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PULSE

A Monthly Update on Advances in Neuromodulation
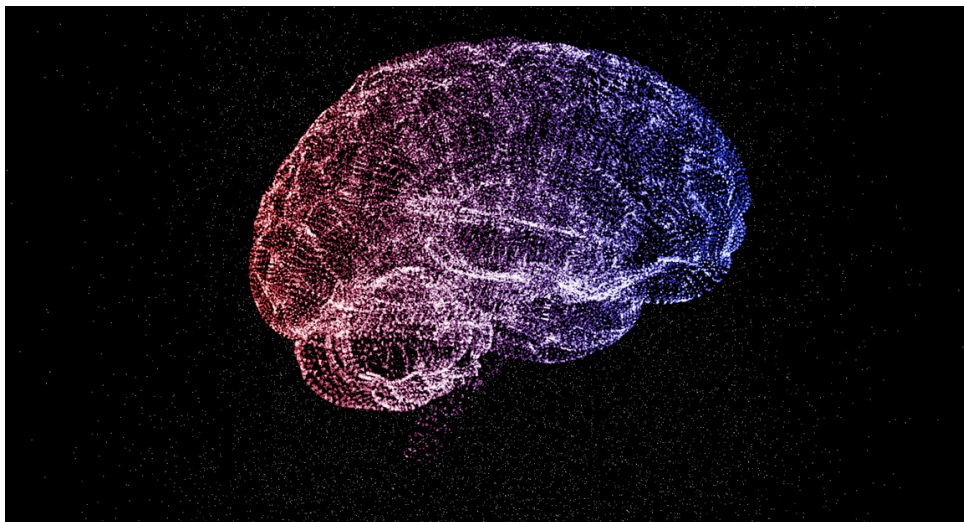
Magnetic Seizure Therapy for Depression Found to Be as Effective as ECT, with Fewer Side Effects

David M Carlson, MD, reviewing Deng Z et al. JAMA Psychiatry 2023 Dec

A large randomized controlled trial of Magnetic Seizure Therapy (MST) vs ECT for major depressive episodes finds similar response and remission rates, with a slightly longer time to remission and fewer physical or cognitive adverse effects.

Electroconvulsive therapy (ECT) is one of the most effective treatments for treatment-resistant depression, but it comes with the potential to experience concerning physical and cognitive side effects. Magnetic Seizure Therapy (MST), a newer therapy, was designed to achieve this antidepressant effect with fewer adverse effects. Thus far, it has shown promise in small trials. This three-site randomized controlled trial compared MST with right unilateral (RUL)

ultra-brief pulse ECT – the best tolerated form of ECT currently available – to assess for both antidepressant effects as well as adverse effects.

Trial participants were adults (mean age 48 ± 14.1 years, 56.2% female) with major depression or bipolar disorder (either I or II) who were referred for ECT to treat a major depressive episode and had a baseline 24-item Hamilton Depression Rating Scale (HDRS-24) score of 18 or higher (mean baseline score 31 ± 7.1). Of the 73 patients, 35 were randomized to receive MST at 100Hz frequency and 100% of device power for 10 seconds, and 38 to RUL ultra-brief ECT at six times the seizure threshold. Participants received treatment three times per week, with identical anesthesia protocols in both arms, until they achieved remission or reached a plateau in response.

For the primary depression outcome, the response was defined as a 50% reduction in HDRS-24 and remission criteria of 60% or greater reduction in HDRS-24 with a total score less than 8. Subjective adverse effects, which included physical (headache, nausea, dry mouth, aches, pain) and cognitive (confusion, memory problems), were assessed using the Columbia ECT Subjective Side Effects Schedule, administered in the afternoon of each treatment day. Statistical analysis consisted of

repeated-measure linear mixed models for continuous measures (including HDRS-24 score), t-tests for between-group comparisons of continuous measures at baseline and end of treatment, chi-squared tests for categorical variables, and Kaplan-Meier survival analysis for examining time to remission.

