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PULSE

A Monthly Update on Advances in Neuromodulation

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Combined rTMS and Auditory Integration Training Significantly Improves Core Symptoms in Children with Autism Spectrum Disorder

Meghan Y. Reddy, MD reviewing Hao et al., Front Psychiatry, Jan 2026

This parallel-group RCT found that low frequency rTMS combined with auditory integration training (AIT) was significantly more effective than rTMS alone in children with autism spectrum disorder (ASD). Following 12 weeks of treatment, the combined intervention yielded superior improvements across core autistic symptoms, emotional behavioral challenges, and repetitive stereotyped behaviors.

ASD is a neurodevelopmental disorder characterized by social communication deficits, repetitive behaviors, and sensory processing abnormalities with a high global prevalence. While there are no specific therapeutic drugs for ASD, low frequency

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rTMS over the DLPFC has been shown to reduce repetitive behaviors. Similarly, AIT, a sound-based therapy that uses modified tones to retrain how the brain processes sound, can be used to refine auditory filtering and address sound sensitivity. Despite the potential for these therapies, high quality research evaluating their combined efficacy is limited.

Researchers enrolled 60 children with ASD between the ages 3-6 years old and randomized them to receive either 12 weeks of combined rTMS and AIT (n=30) or rTMS monotherapy (n=30). Both groups received conventional comprehensive rehabilitation, including speech, cognitive, and social training. The rTMS protocol utilized 400 pulses at 1 Hz frequency at 80% MT targeting the bilateral DLPFC, with stimulation applied to the left hemisphere for the first six weeks and the right for the next six weeks. Of note, due to underdeveloped cerebral cortex in children in addition to the language and social impairments of ASD, RMT was at times undetectable. In these cases, stimulation was administered at 30-50% of maximum output intensity. The AIT intervention involved 30-minute daily sessions five times per week for a four-week course. Clinical outcomes were measured at baseline and after 12 weeks using the Autism Behavior Checklist (ABC), Childhood Autism Rating Scale (CARS), Strengths and Difficulties Questionnaire (SDQ), and Repetitive Behavior Scale-Revised (RBS-R).

While both groups exhibited significant improvements from baseline (statistics were not reported), the combined intervention group showed significantly lower scores than the control group across all primary and secondary measures. Specifically, post-treatment ABC ($t = -2.307$, $P = 0.027$) and CARS ($Z = -3.034$, $P = 0.002$) scores were significantly lower in the study group, suggesting more robust improvements in core ASD features. The combined therapy group also showed significantly lower SDQ total scores ($t=-2.654$, $P = 0.012$), with significant improvement in the emotional symptoms, conduct problems, and prosocial behavior subscales (all $P < 0.05$) when compared to the control group. Lastly, the combined approach resulted in lower RBS-R total scores ($Z = -3.432$, $P < 0.001$), with significant reductions in the stereotyped behaviors, compulsive behaviors, ritualistic behaviors, and restricted behaviors subscales (all $P < 0.05$).

Impact: These RCT findings suggest that the combination of low frequency rTMS and AIT is synergistic and addresses ASD deficits by modulating cortical excitability while simultaneously reducing sensory sensitivity. This combined strategy allows for broad regulation across multiple neural networks, including executive control, the auditory cortex, and social cognition regions, facilitating more comprehensive clinical improvements and better emotional regulation than traditional treatment. However, the study is limited by the absence of neurophysiological indicators such as fMRI or EEG to confirm the underlying brain mechanisms, individualized AIT frequency adjustments, and long-term follow up data to evaluate the durability of the treatment effects. Future studies are needed to expand on these areas.

Hao QH, Wang JY, Yang JD, et al. Clinical efficacy observation of repetitive transcranial magnetic stimulation combined with auditory integration training in children with ASD. Front Psychiatry. 2026;17:1704732. Published 2026 Jan 28. doi:10.3389/fpsyt.2026.1704732

Alpha-Frequency tACS Modulates Individualized Alpha Power and Correlates with Depressive-Symptom Change in a Double-Blind Trial

Sheyna M. Nathwani, MD, reviewing Schwippel et al., Brain Stimulation 2026 July-Aug.

This double-blind, sham-controlled trial demonstrates that prefrontal 10 Hz tACS produces a condition-specific suppression of individual alpha frequency (IAF) power that tracks with depressive-symptom improvement, supporting IAF modulation as a mechanistic biomarker and supporting future personalized, alpha-targeted stimulation approaches.

A promising target for the treatment of MDD is alpha-band activity (8–12 Hz), which is frequently altered in MDD and implicated in maladaptive network dynamics. tACS is a non-invasive technique that manipulates neural oscillations by delivering weak alternating electrical currents through the scalp. A previous study demonstrated that IAF dynamics may be particularly important; however, whether tACS can reliably modulate IAF power — and whether such modulation relates to symptom change — remains unknown. This RCT evaluates whether alpha power suppression at 10 Hz tACS and IAF predicts clinical improvement in MDD.

