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# PULSE

A Monthly Update on Advances in Neuromodulation

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## Neurostructural Frontolimbic Changes after rTMS Treatment in Adolescents with TRD

*Nicole Wong reviewing Seewoo et al. Int J Neuropsychopharmacol 2022 Aug*

***A pooled sample of 63 adolescents with MDD, TRD, and healthy controls suggests that those with MDD and TRD had decreased amygdala volumes relative to healthy adolescents, and that this volume reduction may be normalized by TMS treatment***

Treatment Resistant Depression (TRD), defined as the failure to respond to initial treatment with SSRIs and/or CBT, is clinically common though poorly characterized in the adolescent population. rTMS represents a potential treatment for adolescents with TRD, yet the mechanism of action is incompletely understood. The authors aimed to characterize the adolescent TRD phenotype and examine its response to treatment by obtaining brain MRI volumetric measures before and after rTMS therapy.

## IN THIS ISSUE:

The authors pooled four prior study samples from two research programs to form the study sample, with two of the studies including rTMS (one open-label, one RCT). TRD was defined as having at least one prior failed trial of antidepressant medications; participants who had been unable to complete an antidepressant trial of adequate dose and duration due to intolerance were included if they demonstrated intolerance of four or greater antidepressant medications within one episode. Two of the studies required depressed patients to score greater than 40 on the Children's Depression Rating Scale-Revised (CDRS-R), and one required a score of 20 or greater on the HDRS. Participants from the randomized controlled trial of rTMS were not taking antidepressant or psychotropic medications, whereas in other studies this was allowed. Exclusion criteria across studies were consistent and included contraindications to TMS, pregnancy and/or lack of acceptable birth control for women, comorbid psychotic, bipolar, active substance use, or active eating disorders, as well as OCD and PTSD. Both rTMS trials utilized 3000 pulses of 10Hz stimulation delivered to left DLPFC at 120% MT, and patients received up to 36 treatment sessions over six to nine weeks. All subjects had baseline MRI scans, and TMS-treated subjects also had pre- and post-treatment imaging, allowing for examination of structural changes. Using automatic segmentation, the authors obtained baseline and post-TMS brain MRI volumetric measures.

The pooled sample consisted of healthy adolescents (n=30), adolescents with MDD (n=19), and adolescents with TRD (n=34) with no significant differences in age or gender among groups. Adolescents with TRD and MDD had decreased baseline total amygdala (TRD and MDD: -5%, $p = 0.032$) and caudal anterior cingulate cortex volumes (TRD: -3%, $p = 0.030$; MDD: -0.03%, $p = 0.041$) compared with healthy adolescents. Comparisons between the MDD and TRD groups were not discussed. After 6 weeks of active rTMS, adolescents with TRD had increased total volumes relative to baseline in the amygdala (+4%, $p < 0.001$), DLPFC (+0.5%, $p = 0.024$), and dorsomedial prefrontal cortex (DMPFC; +0.6%, $p = 0.039$), with decreased volume in the ventrolateral prefrontal cortex (VLPFC; -0.8%, $p = 0.047$). Subregion analyses revealed significant volume changes in only the right amygdala and left DLPFC, DMPFC, and VLPFC. Changes in CDRS-R scores were significantly correlated with volume changes in the left DLPFC ($r = -0.52$, $p = 0.028$), left DMPFC ($r = -0.51$, $p = 0.039$), and left VLPFC ($r = -0.52$, $p = 0.026$), but not with amygdala volume changes. There were no significant cerebral volume changes associated with sham rTMS.

**Impact: This retrospective analysis of pooled data from open and controlled trials suggests that neurostructural differences exist in adolescent depression compared to controls, and that TMS in adolescents with depression has the potential to rectify some of these volumetric differences. Limitations include small sample size and the fact that data were pooled from studies performed at different sites and times, so that the effects of site or protocol differences contributing to the observed differences cannot be ruled out. Future work should prospectively examine brain structure and the effects of rTMS treatment in a larger sample size to confirm the authors' findings.**

*Seewoo BJ, Rodger J, Demitrack MA, et al. Neurostructural Differences in Adolescents With Treatment-Resistant Depression and Treatment Effects of Transcranial Magnetic Stimulation. Int J Neuropsychopharmacol. 2022;25(8):619-630. doi:10.1093/ijnp/pyac007*

## tDCS Accelerated Fear Extinction and Safety Learning in Adults with OCD

*Ivana Viani, MD, reviewing Adams et al. Depress Anxiety 2022 Jan*

***In two small pilot studies, healthy adults who received frontopolar tDCS showed changes in functional connectivity between the default mode and salience networks, and adults with OCD demonstrated faster onset of benefit from a behavioral intervention***

Exposure and response prevention therapy is a common and effective treatment for OCD, which involves exposure to feared stimuli with modification of the patient's response. Not all patients with this disorder benefit from behavioral therapy, however, so the authors investigated whether tDCS applied to brain regions involved in fear and safety learning would alter patients' ability to benefit from exposure treatments in two separate experiments.

