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PULSE

A Monthly Update on Advances in Neuromodulation

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rTMS May be More Effective in OCD Patients with Lower Levels of SSRI Resistance

Nicole Wong reviewing Pellegrini et al. Compr Psychiatry 2022 Oct

A meta-analysis of 23 blinded RCTs suggests that rTMS has the largest effect size in patients who are not resistant to SSRIs or who have failed to respond to only one SSRI.

Several meta-analyses report positive effects for rTMS in OCD, but it is unclear which patients are most likely to benefit. By classifying study participants into those with SSRI-resistant and non-resistant OCD using standardized criteria, the authors seek to explore the placement of rTMS in a sequenced-care algorithm of OCD, which includes SSRIs and CBT with Exposure and Response Prevention.

The authors identified studies that 1) assessed participants meeting any ICD/DSM OCD diagnostic criteria, 2) included adolescents and/or adults, 3) were RCTs employing an rTMS therapeutic

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intervention against sham, and 4) were written in English from the earliest publication to July, 2021. The authors did not specify the rTMS parameters of each included study, though they note a high degree of heterogeneity. Targets of the included studies included SMA, OFC, DLPFC, and "deep" TMS. SSRI-resistance was classified using criteria published by Pallanti et al. (2006) and included: stage 1/not resistant, stage 2/one failed SSRI trial, stage 3/two failed SSRI trials, and stage 4/two or more failed SSRI trials and one or more failed CBT trials. The presence of researcher allegiance bias, or bias towards success of the investigational arm of treatment, was assessed using the "researcher allegiance assessment tool" developed by Cuijpers et al. (2012). Hedges' *g* was computed as a marker of effect size for each study. When multiple time points were available for assessment in studies, post-treatment values were used. When trials had multiple interventions (e.g., rTMS at different frequencies), control sample sizes were divided by the number of comparisons made to avoid biasing effect size weighting.

The authors included 23 independent studies (total of 25 comparisons) in their final analysis. Overall, rTMS significantly reduced YBOCS scores (*g*: -0.47; 95% CI: -0.67 to -0.27, $p < 0.001$) with a moderate effect size heterogeneity (I^2 = 39.8%). Subgroup analysis investigating SSRI-resistance as a moderator of response found that studies meeting criteria for stage 1 or stage 2 resistance produced significant results, whereas those meeting criteria for the more resistant stage 3 or stage 4 produced non-significant results: Stage 1 (k=7) *g*: -0.65 (95%CI: -1.05 to -0.25), $p<0.001$, I^2 = 17.4%; Stage 2 (k=6) *g*: -0.47 (95%CI: -0.86 to -0.09), $p=0.02$, I^2 = 0%; Stage 3 (k=4) *g*: -0.39 (95%CI: -0.90 to 0.11), $p=0.13$, I^2 = 84.3%; Stage 4 (k=8) *g*: -0.36 (95%CI: -0.75 to 0.03), $p=0.07$, I^2 = 20.0%. The smaller number of studies classified as stage 3 of SSRI resistance likely contributed to the greater heterogeneity among those studies, with a bimodal distribution involving some studies with a large effect and some with a null effect. The only other significant moderator of the effect size for YBOCS was the baseline severity of depressive symptoms as measured by the HDRS (k=7, $F=6.92$, $p=0.04$). Percentage of females, age, baseline anxious symptoms, and baseline severity and duration of OCD were not found to be significant moderators of treatment. All studies met at least one assessment criterion suggesting the presence of researcher allegiance.

Impact: This meta-analysis of 23 RCTs evaluating rTMS for OCD is the first meta-analysis to stage SSRI-resistance using standardized criteria and examine its moderating effects. The findings suggest that rTMS is more effective for treatment of patients with lower levels of SSRI medication resistance. A limitation of this study is that it pooled several different approaches to rTMS treatment, some of which may be less effective. More modern approaches to treatment (e.g., deep TMS, multi-locus rTMS stimulation) may be more effective for patients with higher medication resistance. Future studies should separately examine different approaches to rTMS treatment to determine which may be most effective for more highly treatment resistant patients.