Of the 73 participants randomized, 53 (73%) completed the trial, with no significant difference in completion rates between groups (MST 82.9%, ECT 63.2%). In the 73-person intention-to-treat group, 46.6% achieved response (MST 51.4%; ECT 42.1%), and 31.5% met remission criteria (37.1%; 26.3%); there was no significant difference in response or remission rate between groups. Among the 53 who completed the study, response was achieved in 60.4% (MST 58.6%; ECT 62.5%) and 43.4% remission (MST 44.8%; ECT 41.7%). Notably, ECT led to significantly faster results, with a mean time to remission of 6.7 treatments vs. 9.0 for MST. In both groups, treatment response was maintained at 2-month and 6-month follow-ups, with no significant differences.

There were five serious adverse events – all in the ECT group (3 cases of worsening depression, 1 case of postictal agitation, and one case of large transient increase in blood pressure) – and four minor adverse events in the MST group (2 cases of nausea and vomiting

post-treatment, 1 case of foot pain unrelated to treatment, and 1 case of treatment not being delivered due to a device-related issue that was repaired). ECT patients had significantly higher severity of nausea and muscle pain, confusion and disorientation, and worse recall of autobiographical memories or autobiographical memory specificity, with t-scores ranging from 2.2 to 3.7 (p= 0.002-0.03). Participants regained orientation faster following MST than ECT at both threshold and suprathreshold levels.

Impact: This trial, the largest to date comparing MST and ECT, finds comparable efficacy with increased tolerability and fewer adverse effects in MST than in ECT. Notably, ECT response rates in this study are lower than generally observed elsewhere in the literature, and this study was not designed or powered to be a true noninferiority trial (though that trial is currently underway). Future work already underway seeks to verify these findings, and additional work into accelerating the antidepressant effects of MST is of great interest to the field.

Deng ZD, Luber B, McClintock SM, Weiner RD, Husain MM, Lisanby SH. Clinical Outcomes of Magnetic Seizure Therapy vs Electroconvulsive Therapy for Major Depressive Episode: A Randomized Clinical Trial. JAMA Psychiatry. Published online December 6, 2023. doi:10.1001/jamapsychiatry.2023.4599

The Impact of rTMS on Rumination Symptoms in Treatment-Resistant MDD

Harinee Maiyuran, MD, reviewing Chu SA et al. Translational Psychiatry 2023 Sept

In this retrospective study of 155 patients, improvements in both rumination and depression were observed after rTMS treatment, thereby demonstrating a correlation between the two and providing insight into how rumination may impede antidepressant response to rTMS.

Rumination is a repetitive, unhelpful focus on or preoccupation with negative emotions and thoughts. It is generally more common among women and strongly associated with

depression. Those with rumination often have more severe depression, compounding any functional impairment already present. Thus far, it has been challenging to

identify consistently effective treatments for rumination, and medications studied have shown limited effect. Much of this work has examined rumination as it

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relates to mild and moderate depression, not in the context of severe or treatment-resistant depression. Rumination has similarly not been examined in depth in the context of rTMS. The authors here investigate how rumination relates to more severe and treatment-resistant depression as well as how it changes throughout rTMS treatment.

This retrospective observational study examined 155 patients (mean age 42.5 ± 14.2, 79 female) undergoing routine clinical rTMS for treatment-resistant MDD at UCLA from 2020 to 2023. Patients underwent 30 repetitive Transcranial Magnetic Stimulation (rTMS) sessions following a measurement-based care paradigm, with most receiving concurrent medication. The Ruminative Responses Scale (RRS) and PHQ-9 were used to measure rumination and depression, respectively, at baseline and every five sessions thereafter until the end of treatment. RRS Brooding and Reflection subscales, a combination score of the two subscales, and the

total score of the remaining RRS questions were also examined. Percent changes in PHQ-9 and RRS (and subscales) were examined, as was depression response defined as ≥50% reduction in PHQ-9 score. Statistical analysis consisted of (1) correlation analyses studying associations between baseline scale scores, changes in scores, and final outcomes, as well as (2) a series of four multilevel modeling linear mixed models exploring the relationships between baseline rumination and rTMS treatment outcomes, each considering a different combination of covariates.

Higher baseline rumination was shown to negatively predict outcomes from rTMS in the treatment of depression, though baseline depression severity was not associated with depression outcomes after rTMS. This impact of rumination was also more significant on subjects who self-reported as female. Though there was a correlation between the improvement in rumination (-20.5%)

and depression (-31.6%), changes in rumination were not found to be mediated by changes in depression, indicating the two are at least partially independent. The relationship between sex and rTMS treatment outcome was strongest within the Reflection, Depressive Rumination, and Brooding subscales, as well as the RRS short-form score.