In the first study, 18 healthy adult community volunteers (mean age 36.4; 44% female, 55% white) were recruited to test how tDCS altered functional connectivity in the medial prefrontal cortex (an area associated with safety learning). Resting state fMRI scans were obtained prior to and after 20 minutes of frontopolar tDCS (1.5mA with 30s ramp up/down) delivered with the anode over Fpz and five cathodes surrounding it. In the second study, 24 adults with OCD (mean age age 33.3; 75% female, 75% white) were recruited for an RCT. Patients were required to not be on medication or have a stable

dose for ≥1 month, and those with manic, psychotic, or major neurological illnesses, people on the autism spectrum, persons with active substance use disorder, and those with contraindications to tDCS were excluded. After selecting an individualized exposure exercise and rating their experience on the subjective units of distress scale (SUDS), participants were randomized to receive frontopolar tDCS (n=13; identical to the first study) or sham (n=13; same montage but with no current applied) delivered over 20 minutes. After tDCS, all patients underwent five 10-minute in vivo exposures, completing SUDS each minute of the exposure. Participants returned 18-36 hours post-tDCS to complete another set of five 10-minute exposure trials without tDCS. Participants and personnel facilitating the exposure trials were blinded; staff administering tDCS were not.

The first study revealed a statistically significant decrease in right hemispheric connectivity between the frontal pole and anterior insula and basal ganglia and increased frontal pole connectivity with the middle and superior frontal gyri (all $p < 0.001$, corrected for multiple comparisons). Significantly decreased connectivity between the default mode and salience networks was also observed ($p < 0.005$, corrected). In the second study, the active tDCS group showed faster decrease in SUDS during the therapeutic exposure challenge with an average reduction in SUDS of 64.6% from the beginning of the first exposure trial to the end of the last exposure trial versus a 24.2% reduction in the sham group ($p<0.01$). Of note, 42% of the sham-tDCS sample was taking psychotropic medications at the time of the study, compared to 25% of the active-tDCS group.

**Impact: Frontopolar tDCS was associated with statistically significant alterations in functional connectivity between default mode and salience networks in healthy adults, and increased speed of fear extinction learning in patients with OCD. These results suggest that tDCS may augment the efficacy of exposure and response prevention therapy in adults with OCD. These results are encouraging, particularly given the ease of use and safety of tDCS treatment. The results must be interpreted with caution due to the small sample size, brevity of exposure intervention studied, absence of long-term follow up, and the subjective safety learning measurement used. Further investigation in a larger number of subjects with more rigorous testing of efficacy is needed to support application to clinical practice.**

*Adams TG, Cisler JM, et al. Transcranial direct current stimulation targeting the medial prefrontal cortex modulates functional connectivity and enhances safety learning in obsessive-compulsive disorder: Results from two pilot studies. Depress Anxiety. 2022 Jan;39(1):37-48. doi: 10.1002/da.23212.*

## ECT for Late-Life Depression: Long-Term Outcomes May Be Comparable to Other Treatments

*David M Carlson, MD reviewing Lambrichts et al. Am J Geriatr Psychiatry 2022 May*

***A five-year follow up of ECT for late-life depression provides long-term data on relapse and risk profile***

Electroconvulsive therapy (ECT) is among the most effective treatments for late-life depression (LLD), which affects nearly 2% of people 55 or older. While ECT leads to remission in 60-80% of cases, approximately half of these patients will experience relapse of depressive symptoms within one year despite continuation treatment. There is little available research on longer-term outcomes and side effects following an acute course of ECT for LLD. In this study, the authors examined relapse, cognition, and mortality over five years after a course of ECT for LLD as a follow up of the Mood Disorders in Elderly Treated with ECT (MODECT) study.

In the MODECT study, 110 adults with a mean age of 72.9 years underwent twice-weekly ECT for LLD with a constant-current brief-pulse (0.5 – 1.0 ms) protocol, initially right unilateral ECT at 6x the seizure threshold. Patients were switched to bilateral ECT at 1.5x seizure threshold if they showed no clinical improvement after six right unilateral treatments or developed more severe symptoms. Treatments were continued until remission (MADRS score <10) or the patient showed no further improvement for two consecutive weeks after a minimum of six unilateral and six bilateral treatments. In this follow up study, the authors looked at outcomes up to five years after the end of the initial study. Cognition and mortality outcomes were assessed from the entire original sample of 110 patients.

Of the original 110 patients, 86 (78%) showed remission or response (decrease in MADRS score of at least 50% from baseline) to the acute treatment, with five-year follow up data available for 85 of 86 patients. Relapse – defined as restart of ECT, hospital admission, or suicide attempt/completion – occurred in 57 patients (67%) during the five-year period, with 45 (80%) of those occurring in the first two years. No correlations were found between relapse and gender, age, number of prior admissions, treatment resistance, presence or absence of psychotic features, or symptom severity at completion of the acute ECT course. Cognitive data were available for 67 (61%) of the original sample, and 26 (39%) demonstrated cognitive impairment (either formally diagnosed with

dementia or with aberrant neuropsychological assessments) at five years after ECT. No association was found between cognitive impairment and clinical characteristics before, during, or immediately following ECT. Five-year mortality following the course of ECT for LLD was 28%, with cardiovascular disease and neoplasm the two most prevalent causes of death. Older age and number of previous psychiatric hospitalizations were associated with 14% (per additional year older) and 10% (per additional hospitalization) increases in relative mortality risk within this cohort. These risks were not explicitly compared with those associated with other acute treatments for LLD as a part of this analysis, though the authors go on to discuss how the risks of ECT are comparable to those of other LLD treatments.

