guided targets were selected based on negative resting-state functional connectivity with the sgACC as determined by fMRI, whereas SC-guided targets were identified using diffusion and then probabilistic tractography to determine DLPFC sites with structural connections to the sgACC. The primary outcome was percentage reduction in 17-item Hamilton Depression Rating Scale (HAM-D) score at week 2. Secondary outcomes included HAM-D changes at weeks 6 and 12, response and remission rates, self-reported depressive symptoms, cognitive performance, and adverse events. Data were analyzed using mixed-effects models for repeated measures (MMRM) with maximum likelihood estimation, where pairwise between-group contrasts were summarized as least-squares mean difference (LSMD).

Of 123 randomized participants, 119 were included in the modified intention-to-treat analysis: 40 in the 5-cm group, 39 in the SC-guided group, and 40 in the FC-guided group. At week 2, SC-guided iTBS produced a statistically significantly greater reduction in HAM-D scores compared with conventional 5-cm targeting, with an LSMD of 8.79% (95% CI, 2.19–15.40; $p=0.010$, Cohen's $d = 0.70$); no significant difference was observed between the 5-cm and FC-guided groups. At week 6, both individualized targeting approaches had an advantage over the 5-cm approach; SC-guided had an LSMD of 12.87% (95% CI, 6.21–

19.54; $p<0.001$, Cohen's $d = 1.03$), while FC-guided had an LSMD of 9.41% (95% CI, 2.84–15.98; $p=0.005$, Cohen's $d = 0.75$). By week 12, however, no significant between-group differences remained. Response and remission rates, adverse events, and cognitive changes were comparable across all three treatment groups and timepoints, and no seizures or manic episodes occurred.

Impact: Although all arms of the study had clinically relevant improvement in symptoms, this trial provides some evidence that individualized targeting may improve the early antidepressant efficacy of accelerated iTBS compared with conventional 5-cm targeting. The strongest effect was observed with SC-guided targeting ($d=0.70$ at week 2; $d=1.03$ at week 6), with FC-guided targeting only outperforming conventional targeting at week 6 ($d = 0.75$). Importantly, neither approach maintained a significant advantage over 5-cm targeting by week 12. These findings suggest that individualized targeting may accelerate clinical improvement without necessarily increasing the ultimate magnitude of response. Studies with longer follow-up periods are needed to truly assess these differences and thus justify the movement towards more personalized targeting approaches.

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)