Impact: This study, one of the first to examine rumination and depression together in the context of rTMS, provides key insights into the overlap and delineation of depression and rumination, in addition to highlighting a key symptom that may impede response for many of our patients. Future work validating and expanding these findings in a prospective controlled manner could be valuable in identifying moderators and mediators of rTMS treatment response in MDD.

Chu, S.A., Tadayonnejad, R., Corlier, J. et al. Rumination symptoms in treatment-resistant major depressive disorder, and outcomes of repetitive Transcranial Magnetic Stimulation (rTMS) treatment. Transl Psychiatry 13, 293 (2023). _Accelerated rTMS Re-treatment Observed as Effective Option for Prior Responders_.

Accelerated rTMS Re-treatment Observed as Effective Option for Prior Responders

Michael K. Leuchter, MD, reviewing Geoly et al. The American Journal of Psychiatry 2024 Jan

This open-label cohort study of 27 individuals undergoing re-treatment following a depressive relapse after response to an initial course of accelerated rTMS using the Stanford Neuromodulation Therapy (SNT) protocol found similar response and remission rates, as well as overall levels of symptom improvement, between initial and repeat treatment courses. It builds on prior work suggesting re-treatment is an effective strategy for those who relapse after a course of rTMS and expands the concept in the realm of accelerated treatment.

While rTMS is known to be an effective treatment for treatment-resistant MDD, the durability of its benefit is a matter of great interest and far less study. The few that have examined this question generally found, that over 60% of responders maintained clinical response after 12 months in conventional rTMS treatment. Further work has demonstrated that re-treatment with rTMS is a viable (and, in fact, reasonable)

treatment approach for those who respond to an initial course of rTMS and subsequently experience a depressive relapse. It has quite notably been observed that some accelerated rTMS protocols, most notably the Stanford Neuromodulation Therapy (SNT) protocol, appear to have substantially lower durability of benefit compared to other protocols in the literature. However, re-treatment has been observed to be

a viable strategy for the SNT protocol on a case-series level. This study seeks to apply these known concepts to the Stanford Neuromodulation Therapy (SNT) protocol in an open-label fashion.

This open-label study of 27 participants (age 20 to 79, 14 female) who underwent SNT protocol and experienced a relapse (MADRS score ≥20) following improvement during

an initial treatment course examines treatment outcomes following a participant-requested repeat course using SNT protocol (fMRI navigated 1800 pulses iTBS delivered at 90% MT to a specific L DLPFC region of interest for 10 sessions per day over 5 days). Depressive symptoms were assessed using the MADRS, HDRS-17 item, and HDRS-6 item before re-treatment, immediately after SNT re-treatment, and one month after completing re-treatment. No longer-term follow-up was assessed in this study. Response and remission rates for both the initial treatment and the re-treatment rTMS courses were compared. Raw scale scores and percent change in symptoms at follow-up time points were also compared between the initial and re-treatment courses.

The mean time between initial and re-treatment courses was 26.5 ± 25.1 weeks. There were no significant differences in MADRS response (initial 85.18%, re-treatment 88.89%) or remission (initial 81.48%, re-treatment 85.18%) between initial treatment and re-treatment courses immediately following treatment, nor were there significant differences between courses in raw scale score or percent change in scale score immediately following a treatment course or after one month of follow-up. Response and remission rates after one month of follow-up are not presented, nor is sufficient information presented for the reader to calculate these rates. Targeted analysis of suicidality suggests re-treatment may improve suicidality beyond the improvement noted during the initial treatment course (t=-3.3, p=0.003).

Impact: This open-label study examining re-treatment following relapse in the context of the SNT protocol suggests re-treatment with the SNT protocol is a viable treatment strategy. More broadly, it expands prior known work demonstrating the effectiveness of re-treatment to accelerated protocols, providing valuable knowledge as the appeal and accessibility of these protocols continue to grow. However, it provides little insight into the durability of the benefit. Further work in larger samples exploring durability and validating re-treatment in a controlled fashion could provide valuable insights.

Geoly AD, Williams NR. Sustained Efficacy of Stanford Neuromodulation Therapy (SNT) in Open-Label Repeated Treatment. Am J Psychiatry. Published online 2024.

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)

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)

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