This double-blind, sham-controlled randomized trial enrolled 20 adults with MDD, assigned 1:1 to receive prefrontal 10 Hz tACS or sham for five consecutive days. Resting-state 128-channel EEG was recorded

at three time points: before stimulation on Day 1 (D1, baseline), Day 5 (D5, end of intervention week), and at a two-week follow-up (FU). Alpha frequency was defined as 10 Hz, and individual alpha frequency (IAF) was defined as each participant's dominant frequency peak around the alpha range on resting-state EEG, allowing the alpha frequency to be individualized rather than using a fixed frequency band. Active tACS delivered sinusoidal 10 Hz for 40 minutes targeting the bilateral prefrontal cortex; sham used identical electrode placement but delivered only 40 seconds of 10-Hz tACS. Primary outcomes assessed changes in alpha power and their relationship to depressive-symptom change on the HDRS-17. Secondary analyses evaluated whether alpha suppression at 10 Hz and IAF predicted HDRS-17 improvement, including between-group differences in alpha power suppression (D5-D1, FU-D1) and within-group associations between alpha suppression and HDRS-17 improvement.

Across the study, between-group comparisons showed no significant differences in prefrontal alpha power changes at either 10 Hz or IAF in D5-D1 or FU-D1. Right prefrontal 10 Hz power demonstrated a trend-level reduction in the active-tACS group relative to sham ($p=0.066$). Within the active-tACS group, greater IAF power suppression in each hemisphere was associated with greater HDRS-17 improvement in FU-D1 (left: $\rho = 0.81$, $p = .008$; right: $\rho = 0.67$, $p = .0498$). Early IAF power suppression during D5-D1 predicted later symptom improvement at FU-D1 (left: $\rho = 0.73$, $p = .027$; right: $\rho = 0.74$, $p = .022$). This effect was absent in the sham group (left: $\rho = 0.24$, $p = .5$; right: $\rho = 0.11$, $p = .76$). Moreover, greater bifrontal IAF PSD reductions during intervention (D5-D1) were associated with greater improvement in HDRS-17 at follow up (FU-D1) in the tACS group (left: $\rho = 0.73$, $p = .027$; right: $\rho = 0.74$, $p = .022$). Analysis of individual EEG channels revealed significant correlations between IAF reductions and HDRS-17 improvement (FU-D1) in 24 electrodes ($p < 0.05$, corrected for false discovery rate), predominantly over frontal-central and left parietal regions. Importantly, depression scores declined substantially over time in both groups ($p<0.001$), with no significant time x condition interactions for HDRS-17 ($p > 0.05$, repeated-measures ANOVA), suggesting there was no difference in clinical improvement over time between the active and sham tACS groups.

Impact: This double-blind, sham-controlled study identifies individual IAF power suppression as a potential early biomarker of antidepressant response. Findings suggest that five days of prefrontal 10 Hz tACS may engage depression-relevant alpha oscillatory mechanisms, with clinical improvement specifically linked to suppression of IAF power. This may further support the development of personalized, IAF-targeted tACS approaches that tailor intervention to individual neural dynamics. However, both the active and sham stimulation groups showed improvements in depressive symptoms, with no significant between-group differences, raising questions about whether tACS provides clinical benefits beyond placebo effects. Larger, higher-powered trials with individualized stimulation parameters and longer follow-up are warranted to confirm efficacy and determine optimal dosing, electrode montage, and treatment duration.

Schwippel T, Pupillo F, LaGarde H, Stein A, Zhang M, Rubinow DR, Frohlich F. Suppression of endogenous alpha power predicts clinical response to 10 Hz tACS in major depressive disorder: A double-blind randomized controlled trial. Brain Stimul. 2026 Jul-Aug;19(4):103131. doi: 10.1016/j.brs.2026.103131. Epub 2026 May 29. PMID: 42217541.

Single-Day Neuroplasticity-Enhanced TMS Produces High Response and Remission Rates in Medication-Resistant Depression

Praveen P. Rajaguru MD, MPH reviewing Vaughn et al., Transcranial Magnetic Stimulation, 2025

In this retrospective case series, authors evaluated the safety and efficacy of the Optimized, Neuroplasticity-Enhanced techniques in Depression (ONE-D) protocol which delivered an entire course of iTBS within a single day by combining accelerated TMS with pharmacologic enhancement of neuroplasticity using d-cycloserine and lisdexamfetamine. Among 32 adults with medication-resistant unipolar depression, depression severity improved significantly across multiple outcome measures over six weeks, with a remission rate of 71.2%, with clinical improvement durable through 6 months and no serious adverse effects. This suggests that an accelerated approach to TMS treatment of depression may be both safe and effective.

