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# PULSE

A Monthly Update on Advances in Neuromodulation

Produced by the Neuromodulation Division of the Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA

Anthony Jang, MD, Managing Editor | AlJang@mednet.ucla.edu
Aaron Slan, MD, Editor-in-Chief | aslan@mednet.ucla.edu

## tDCS is Safe and Efficacious in Treating Symptoms of OCD, Depression, and Anxiety in OCD Patients

*Meghan Y. Reddy, MD reviewing Moshfeghinia et al., Neurosci Biobehav Rev., Apr 2025*

***This systematic review and meta-analysis evaluated the results from 10 RCTs on tDCS treatment in patients with OCD and found that tDCS reduced OCD, anxiety, and depression symptoms acutely after treatment. Effects were also sustained over time highlighting tDCS as a non-invasive method to treat OCD symptoms.***

OCD is often treated with SSRIs and CBT, while neuromodulation treatment is emerging as a novel alternative. tDCS, specifically, would represent a safe and noninvasive treatment option for OCD. However, existing systematic reviews and meta-analyses are based on a limited number of trials and have yielded inconsistent results. One, in particular, found no benefit of tDCS in reducing

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OCD symptoms. This most recent meta-analysis provides a unique opportunity to incorporate new RCT data into an updated assessment of the safety and efficacy of tDCS in patients with OCD.

This systematic review and meta-analysis followed PRISMA guidelines and searched major databases for RCTs that explored tDCS treatment in patients with OCD published through March 2025. Studies were included if participants were diagnosed with OCD and were treated with tDCS, either as monotherapy or in combination with other therapeutic modalities. OCD symptoms were measured using the Y-BOCS, depressive symptoms were measured using HAM-D, anxiety symptoms were measured with BAI, and clinical functioning was measured with CGI. Outcomes were assessed immediately after treatment (acute) and 1–2 months post-treatment (follow-up). Given the high degree of methodological heterogeneity, a random effects model was used. Heterogeneity was assessed using the $\chi^2$ and $I^2$ test. Sensitivity analyses evaluated the robustness and stability of the results. Egger's test and Begg's test were used to assess for publication bias.

Meta analysis results were reported separately for symptoms of OCD, depression, and anxiety. For OCD, a total of 10 RCTs met inclusion criteria (total n = 386). There was a statistically significant improvement in OCD symptoms as assessed by change in Y-BOCS acutely after treatment with tDCS (SMD = -0.56, 95 % CI: −0.87 to −0.26; $I^2$ = 49.85 %) which was sustained at follow-up (SMD = −0.69, 95 % CI: −1.22 to −0.17; $I^2$ = 71.36 %). For depressive symptoms, 6 studies were included (total n = 261) in the meta-analysis which found a statistically significant improvement in depressive symptoms as assessed by change in HAM-D acutely after treatment with tDCS (SMD= -1.57, 95 % CI −2.64 to −0.50; $I^2$= 93.47 %) which was sustained at follow-up (SMD= -2.02, 95 % CI −3.00 to −1.04; $I^2$= 83.3 %]). For anxiety symptoms, meta-analysis of 5 studies (total n = 225) showed a statistically significant improvement in anxiety symptoms as assessed by change in BAI acutely after treatment with tDCS (SMD= -1.11, 95 % CI −1.85 to −0.37; $I^2$= 74.43 %), but this effect was not sustained at follow-up (SMD= -1.13, 95 % CI −3.05–0.78, $I^2$=93.89 %). For CGI scores, analysis of 3 studies (total n = 155) yielded a paradoxical increase in CGI scores after treatment with tDCS (SMD=0.4, 95 % CI 0.08–0.72; $I^2$=0 %). Incidence of adverse effects showed a non-significant OR of 1.20 (95 % CI: 0.86, 1.68; p = 0.280; $I^2$ = 56.67 %) across all studies, although specific adverse events such as tingling, skin redness, neck pain, and burning sensations were significantly increased for active versus sham tDCS.

**Impact: This systematic review and meta-analysis examines both the acute and subacute effects of tDCS, offering insights into immediate and sustained therapeutic benefits for treatment of OCD, anxiety, and depressive symptoms in patients with OCD. By focusing on RCTs, the findings support the hypothesis that tDCS is beneficial for alleviating OCD and associated mood symptoms, with an overall adverse effect profile comparable to that of sham treatment. However, this study is limited by the small number and sample sizes of available trials, substantial heterogeneity across studies ($I^2$ = 49.85–93.47%), evidence of potential publication bias (as indicated by Egger's and Begg's tests, p < 0.05), and subgroup analyses suggesting that the geographic origin of the studies significantly influenced the results, warranting cautious interpretation.**

