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PULSE

A Monthly Update on Advances in Neuromodulation

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dTMS May Improve Depression Among Adolescents with TRD

Audrey D. Nguyen, MD, MPH reviewing Thai et al., J Affect Disord, 2024 March

In a preliminary open-label, dose-finding study, dTMS was associated with significant reductions in depressive symptoms in adolescents with TRD. The treatment was generally well-tolerated, though one participant experienced a convulsive syncope. These findings suggest dTMS may be a promising intervention for adolescent TRD, warranting further investigation.

Deep rTMS (dTMS) has shown promise in treating depression, attributed in part to stimulation of subcortical brain regions implicated in the pathophysiology of MDD. While dTMS has been FDA-approved for adults with TRD, its efficacy and tolerability in youth remain underexplored. Previous studies of rTMS in adolescents with TRD have reported response rates ranging from 33% to 100%. While data are expanding, particularly following FDA clearance for conventional rTMS

in individuals aged 15 and older, evidence in adolescents still lags behind that for adults. This study aimed to bridge that gap by evaluating the safety, tolerability, and preliminary efficacy of dTMS in adolescents with TRD.

This study initially began as a randomized, sham-controlled trial using BrainsWay's proprietary H1 coil. However, after one participant experienced a convulsive syncope event in the initial phase, the study was modified to an open-label, dose-finding trial. Adolescents aged 12-18 years with TRD (defined as a lack of response to at least one adequate trial of antidepressant therapy) were enrolled in a six-week trial of dTMS. Participants received 30 sessions of dTMS with an H1 coil positioned over the left DLPFC delivering 1,980 pulses per session at 10 Hz. Intensity levels of 80%, 100%, and 120% of motor threshold (MT) were sequentially tested for safety among at least three participants before advancing. The primary outcome was depression severity, assessed by the Children's Depression Rating Scale-Revised (CDRS-R), with response defined as a ≥50% reduction from baseline to post-treatment (scaled to the minimum score of 17). Secondary outcome measures included self-reported depression, anxiety, anhedonia, suicidality, and cognitive performance assessed before and after treatment.

Fourteen out of 15 participants completed all pre- and post-cognitive assessments and dTMS treatment sessions. Six participants (42.9%) reached clinical response, with a mean reduction in CDRS-R scores of 39.2% ($p<0.001$). Among responders, 83.3% (n = 5) received the highest stimulation intensity of 120% of MT. One participant experienced a convulsive syncope during the first session and ultimately discontinued participation. Otherwise, mild headache was the most commonly reported adverse effect ($p = 0.024$). There were no significant treatment-related increases in mania, suicidality, or cognitive impairments. Secondary outcomes, including measures of depression and suicidality, showed significant reductions from baseline to post-treatment ($p<0.001$), with improvements sustained at each follow-up visit.

Impact: This prospective, open-label study is the first to investigate the safety and clinical response of dTMS in adolescents with TRD. The findings suggest dTMS is generally well-tolerated and associated with significant reductions in depression severity, particularly at higher stimulation intensities. However, the occurrence of a convulsive syncope highlights the need for careful monitoring of seizure risk. Study limitations include the small sample size and lack of randomization across intensity levels. Larger, randomized trials are necessary to confirm these results and further evaluate the efficacy and safety of dTMS in this population.

Thai M, Nair AU, Klimes-Dougan B, et al. Deep transcranial magnetic stimulation for adolescents with treatment-resistant depression: A preliminary dose-finding study exploring safety and clinical effectiveness. J Affect Disord. 2024;354:589-600. doi:10.1016/j.jad.2024.03.061

Comorbid Personality Disorders Associated with Reduced Efficacy of rTMS in TRD

Visesha Kakarla, MD reviewing Maciaszek et al., Front Psychiatry, 2024 Nov

This post-hoc analysis of data from a double-blind, sham-controlled RCT examined the impact of comorbid personality disorders (PD) on the efficacy of rTMS for TRD, finding that PDs reduced MADRS score improvements.