Pellegrini L, Garg K, Enara A, et al. Repetitive transcranial magnetic stimulation (r-TMS) and selective serotonin reuptake inhibitor-resistance in obsessive-compulsive disorder: A meta-analysis and clinical implications. Compr Psychiatry. 2022;118:152339. doi:10.1016/j.comppsych.2022.152339

High-frequency rTMS to the Precuneus May Preserve Cognitive Function in Mild-Moderate Alzheimer's Disease

David Lee reviewing Koch et al. Brain 2022 Nov

This phase 2 randomized, sham-controlled trial demonstrates that 20 Hz rTMS of the precuneus may preserve cognitive and functional capacity in those with mild-to-moderate Alzheimer's disease (AD).

Prior work has suggested that the neuropathological changes in AD, particularly amyloid plaque and neurofibrillary tangle deposition, start in the posterior cortical regions of the brain including the precuneus, which serves as a hub for the Default Mode Network (DMN). Based on this work, the authors proposed that precuneal rTMS in patients with early AD might slow cognitive and functional decline. Their initial pilot RCT of 2-weeks of rTMS in patients with mild AD demonstrated enhancement of long-term memory and increased neural activity in the DMN. These same authors then expanded their work into this phase 2, sham-controlled, double-blinded trial of rTMS in mild-to-moderate AD patients.

The authors recruited 45 patients (n=22 active, n=23 sham) aged 50-85 (mean: 73.7) years with Clinical Dementia Rating (CDR) scores of 0.5-1 (mild-moderate dementia), cerebrospinal fluid evidence of amyloid and tau pathology, one caregiver, at least 6 months of conventional acetylcholinesterase inhibitor treatment, and without other co-morbid neuropsychiatric disorders. Patients received a total of 24 weeks of treatment, with two

weeks of five sessions per week followed by 22 weeks of one session per week maintenance treatment. Each session consisted of 40 trains of 40 pulses of 20 Hz rTMS. The coil location over the precuneus was based on individual structural imaging with Montreal Neurological Institute (MNI) coordinates. Stimulation intensity was determined utilizing a modified E-field correction to adjust to the equivalent of 100% MT (determined using TMS Evoked-potentials [TEPs] that included simultaneous EEG assessment of cortical excitability) over M1. A sham coil was used to provide sham stimulation to the same area. A general linear mixed model (GLMM) was used to compare between groups and included the composite CDR (CDR-SB) score (primary outcome), Mini-Mental State Examination (MMSE) score, Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale (ADCS-ADL), and Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-COG), as well as cortical excitability as determined by TEP at baseline and week 24 of the study.

There were no significant between-group differences in demographics and baseline clinical assessment scores. In the active rTMS group, CDR-SB, MMSE, and ADCS-ADL scores remained stable over the 24 weeks of the study, whereas these measures reflected significant cognitive and functional decline in the sham group. Mean changes in the active group were generally less than a single point of change on each scale (CDR-SB = -0.25, ADCS-ADL = -0.70, ADAS-COG = -0.67 MMSE = 0.30), while mean changes in the sham group were significantly larger (CDR-SB = -1.42, ADCS-ADL= 7.54, ADAS-COG = -4.19 MMSE = 1.75), with group by time interactions supporting the statistical significance of these differences (CDR-SB p=0.038, ADCS-ADL p<0.001, ADAS-COG p<0.001, MMSE p=0.041).Two additional scales were examined and no between-group differences were observed. Additionally, TEP amplitude remained stable for the treatment group, whereas decreased amplitude was observed in the sham group (mean decrease of 1.23 microvolts, group-time interaction p= 0.011).

Impact: In this randomized sham-controlled study of 20 Hz rTMS to the precuneus in patients with mild-moderate AD, precuneal rTMS was found to be an effective non-invasive treatment method for preserving cognitive and functional capacity. Additionally, this study provides insight into a possible mechanism of this cognitive and functional preservation through the preservation of cortical excitability in the active group. Future work replicating these findings, examining their durability, applying them to more advanced AD, and exploring the possibility of precuneal rTMS as a disease-modifying treatment will be of great interest and impact for the treatment of AD.