Conventional TMS is an effective treatment for medication-resistant depression but typically requires daily treatment sessions over four to six weeks, limiting access for many patients even with the advent of accelerated multi-day treatment protocols. Although the first study of accelerated TMS was completed in 1.5 days with durable effects, no further studies have attempted to replicate a similarly accelerated protocol. The ONE-D protocol was developed to further reduce treatment burden by administering 20 sessions of iTBS within a single day (600 pulses with 30-min intersession intervals in under 10 hours), while using evidence-based augmentation methods including d-cycloserine and lisdexamfetamine. This study evaluated the feasibility, safety, and real-world clinical effectiveness of the ONE-D protocol in adults with medication-resistant depression.

Authors conducted a retrospective, naturalistic case series using de-identified observational data collected at clinics participating in the OBSERVER clinical TMS registry. Thirty-two adults undergoing treatment for major depressive disorder and deemed clinically appropriate by their provider for TMS but unable to participate in multi-day regimens underwent the ONE-D protocol. The protocol consisted of 20 iTBS sessions targeting the left DLPFC, delivered over 9.5 hours at 30-minute intervals. Each session comprised 600 pulses delivered as 50-Hz triplet bursts at 5 Hz (2 s on, 8 s off) at 120% of RMT, preceded by a three-train acclimatization titration. One hour before stimulation, participants received d-cycloserine 125 mg and lisdexamfetamine 20 mg to enhance neuroplasticity.

Depression severity was assessed using the HDRS-17, BDI-II, PHQ-9, and GAD-7 at baseline, weekly for six weeks, and again at 12 and 26 weeks following treatment. Outcomes were analyzed using mixed-effects models with an intention-to-treat approach.

All 32 participants completed the entire 9.5-hour treatment protocol. 19/32 were TMS treatment naïve, and average length of depressive episode was 18.0 months ±SD19.5. The most common side effect was scalp discomfort (mean ± standard deviation = 5.8 ± 2.1 during stimulation, on a 10-point scale), and no serious adverse events, seizures, or treatment discontinuations occurred. Depression severity improved significantly across all primary outcome measures over follow-up, following a delayed, exponential-decay-like trajectory with a plateau in responses observed around 4-6 weeks. From baseline to week 6, mean scores improved on the HDRS-17 (mean ± standard deviation = 22.6 ± 5.3 to 5.5 ± 4.2; Cohen's d = 3.58), BDI-II (37.5 ± 9.0 to 7.6 ± 7.8; d = 3.73), PHQ-9 (18.4 ± 3.5 to 4.6 ± 4.2; d = 3.36), and GAD-7 (14.3 ± 5.2 to 2.7 ± 2.9; d = 3.71). At six weeks, response and remission rates peaked; via HDRS-17, 87.5% achieved response and 71.2% achieved remission; via BDI-II 90.6% achieved response and 68.8% achieved remission; and via PHQ-9 response was 87.5% and remission was 56.3%. Clinical improvement remained durable; for example, HDRS-17 response and remission rates were 84.4% and 71.2% at week 12, respectively. By week 26, 50.0% remained in remission, while 25.0% experienced relapse necessitating retreatment. Baseline symptom severity, prior TMS trials, and prior antidepressant trials were not predictive of response.

Impact: This real-world case series demonstrates that a complete therapeutic course of iTBS may be delivered safely and with durable efficacy within a single day when combined with pharmacologic enhancement of neuroplasticity. The observed response and remission rates compare favorably with those reported for conventional multi-week TMS protocols and remained durable in some participants for up to six months — interestingly, with a longer time to efficacy than other accelerated protocols, such as the 5-day accelerated SAINT protocol, where the mean time to remission was 2.6 days. Full interpretation is limited by the open-label design, lack of randomization, absence of a control group, and concurrent administration of d-cycloserine and lisdexamfetamine that limits conclusions as to the relative importance of each agent in facilitating the observed efficacy. However, these findings do support the feasibility of increasingly accelerated neuromodulation strategies designed to improve treatment accessibility. In the future, RCTs comparing the ONE-D protocol with conventional daily and more traditional accelerated TMS protocols (e.g., SAINT) are needed to determine whether the observed clinical benefits result from treatment acceleration, pharmacologic neuroplasticity enhancement, or their combined effects.