Between 30%–60.5% of patients undergoing rTMS for TRD do not have a significant improvement in symptoms, prompting a search for moderators of treatment response. Few prior studies have examined the effect of comorbid PD on rTMS efficacy, with most relying on retrospective surveys or facing high dropout rates.

This retrospective analysis examined data from a double-blind, sham-controlled RCT which enrolled 40 adult participants with TRD (defined as depression without adequate response to 4-6 weeks of pharmacologic treatment). Patients were randomized to active rTMS (n = 25) or sham (n = 15), with the active group comprising 10 Hz rTMS (n = 16) and iTBS (n = 9). The 10 Hz rTMS protocol delivered 3,000 pulses/session at 120% MT to the left DLPFC daily for 6 weeks. For iTBS, 600 pulses/session were delivered at 80% MT to the left DLPFC, 4 sessions a day for 2 weeks. Sham stimulation utilized coils with magnetic shields and simulated auditory and somatosensory effects of rTMS. All participants were evaluated at baseline (T0), post-treatment (T1), and at 3-month follow-up (T2). Primary outcomes were reduction in MADRS at T1 and T2, assessed using analysis of covariance (ANCOVA), as well as post-hoc linear stepwise regression to account for confounders.

Of the 40 participants, 37.5% (n = 15) were diagnosed with PD

through standardized assessment, including borderline (n = 8), narcissistic (n = 5), and histrionic (n = 2) PD. The study showed no significant differences in MADRS score reductions between active and sham, with active rTMS achieving reductions of 47.9% at T1 and 45.7% at T2 compared to 39.9% and 34.2% for sham. Post-hoc ANCOVA showed comorbid PD significantly reduced symptom improvement at T1 ($F = 18.8$, $p < 0.001$), though not at T2. There was also no statistically significant effect on MADRS score reductions based on age, education years, female sex, MT%, rTMS type, or disease duration. However, linear regression analysis revealed a significant negative association between comorbid PD and reduced MADRS scores from T0 to T1 ($p<0.001$).

Impact: This post-hoc analysis of an RCT found that comorbid PD significantly reduces the effectiveness of rTMS for TRD, with lower MADRS reductions observed in both active and sham treatment groups when a PD was present. These results align with research indicating that individuals with comorbid personality disorders often experience less favorable outcomes in depression treatment. While the study did not find a significant overall difference in symptom reduction between active and sham groups, the similar negative influence of PDs on outcomes in both groups suggests that factors beyond the active stimulation itself are at play, such as non-specific treatment effects, or potentially suggests an issue with the study methodology. The overrepresentation of Cluster B PDs raises questions about selection bias and generalizability, and the lack of differentiation between subtypes within this cluster represents an additional limitation. Variability in traits such as impulsivity, emotional instability, and grandiosity among CBPDs may differentially affect treatment response. Additional limitations include the small sample size, non-standard rTMS protocols (e.g., iTBS delivered at sub-therapeutic intensity, below the typical ≥90% MT), and no measure of blinding efficacy. Future research should examine PD effects in larger samples, neurobiological mechanisms, and explore psychotherapy-TMS synergies for TRD with comorbid PDs.

Maciaszek J, Rymaszewska J, Wieczorek T, et al. Preliminary findings of a randomized controlled trial investigating the efficacy of transcranial magnetic stimulation in treatment-resistant depression: a post-hoc analysis on the role of co-occurring personality disorders. Front Psychiatry. 2024;15:1363984. Published 2024 Nov 11. doi:10.3389/fpsyt.2024.1363984

Cognitive Remediation Paired with tDCS Slows Cognitive Decline in Older Adults with Depression and MCI

Mohamad Shamas, PhD, reviewing Rajji TK, et al. JAMA Psychiatry 2025 Jan

This double-blind RCT assessed whether cognitive remediation (CR) combined with prefrontal tDCS could slow cognitive decline in older adults with remitted MDD (rMDD) and/or mild cognitive impairment (MCI). The intervention significantly slowed cognitive decline, particularly in those with rMDD and noncarriers of APOE ε4; however, it showed limited acute cognitive improvements and did not significantly delay progression to dementia.