Koch G, Casula EP, Bonnì S, et al. Precuneus magnetic stimulation for Alzheimer's disease: a randomized, sham-controlled trial. Brain. 2022;145(11):3776-3786. doi:10.1093/brain/awac285

Successful Treatment of TRD with ECT is Mediated by Improvements in Negative Cognitive Schemas

Harinee Maiyuran, MD reviewing Scheepens et al. J Affect Disord 2022 Aug

In this randomized controlled trial, ECT was found to alter negative cognitive schemas, but an emotional memory reactivation task prior to ECT did not significantly change clinical response.

MDD can present with a large range of symptoms, but a particularly common symptom within this heterogenous disorder is a broadly negative interpretation of life events termed "negative schemas." Previous research has shown that negative schemas (measured as negative cognitions using the Dysfunctional Attitude Scale [DAS]) can both contribute to and perpetuate depressed mood in MDD and TRD. ECT is one of the most effective treatments for TRD, with 50% of patients reporting improvement after receiving ECT. In this study the authors sought to examine whether a tried and true treatment for TRD (ECT) can alter the negative schemas that many depressed patients possess by priming patients to recall emotional memories just prior to ECT sessions.

In this RCT, inpatients and outpatients aged 18-70 years from three hospitals in the Netherlands were recruited between 2014-2018. Inclusion criteria included a diagnosis of MDD and a clinical indication for ECT, while exclusion criteria included psychotic symptoms, diagnosis of a primary psychotic or bipolar disorder, substance abuse, and cognitive disorders based on DSM-IV-TR-criteria. Patients were randomized to receive either control memory (neutral information; CMR-ECT) or emotional memory (maladaptive thoughts; EMR-ECT) reactivation prior to ECT sessions. The emotional memory reactivation was based on interviews with a clinical

psychologist conducted two weeks before ECT in which patients wrote down vivid autobiographical episodes. Prior to each ECT session, a study coordinator would read one of three selected memories to prime the patient. In the control group, the coordinator read information about sleep, exercise, or substance use in relation to mental health. Scales were administered at baseline and the end of treatment to assess depression, negative schemas, and cognitive function, and included the HDRS, DAS, and Mini-Mental State Exam (MMSE). ECT was administered twice a week using a brief (0.5ms) pulse, starting with right unilateral (RUL) in most cases and switching to bilateral if deemed clinically appropriate or after six ineffective RUL treatments. ECT was conducted until remission or plateauing of improvement.

After six patients dropped out of the study and seven had missing DAS scores, the final sample was 59 patients with 30 receiving EMR-ECT and 29 receiving CMR-ECT and no significant baseline differences between groups. ECT was effective for the whole sample, with a significantly lower HDRS post-ECT ($p < 0.001$, $d = 1.0$), a response rate of 42.4%, and a remission rate of 25.4%. DAS scores also were significantly lower after ECT in the whole sample ($P < 0.001$, $d = 0.51$). There were no significant differences between the two treatment groups in HDRS or DAS outcomes. Mediation modeling revealed that there was a significant indirect effect of baseline DAS on post-ECT HDRS mediated through post-ECT DAS, suggesting the clinical improvements in mood were mediated through improvement in negative cognitive schemas. There was no significant change in mean MMSE score for the whole group post-ECT.

Impact: In this study, ECT was found to improve negative schemas, which may provide insight into possible mechanisms through which ECT is effective for TRD. However, the primary intervention in this RCT (reactivation of negative schemas) was found to have no additional benefit when compared to a neutral control. Thus, while this study is unlikely to lead to any changes in clinical practice directly, it may prove useful in the search for more effective treatments for TRD.