*Moshfeghinia R, Najibi A, Golabi F, et al. Efficacy and safety of transcranial direct current stimulation (tDCS) in patients with obsessive-compulsive disorder (OCD): A systematic review and meta-analysis of randomized controlled trials. Neurosci Biobehav Rev. 2025;173:106171. doi:10.1016/j.neubiorev.2025.106171*

## Dual-Modality Neurostimulation with tDCS and rTMS Improves Short- and Long-Term Outcomes in Chronic Insomnia

*Sheyna M. Nathwani, MD, reviewing Zhou et al., BMC Medicine, 2024 Nov.*

***In a randomized, double-blind, parallel-controlled trial of adults with chronic insomnia, combined tDCS and rTMS produced significantly greater reductions in sleep quality scores than either monotherapy. These improvements were accompanied by higher response and remission rates after four weeks of treatment and persisted three months post-treatment.***

Insomnia disorders are among the most common sleep disturbances, affecting 10–20% of adults, with about half developing chronic symptoms that contribute to substantial health burdens. First-line medications' adverse effects can limit use, driving interest in non-pharmacologic options such as rTMS and tDCS. As independent interventions, both have shown to decrease Pittsburgh Sleep Quality Index (PSQI) scores, reflecting improved subjective sleep quality. This study is the first to evaluate combined rTMS and tDCS therapy against each monotherapy for chronic insomnia.

In this randomized, double-blind, parallel-controlled trial, 157 adults with chronic primary insomnia, diagnosed per ICD-11 criteria and with PSQI > 5, were enrolled. All participants used zopiclone before and throughout the trial. Participants were randomly assigned to one of three groups: active tDCS and rTMS (Combined treatment group), sham tDCS with active rTMS (Active rTMS group), or active tDCS with sham rTMS (Active tDCS group). Each received 20 treatment sessions over 4 weeks. tDCS was applied bilaterally to the DLPFC at 2 mA for 20 minutes, followed 30 minutes later by rTMS delivered at 1 Hz to the right DLPFC. Sham protocols simulated the sensations of stimulation. Assessments occurred at baseline, 2 weeks, 4 weeks, and 3 months post-treatment. Primary outcomes included PSQI response rate (≥50% symptom reduction) and remission rate (PSQI < 5). Secondary measures evaluated the Hamilton Depression (HAMD) and Hamilton Anxiety (HAMA) rating scales.

At 2 weeks, total PSQI scores differed significantly between the Combined and Active tDCS groups (7.36 ± 1.61 vs. 9.31 ± 2.28, $p < 0.001$) and between the Combined and Active rTMS groups (7.36 ± 1.61 vs. 8.42 ± 2.70, $p < 0.05$). Participants in the Combined group also showed greater improvements in sleep quality, duration, and efficiency compared with the Active tDCS group ($p < 0.05$). These effects persisted at 4 weeks and 3 months post-treatment, with significantly lower total PSQI scores in the Combined versus Active tDCS (6.27 ± 2.44 vs. 8.78 ± 2.87, $p < 0.001$ at 4 weeks; 7.02 ± 1.70 vs. 9.16 ± 2.21, $p < 0.001$ at 3 months) and versus Active rTMS groups (6.27 ± 2.44 vs. 7.68 ± 2.89, $p < 0.05$ at 4 weeks; 7.02 ± 1.70 vs. 8.12 ± 2.04, $p < 0.05$ at 3 months). The Combined treatment group demonstrated the highest response and remission rates, followed by the Active rTMS and Active tDCS groups. Response rate differences were significant at 2 weeks ($\chi^2 = 22.507$, $p < 0.001$), 4 weeks ($\chi^2 = 27.717$, $p < 0.001$), and 3 months ($\chi^2 = 8.191$, $p = 0.017$). Remission rates were also highest in the Combined group, with significance only at 4 weeks ($\chi^2 = 13.579$, $p = 0.001$). At 3 months post-treatment, PSQI improvement remained significant among participants aged 18–50, but not 51–65. Additionally, male participants showed significantly greater PSQI reduction than females. While HAMA scores did not differ significantly, total HAMD and insomnia factor sub-scores were significantly lower in the Combined group than in the Active rTMS and Active tDCS groups ($p < 0.05$). Treatment was well tolerated, with few adverse effects and preservation of blinding integrity.