**Impact: This study of five-year outcomes following ECT for LLD found 67% of patients experienced relapse, 39% experienced cognitive impairment, and 28% experienced mortality. This cohort study certainly provides valuable insight, and future work would ideally examine both how these risks compare to other acute treatments for depression directly, and how ECT can be optimized to reduce these risks.**

*Lambrichts S, Wagenmakers MJ, Vansteelandt K, et al. Long-term Outcome Following Electroconvulsive Therapy for Late-Life Depression: Five-Year Follow-up Data From the MODECT Study. Am J Geriatr Psychiatry. 2022;30(12):1283-1294. doi:10.1016/j.jagp.2022.05.010*

# Meta-Analysis Suggests High-Frequency rTMS May Be an Effective Treatment for PTSD

*David M Carlson, MD reviewing Harris & Reece J Affect Disord 2021 Jun*

***This meta-analysis of 19 studies finds rTMS – particularly high-frequency rTMS – to be a highly effective treatment for PTSD, though findings are limited by the quality of the current literature***

The lifetime risk of PTSD in the United States is 8.7%, and current treatments include SSRI medications and psychotherapies including prolonged exposure, cognitive processing, or eye movement desensitization and reprocessing therapy. These interventions lead to full remission in about a third of patients, indicating a need for additional treatment modalities.

In this meta-analysis, the authors searched PsychINFO, Scopus, Google Scholar, and Medline through September 15, 2020, for publications including keywords related to rTMS and PTSD. The authors selected 19 primary research articles, including 10 RCTs, six open trials, two chart review studies, and one double-blind cross-over study. Only studies providing information sufficient to calculate an independent effect size using outcome measures from PTSD questionnaires were included. Statistical analyses were completed on 26 active rTMS groups comprised of 376 participants. Mean ages ranged from 27-55, and outcome measures included CAPS, PCL, IES and M-PTSD scales. rTMS parameters varied between the studies as follows: nine active TMS groups received low frequency stimulation (1 Hz) vs. 17 groups with high-frequency (4+ Hz); seven groups received <15,000 pulses per treatment vs. 14 groups with 15,000-36,000 pulses vs. five groups with >36,000 pulses; 12 groups received <11 treatment sessions vs. four groups with 11-19 sessions vs. 10 groups with >19 sessions; and four groups received stimulation targeting the left DLPFC vs. 13 groups targeting the right DLPFC vs. nine groups targeting other regions. Notably, all four studies targeting left DLPFC used high-frequency stimulation, whereas other cortical targets used a mix of low- and high-frequency stimulation.

A random effects model found a strong overall positive effect size of d = 1.17 (95% CI: 0.89-1.34). Further analyses indicated a significantly greater effect for high frequency rTMS (d=1.44) compared to low frequency (d=0.72, p<0.001). No significant correlations were found between larger doses (e.g., number of sessions, number of pulses, or pulse intensity) and stronger treatment effects. The authors also found no difference in efficacy between rTMS targeting the left vs. right DLPFC, however notably absent from this analysis was a comparison of rTMS targeting accounting for stimulation frequency. A significant Q-statistic of 93.9 and $I^2$ value of 73.3 (p<0.001) suggested that unexplained variance was present in the data due to differences among the studies, and a funnel plot suggested higher standard errors among studies with higher effect sizes.

**Impact: This meta-analysis supports the efficacy of rTMS treatment of PTSD. The results suggest that high-frequency stimulation delivered to left DLPFC may be superior to low-frequency stimulation delivered to other targets, although there was no difference detected overall between left or right DLPFC targets, and no significant dose-response effects. The quality of the literature base was only fair, reflecting a high degree of heterogeneity among the studies in approaches to treatment. Future studies should perform head-to-head comparisons of different forms and sites of stimulation, including iTBS, in order to better identify those parameters that most affect treatment outcome in PTSD.**

*Harris A, Reece J. Transcranial magnetic stimulation as a treatment for posttraumatic stress disorder: A meta-analysis. J Affect Disord 2021 Jun 15;289:55-65.*

# Abbrevations

*cTBS (continuous theta burst stimulation)*
*DBS (deep brain stimulation)*
*dTMS (deep transcranial magnetic stimulation)*
*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)*
*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)*

*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)*

*ADHD (attention-deficit/hyperactivity disorder)*
*AUD (alcohol use disorder)*
*GAD (generalized anxiety disorder)*
*MDD (major depressive disorder)*
*OCD (obsessive compulsive 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)*
*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)*
*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)*
*OFC (orbitofrontal cortex)*
*SMA (supplementary motor area)*