Older adults with MCI or rMDD are at increased risk for cognitive decline and dementia, and depression – even when in remission – can significantly elevate the risk of dementia in late life. Although previous trials have investigated the use of CR combined with tDCS in MCI populations, none have examined its efficacy in rMDD or beyond 12 weeks. The Prevention of Alzheimer's Dementia with Cognitive Remediation Plus Transcranial Direct Current Stimulation in Mild Cognitive Impairment and Depression (PACt-MD) trial aimed to evaluate the long-term efficacy of combined CR and tDCS in older adults with MCI, rMDD, or both.

This double-blind RCT enrolled 375 participants aged ≥60 years with either rMDD, MCI, or both. Participants were randomized into either an active intervention group (receiving concurrent CR and tDCS) or a sham group (receiving sham versions of both interventions). Treatments occurred daily, 5 days a week for 8 weeks, followed by biannual 5-day booster sessions. CR sessions, conducted in small groups of 3-8 participants, focused on titrating cognitive exercise difficulty based on individual performance along with coaching to improve complex task-solving. Sham CR used low-difficulty exercises with no cognitive coaching. tDCS was administered for 30 minutes during each CR session, targeting the prefrontal cortex (anode: Fz; cathode: Iz). Active tDCS delivered 2 mA for 30 minutes, while sham tDCS included a brief ramp-up and ramp-down without sustained current. Cognitive scores were analyzed using mixed-effects models, while progression to dementia was assessed using Kaplan-Meier and Cox models.

Participants were followed for a median of 48 months (range: 2.1–85.9 months). At the 60-month primary time point, 64 participants (17%) remained in the study (active: 33, sham: 31). A significant treatment effect was observed for the primary outcome at month 60, with an adjusted z-score difference of 0.21 (95% CI: 0.07–0.35, $p = 0.006$). The interaction term of treatment with time was also significant ($p = 0.04$). In terms of cognitive

domains, executive function and verbal memory showed significant improvements (p = 0.04 and p = 0.02, respectively), with greater effects observed among noncarriers of APOE ε4 (p < 0.001). However, acute cognitive gains at month 2 were not significant, and progression to dementia did not differ significantly between groups.

Impact: This double-blind RCT demonstrated that combined CR and tDCS are promising interventions for slowing cognitive decline in high-risk older adults with rMDD and/or MCI. The intervention demonstrated significant long-term benefits, particularly in executive functioning and verbal memory, and was most effective in noncarriers of APOE ε4. However, only 17% of participants remained in the study at the 60-month primary endpoint, raising concerns about potential bias from high dropout rates. Those with faster cognitive decline may have been more likely to drop out, though this would likely lead to underestimation of the true treatment effect. Future studies with enhanced retention strategies and larger long-term cohorts are needed to confirm these results and further explore their clinical utility.

Rajji TK, Bowie CR, Herrmann N, et al. Slowing Cognitive Decline in Major Depressive Disorder and Mild Cognitive Impairment: A Randomized Clinical Trial. JAMA Psychiatry. 2025;82(1):12-21. doi:10.1001/jamapsychiatry.2024.3241

Combined tDCS and rTMS More Effective for Depression than Either Modality Alone

Mandeep Singh, MD, MBA reviewing Zhou et al., JAMA Netw Open 2024 Nov

In this double-blind, sham-controlled, factorial-design RCT, adult patients with MDD treated with combined tDCS and rTMS showed significantly greater HDRS reductions than either intervention alone.

rTMS is an effective treatment for MDD, and tDCS shows promise though requires further evidence. Research suggests that tDCS excites the cortex for up to 90 minutes and that rTMS applied after tDCS results in more lasting changes in cortical excitability and plasticity. This trial was thus designed to test whether the combination of tDCS and rTMS is more effective than either treatment alone.