**Impact: This randomized, double-blind trial demonstrates that combined tDCS and rTMS therapy provides greater and more sustained improvement in insomnia symptoms than either intervention alone. The findings suggest durable therapeutic effects extending at least three months post-treatment, underscoring the promise of combined neurostimulation in chronic insomnia management. However, reliance on subjective sleep measures and concurrent zopiclone use may limit interpretation, highlighting the need for future studies to incorporate objective sleep assessments, control for medication effects, and examine the influence of comorbid depression and anxiety.**

*Zhou, Q., Liu, Z., Yu, C. et al. Effect of combined treatment with transcranial direct current stimulation and repetitive transcranial magnetic stimulation compared to monotherapy for the treatment of chronic insomnia: a randomised, double-blind, parallel-group, controlled trial. BMC Med 22, 538 (2024). https://doi.org/10.1186/s12916-024-03751-y*

## Post-operative rTMS targeting DLPFC decreases incidence of delirium in elderly patients

*Kaleab Tessema, MD PhD, reviewing Zhou & Gao et al., Brain Stimulation, 2024 Dec*

***In a double-blind RCT including elderly patients undergoing major abdominal surgery, rTMS targeting the left DLPFC in the immediate post-operative period decreased the incidence of post-operative delirium in the 3 days after surgery compared to sham rTMS.***

Post-operative delirium (POD) causes significant morbidity and mortality, especially in elderly patients undergoing major surgeries. There are no targeted interventions that have been established for prevention and treatment of POD. Thus, there is a critical need to better understand the mechanistic drivers of POD and how they can be targeted. rTMS presents an appealing candidate to address POD given its relative safety, technical versatility (via fine tuning of parameters), and demonstrated ability to improve cognitive performance. While the mechanisms by which rTMS affects cognitive performance are not completely understood, studies have implicated synaptic remodeling and neuronal excitability as possible mediators. In the context of rTMS for cognitive disorders, the DLPFC is commonly targeted due to its role in modulating memory, attention,

and emotion. Finally, high-frequency rTMS in particular has demonstrated positive effect on neurocognitive function in patients with neuropsychiatric conditions. Thus, the authors aimed to investigate whether (and how) 10Hz rTMS targeting the left DLPFC could represent a safe and effective strategy for prevention of POD in elderly patients undergoing major abdominal surgeries.

This single-center, double-blind RCT included 122 patients who were at least 60 years of age and scheduled for major abdominal surgery. 61 patients were randomized to the treatment group and were administered a single session of rTMS to the left DLPFC (10Hz, 2000 pulses, 25 s ITI) immediately after extubation. 61 patients were randomized to the control group and were administered sham rTMS. Data were analyzed via intention-to-treat, with 7 patients (3 in the treatment group, 4 in the control group) lost to follow-up due to admission to intensive care units. The primary outcome was POD incidence within the three days following the surgery. Patients were evaluated via the Confusion Assessment Method (CAM) at least two hours after the surgery and twice daily thereafter. Secondary outcomes included delirium subtype, delirium duration, delirium severity (via Delirium Rating Scale Revised-98), depression (via Self-Rating Depression Scale), anxiety (via Self-Rating Anxiety Scale), pain (via Numeric Rating Scale), and post-rTMS levels of brain-derived neurotrophic factor (BDNF; indirect measure of neuroplasticity) and neurofilament light chain (NfL; indirect measure of neuronal damage).

Patients in the treatment group had a lower incidence of delirium (11.5% vs 29.5%, RR 0.39, p=0.01) compared to the control group, with no significant difference in duration (median 2 days, p=0.78), peak severity (mean 25.6, p=0.31), or subtype composition of delirium. Additionally, there were lower depression scores at the first time point (26.0 [IQR, 25.0–26.0] vs. 29.0 [IQR, 28.0–30.3], p<0.001), lower anxiety scores at the first time point (28.0 [sic] [IQR, 25.0–27.0] vs. 28.0 [IQR, 27.8–29.3], p<0.001), lower post-operative pain scores (p<0.05 for all time points), lower patient-controlled analgesia dosage (50.0 vs 54.0 mL, p<0.001), higher BDNF levels (8.47 vs 5.76 ng/mL, p=0.02), and lower NfL levels (0.05 vs 0.06 ng/mL, p=0.02) in the treatment group compared to the control group. There were no significant differences in incidence of post-operative adverse events, duration of hospitalization, or average hospitalization cost. Mediation effect analysis, which was performed to better understand the mechanisms by which rTMS may reduce POD risk, suggested that increasing BDNF levels (z=−3.72, p<0.001) is a candidate mechanism for this effect, while the aforementioned differences in NfL levels, depression scores, anxiety scores, and patient-controlled analgesia dosage were not significant candidate mechanisms.