Vaughn, D. A., Marino, B., Engelbertson, A., Dojnov, A., Johnson, L., Stine, M., Vila-Rodriguez, F., Weiss, N., Nanos, G., & Downar, J. (2025). Real-world effectiveness of a single-day regimen for transcranial magnetic stimulation using Optimized, Neuroplasticity-Enhanced techniques in Depression (ONE-D): An open-label case series. Transcranial Magnetic Stimulation, 5, 100200. https://doi.org/10.1016/j.transm.2025.100200

Accelerated iTBS Decreases Default Mode Network Connectivity Across Unipolar and Bipolar Depression: A Candidate Transdiagnostic Biomarker of Treatment Response

Praveen P. Rajaguru MD, MPH reviewing Sheline et al., Transcranial Magnetic Stimulation, 2026

In this neuroimaging study of accelerated intermittent theta-burst stimulation (aiTBS), treatment produced significant reductions in within-default mode network (DMN) connectivity that correlated with improvement in depressive symptoms across both unipolar and bipolar treatment-resistant depression. These findings were not observed in the sham-treated bipolar depression group, supporting changes in DMN connectivity as a candidate transdiagnostic biomarker of antidepressant response.

The default mode network (DMN) is a network whose dysfunction has been heavily implicated in depression. Alterations in DMN function have been linked with emotional and cognitive aspects of depression, including rumination. Although the clinical effects of TMS treatment have been well described, the underlying functional brain correlates remain incompletely characterized. To bridge this gap, this study investigated changes in within-DMN connectivity following an aiTBS protocol in individuals with treatment-resistant major depressive disorder (MDD) or bipolar depression (BD) and examined whether these changes were associated with improvements in depressive symptoms.

Data were pooled from two prospective studies, including an open-label trial of adults with treatment-resistant MDD and a randomized, double-blind, sham-controlled trial of BD. Individuals had to be on a stable medication regimen prior to participation. Thirty-four adults with transdiagnostic TRD (18 females, 16 males) and baseline MADRS scores ≥20 were included and underwent resting-state functional MRI before and after treatment to assess functional connectivity. Twenty-two participants (10 MDD, 12 bipolar depression) received active aiTBS, while 12 participants with bipolar depression received sham stimulation. Sham stimulation was delivered using the MagVenture double-sided coil which delivered electrical pulses that mimic the sensation of receiving aiTBS. Treatment consisted of 10 sessions of personalized left dorsolateral prefrontal cortex (DLPFC) aiTBS per day (one session per hour; 18,000 pulses per day) at 90 % RMT for five days. Individualized stimulation targets were selected using functional connectivity mapping. Resting-state functional connectivity analyses focused on intrinsic brain networks, particularly the DMN, and changes in connectivity were correlated with changes in depression severity measured by the MADRS.

In the included 34 patient sample, no significant differences in demographics or prior psychiatric history were observed. The primary outcome was not affected by diagnosis (BD vs. MDD), so all data was pooled. Active aiTBS significantly reduced within-DMN functional connectivity compared with baseline (Δ mean ± SD Z-normalized Pearson's r [rz], –0.017 ± 0.0270.; t[21] = –2.89, p = .01; Cohen's d = –0.62), with no significant differences in connectivity observed between the active BD or MDD groups. The sham group showed no significant changes in within-DMN connectivity. There was a significantly greater decrease in MADRS scores in the pooled active aiTBS vs sham group (–14.68; p < .0001). Mean MADRS scores also decreased significantly from baseline following active treatment (–18.50; p < .0001). In contrast, sham-treated participants demonstrated no significant changes in within-DMN connectivity or depressive symptoms. MADRS change was correlated with within-DMN connectivity changes in the active aiTBS group (r = .47, p = .03) which remained significant (r^2 =.23, p = .04) even when controlling for targeting, MRI scan parameters, or diagnosis. Treatment-related changes in the active group were localized primarily to the posterior DMN.

Impact: This study provides evidence that reduced within-default mode network connectivity represents a candidate transdiagnostic biomarker of response to aiTBS. Rather than demonstrating diagnosis-specific mechanisms, aiTBS appeared to address network-level pathology shared in both unipolar and bipolar depression, with connectivity changes predicting clinical improvement. However, interpretation is limited by the absence of a sham-control group for participants with MDD. As the DMN has been shown to underly depressive rumination, and secondary outcomes demonstrated

improvement in rumination scores, it also appears likely that aiTBS-related connectivity changes may address a difficult to treat aspect of depression. This study had limitations including pooling of data from separate studies with varying parameters and a low sample size. In addition to addressing these weaknesses, future studies may also explore the influence of neural circuit heterogeneity, targeting methodology, and effects of medication. If replicated in larger sham-controlled cohorts, resting-state DMN connectivity could serve as an objective biomarker for treatment monitoring, target optimization, and patient selection in accelerated TMS protocols.

Sheline, Y. I., Batzdorf, A. S., Makhoul, W., Balderston, N. L., Lynch, K. G., Cash, R. F. H., & Liston, C. M. (2026). Decreased within-default mode network connectivity with accelerated intermittent theta burst stimulation across unipolar and bipolar depression: Candidate transdiagnostic circuit marker for treatment response. Transcranial Magnetic Stimulation, 6, 100205. https://doi.org/10.1016/j.transm.2026.100205

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)