This double-blind, sham-controlled RCT enrolled 240 adults diagnosed with MDD from inpatient psychiatric units in China. Participants had HDRS >20 and no history of epilepsy; brain tumors; trauma; recent (≤3 months) TMS, tDCS, or ECT; or neurological implants. Participants were randomized into four groups: 1) active tDCS + active rTMS; 2) sham tDCS + active rTMS; 3) active tDCS + sham rTMS; and 4) sham tDCS + sham TMS (n = 60 per group). MRI-guided neuronavigation was used to target the left DLPFC (anode for tDCS and rTMS) and the right DLPFC (cathode for tDCS). tDCS was administered at 2 mA for 20 minutes, followed 30-60 minutes later by rTMS delivered at 10 Hz for 1600 pulses at 110% rMT. Treatments were administered daily over two weeks for a total of 10 sessions. The primary outcome, change in HDRS scores from baseline to week 2, was analyzed using ANOVA. Response and remission rates, defined as ≥50% reduction from baseline and HDRS <9, respectively, were compared using chi-square tests.

Of the 240 participants randomized, 219 (91.3%) completed the two-week treatment and follow-up assessments. ITT analysis showed that the dual-active group had the greatest reduction in mean HDRS from baseline to week 2 (18.3), significantly greater than the sham tDCS + active rTMS (14.9), active tDCS + sham rTMS (9.2), and dual-sham (10.8) groups (p < 0.001). Post-hoc pairwise comparisons confirmed these reductions were greater for the active tDCS + active rTMS group than for all other groups (p < 0.001). Additionally, sham tDCS + active rTMS showed a significantly greater reduction in mean HDRS than both active tDCS + sham rTMS (p < 0.001) and dual-sham (p < 0.001) groups, while no significant difference was observed between active tDCS + sham rTMS and dual-sham (p = 0.10). Factorial analysis revealed significant main effects for both tDCS and rTMS as well as a significant interaction effect (p < 0.001), indicating a synergistic benefit of the combined intervention. At week 2, response rates were 85.0%, 73.3%, 30.0%, and 31.7%, while remission rates were 50.0%, 46.7%, 25.0%, and 13.3% for the dual active, sham tDCS + active rTMS, active tDCS + sham rTMS, and sham group, respectively (p < 0.001 for all group comparisons). At week 4, response rates climbed and were similar across all groups (~90%), but remission rates remained significantly higher in the dual-active group compared to other groups (p < 0.001). Participants tolerated the treatments well, with no serious adverse events reported. The most common adverse effects were headaches (n=8) and skin redness (n=7).

Impact: This double-blind, sham-controlled, factorial-design RCT demonstrates that combining tDCS and rTMS offers superior efficacy in reducing depressive symptoms compared to either modality alone, with evidence of synergistic effects. Notably, response rates climbed dramatically across all groups at week 4 (~90%), suggesting the

potential contribution of nonspecific factors. Limitations include the short trial duration, which limits insights into the long-term efficacy and durability of the combined approach. Additionally, the hospital-based setting may limit generalizability to outpatient populations, and the exclusion of patients with comorbid neuropsychiatric conditions further narrows its applicability. Future studies should investigate the mechanisms underlying this potential synergy, explore treatment optimization, and assess long-term outcomes in more diverse populations. Comparative studies with other neuromodulation techniques, such as ECT or accelerated rTMS, could provide further insight into the relative benefits of this dual-modality approach.

Zhou D, Li X, Wei S, et al. Transcranial Direct Current Stimulation Combined With Repetitive Transcranial Magnetic Stimulation for Depression: A Randomized Clinical Trial. JAMA Netw Open. 2024;7(11):e2444306. doi:10.1001/jamanetworkopen.2024.44306

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)