Scheepens DS, van Waarde JA, Ten Doesschate F, et al. Negative cognitive schema modification as mediator of symptom improvement after electroconvulsive therapy in major depressive disorder. J Affect Disord. 2022;310:156-161. doi:10.1016/j.jad.2022.04.088

Factors Associated with Response to ECT for Mania Identified in Registry Study

Tashalee R. Brown, MD, PhD reviewing Popiolek et al. JAMA Netw Open 2022 Jun

Patients treated with ECT for a manic episode saw an 84% response rate based on CGI scores. More severe manic symptoms were associated with higher response rates, while comorbid anxiety and OCD disorders were associated with lower response rates.

ECT is an effective and safe treatment for many psychiatric conditions, including psychiatric emergencies such as mania. Rapid treatment response in mania is particularly important, although ECT generally is not recommended as a first line treatment. In this study the authors used Swedish registry data to search for factors associated with response to ECT in patients with mania in the hope that treatments could be matched to patients based upon symptoms.

This retrospective observational national register-based study evaluated data for individuals admitted to any hospital in Sweden and treated with ECT for mania between 2012-2019. Data was obtained from a composite of the Swedish National Quality Registry for ECT, The Swedish National Patient Register, and The Longitudinal Integrated Database for Health Insurance and Labour Market Studies. Inclusion criteria included diagnosis of a manic or mixed episode based on ICD-10 codes and presence of CGI scores. Data on ECT administration included device (Mecta or Thymatron System IV), pulse width (all brief pulse), charge, and seizure duration. The authors used binary logistic regression and performed univariate and multivariable analyses to assess response and remission rates and evaluate the prognostic value of clinical covariates. Response was defined as a CGI Improvement (CGI-I) score of 1-2 while remission was defined as a CGI Severity (CGI-S) score of 1-2, both assessed within one week of completion of ECT. Severity of mania was based on CGI-S score before ECT. Comorbid psychiatric conditions evaluated included: anxiety disorder, obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder, autism, personality disorder, and substance use disorder.

A total of 571 patients (211 men [37.0%]; median age: 46 years) were included in the study. Of the 571 patients, 482 individuals (84.4%) met criteria for response to ECT. Remission was achieved in 139 of 495 patients with a CGI-S score (28.1%). Severity of mania was associated with response to ECT in multivariate analysis. Patients who were “markedly ill”

(adjusted OR [aOR]: 2.93; p = 0.02), “severely ill” (aOR: 2.60; p = 0.04), or “among the most extremely ill” (aOR: 7.94; p = 0.002) had higher odds of responding to ECT than those with mild or moderate illness. Factors associated with lower response included comorbid anxiety (aOR: 0.48; p = 0.02) and OCD (aOR: 0.17; p = 0.003). Furthermore, treatment with antidepressants was associated with lower odds of achieving remission in univariate (OR: 0.45; p = 0.006) but not multivariate analysis (aOR: 0.61; p = 0.10). The median number of treatments in this study was six (range: 1-24). No ECT settings (i.e., charge, pulse width, and seizure duration) were found to be associated with response to ECT. Of note, per authors, titration of ECT is not common in Sweden. There was no association between antimanic treatment within 100 days before ECT and response (OR: 0.96; p = 0.86).

Impact: This retrospective registry-based study suggests that ECT is very effective when used to treat an acute manic episode, with greater severity of mania associated with higher odds of response to ECT. The authors also found that mania with comorbid anxiety and OCD was associated with a lower response rate. Conclusions from this study should be made with caution as it is nonrandomized and uncontrolled, which prevents any conclusions regarding the potential causality of treatment outcomes. Moreover, evaluation of treatment response and remission relied on CGI scores rather than mania-specific scales which limits understanding of whether manic symptoms vs. other psychiatric symptoms were improved by ECT treatment.

Popiolek K, Bejerot S, Landén M, Nordenskjöld A. Association of Clinical and Demographic Characteristics With Response to Electroconvulsive Therapy in Mania. JAMA Netw Open. 2022;5(6):e2218330. Published 2022 Jun 1. doi:10.1001/jamanetworkopen.2022.18330

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)