**Impact: This study suggests that rTMS targeting left DLPFC may represent an effective strategy for prevention of post-operative delirium in elderly patients undergoing major abdominal surgery. rTMS may exert this effect via increasing levels of BDNF and thereby possibly promoting neuroprotection and neuroplasticity. Further investigation can focus on increasing sample size, expanding to multiple clinical sites, improving blinding via enhanced sham stimulation, adding baseline measures of BDNF and NfL to account for pre-existing differences, and testing different TMS protocols to expand upon these results and optimize parameters for this novel indication.**

*Zhou C, Gao YN, Qiao Q, et al. Efficacy of repetitive transcranial magnetic stimulation in preventing postoperative delirium in elderly patients undergoing major abdominal surgery: A randomized controlled trial. Brain Stimulation. 2024;18(1):52-60. doi:https://doi.org/10.1016/j.brs.2024.12.1475*

## Cerebellar cTBS Demonstrates Promising Benefits in Drug-Resistant Epilepsy

*Praveen P. Rajaguru MD, MPH reviewing Wang et al., Epilepsia, 2024 Nov*

***In this double-blind, single-center, sham-controlled, crossover RCT, continuous theta burst stimulation (cTBS) of the bilateral cerebellar dentate nucleus yielded a 25% reduction in seizure burden and a higher proportion of patients with 50% or greater reduction in seizure frequency with good tolerability.***

Roughly one-third of patients with epilepsy continue to experience seizures despite optimal pharmacological treatment (i.e. drug-resistant epilepsy, or DRE). The cerebellar dentate nucleus (CDN) has anatomical connectivity with various cortical and thalamic circuits and has been implicated in seizure pathophysiology. Animal models and pilot studies have shown that it may be an appropriate target for non-invasive neuromodulation to decrease seizure burden. This trial tested whether cTBS to the dentate nucleus (CDN-cTBS) could reduce seizure burden in DRE.

This double-blind, single-center, sham-controlled, crossover RCT studied adults with DRE ≥ 2 years and a baseline seizure frequency of ≥2/month. Eligible and included subjects (n=44) were randomized to active-first (n=21) or sham-first (n=23) groups, with ten treatments performed prior to a two-month washout period and cross-over. The active treatment consisted of cTBS (three stimulus pulses at 50 Hz repeated at 5 Hz) for a total of 600 stimuli within 40 s. The left and right CDN were sequentially stimulated twice with 5-minute intervals between each treatment (left CDN-cTBS, 5-min interval, right CDN-cTBS, 5-min interval, left CDN-cTBS, 5-min interval, and right CDN-cTBS), resulting in a total of 1200 stimuli per hemisphere. Sham treatment was delivered at 10% of the MT. Primary outcomes were the percentage of seizure reduction and the proportion of patients with ≥50% reduction in seizure frequency from baseline within 2 months following cTBS treatment. Secondary outcomes included the number of interictal epileptiform discharges (IEDs) recorded within 24 hours at the first and second months after treatment, psychometrics (e.g., MoCA, HAM-A, HAM-D), and adverse events.

A total of 38 patients were included in the ITT analysis (N=18 in the active-first group; N=20 in sham-first group), with a median baseline seizure frequency of 4.0 seizures per month. The groups did not significantly differ in baseline characteristics. The difference in seizure reduction was 25% greater with active compared to sham stimulation (95% CI 5%–46%; p = .018). The difference in 50% responder rate was 24% greater with active compared to sham stimulation (95% CI 11%–40%; p=.029). On average, 25.50 fewer IEDs were observed within 24 hours of last treatment in active compared to sham stimulation (95% CI = −116.50 to −2.50, p=.020). None of the psychometrics or questionnaires had significant differences across treatments after 2 months. Minimal adverse effects were reported during active stimulation with headache (N=2, 5%), tinnitus (N=1, 3%) and dizziness (N=1, 3%), occurring and resolving spontaneously after stimulation. No seizures or serious adverse events were observed.

**This double-blind, single-center, sham-controlled, crossover RCT suggests that CDN-cTBS may be an effective and safe option in reducing seizure burden for adults with DRE. Active CDN-cTBS created a significant reduction in seizure frequency when compared to sham treatment. Coupled with the decrease in IEDs within 24 hours of treatment, this study suggests both clinical and electrophysiological benefits. No serious adverse effects were observed, supporting high tolerability. A caveat to the observed efficacy is that symptoms were only observed for two months following each treatment, and reduction in IEDs beyond the 24-hour posttreatment period was not observed. In addition, carryover effects due to possible inadequate washout, as well as self-unblinding that can occur with the crossover study design may have led to an inaccurate estimate of the true efficacy of CDN-cTBS. Future studies may consider increased sample sizes and heterogenous populations, studying different treatment lengths and washout periods, and using fMRI and other imaging methods to further elucidate the mechanism of efficacy. In addition, testing of additional anatomical targets, identifying patient predictors of response, and developing optimal dosing protocols will need to be identified to maximize clinical efficacy.**

*Wang YY, Ma L, Shi XJ, et al. Cerebellar transcranial magnetic stimulation to treat drug-resistant epilepsy: A randomized, controlled, crossover clinical trial. Epilepsia. 2025;66(1):240-252. doi:10.1111/epi.18168*

*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)*