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PULSE

A Monthly Update on Advances in Neuromodulation

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IN THIS ISSUE:

rTMS is effective for the treatment of depression with comorbid anxiety disorder

Tiana J Raphel MD reviewing Clarke E et al. J Affect Disord 2019 June

In a single-site, naturalistic, retrospective study of patients receiving rTMS for treatment resistant depression, outcomes were similar in patients with versus without comorbid anxiety disorders.

Comorbid anxiety is associated with worse treatment outcomes in patients with depression. While repetitive Transcranial Magnetic Stimulation (rTMS) has shown efficacy in treatment resistant depression (TRD), little research examines the efficacy of rTMS in depressed patients with comorbid anxiety disorders. To investigate this question, researchers compared rTMS outcomes among patients with TRD in those with and without comorbid anxiety disorders.

Analyses were done on a retrospective dataset of outpatients referred to an rTMS center from private practice providers. The sample included 248 rTMS-naïve patients with TRD: 172 (69%) had comorbid anxiety diagnoses and 76 (31%) did not. TRD was defined as at least two adequate trials of antidepressants, and 44% of the population had previously received Electroconvulsive Therapy (ECT). rTMS was delivered at 110% MT with either right unilateral (15 min 1Hz stimulation to right dorsolateral prefrontal cortex [DLPFC]) or sequential bilateral (15 min 10 Hz stimulation to left DLPFC followed by 15 min 1 Hz to right DLPFC) stimulation paradigms. Rating scales were administered at baseline and at the end of a full treatment course. Remission was defined as a 21-item Hamilton Depression Rating Scale (HAM-D) score ≤ 7 and response was defined as an improvement of ≥50% from baseline in the HAM-D at the end of the treatment course of unspecified length. The study also measured the Hamilton Anxiety Rating Scale (HAM-A), the Montgomery-Asberg Depression Scale (MADRS), and the Zung Self-Rating Depression Scale (ZUNG).

Overall, response rates with rTMS were similar between TRD patients with (40%) and without (37%) comorbid anxiety disorders ($p = 0.795$), as were remission rates (23% among those with comorbid anxiety, 33% among those without; $p = 0.151$). rTMS was found to improve outcomes for each subtype of comorbid anxiety disorder ($p < 0.001$ for all), though patients with comorbid agoraphobia with panic disorder had decreased remissions rates when compared to patients without any comorbid anxiety disorder. Outcomes for HAMA-A, HAMA-D, MADRS, and ZUNG were similarly significantly improved following rTMS whether patients had anxiety or not.

Impact: This study assessed the effect of rTMS on a population that is often excluded in other studies of rTMS but will likely represent a large portion of people who have treatment resistant depression - those with comorbid anxiety disorders. Whereas comorbid anxiety was linked to worse outcomes in other treatments of TRD, this study suggests that with rTMS those with comorbid anxiety may have similar outcomes to TRD patients without comorbid anxiety disorders.

Clarke E, Clarke P, Gill S, Paterson T, Hahn L, Galletly C. Efficacy of repetitive transcranial magnetic stimulation in the treatment of depression with comorbid anxiety disorders. J Affect Disord. 2019;252:435-439.

Positive Outcomes in Clinical Trial of Stanford Neuromodulation Therapy (SNT) for MDD

Collin M. Price, MD reviewing Cole et al. Am J Psych 2021 Oct

A double-blind, sham-controlled study of the Stanford neuromodulation therapy (previously SAINT) yielded rapid improvements in TRD, with an effect size large enough to justify early termination of the clinical trial.

During a previous open-label study, an fMRI-targeted Transcranial Magnetic Stimulation (TMS) protocol for Treatment Resistant Depression (TRD) yielded roughly 90% remission in just five days. The protocol, previously termed the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) and now called the Stanford Neuromodulation Therapy (SNT), was recently evaluated in a double-blind, sham-controlled study, which was halted after interim analysis demonstrated a large effect size for active vs. sham conditions.

The interim analysis included 29 patients with TRD who were randomized to active (N=14) or sham (N=15) SNT. Each patient initially underwent structural and resting-state functional MRI (rs-fMRI) scans. These scans were used to localize personalized stimulation sites in the left dorsolateral prefrontal cortex (DLPFC), based on functional connectivity with the subgenual anterior cingulate cortex (sgACC). Prior to TMS using intermittent theta burst stimulation (iTBS), a Localite neuronavigation system was used to target a MagVenture coil over the personalized target. Ten sessions of active or sham iTBS were delivered per day for five consecutive days, yielding a total of 90,000 pulses. Pulse intensity was adjusted for cortical target depth with a goal of 90% motor threshold intensity at each target. Participants were blinded using either sham direct current pads (N=7) or a sham noise generator (N=22), and all staff were blinded to treatment group. The primary outcome was change in Montgomery-Asberg Depression Rating Scale (MADRS) from baseline to week 5.

The primary outcome demonstrated a 53% reduction in MADRS score from baseline to week 5 (four weeks after treatment ended) in the active group, compared to 11% in the sham group

(d=1.4). MADRS response (reduction ≥50%) and remission (score ≤10) rates, obtained immediately after treatment and at 4 weekly follow-ups, ranged from 69-85% and 46-67%, respectively, in the active group; this compared to 7-20% and 0-10%, respectively, in the sham group. Generalized linear mixed-effects models showed significant main effects for group, time, and group x time for MADRS scores. Assessment of patient blinding revealed no significant variation from chance.

Impact: This follow-up, double-blind, sham-controlled study of the SNT protocol validated the impressive results from a prior open-label study. The clinical improvements demonstrated here were significant enough to justify early termination of the study, underscoring the potential for this treatment. Given the time-limited nature in addition to the strong efficacy, the SNT protocol may be poised to generate a dramatic shift in the way TMS is delivered to treat TRD.

Cole EJ, Phillips AL, Bentzley BS, et al. Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial [published online ahead of print, 2021 Oct 29]. Am J Psychiatry. 2021;appiajp202120101429.

Twice versus Once Daily rTMS Treatment Does Not Accelerate Antidepressant Response

Michael K. Leuchter, MD reviewing Blumberger et al. Brain Stimulation 2021 September

This randomized controlled trial examined the use of once versus twice daily rTMS for the treatment of MDD and found that twice daily treatment did not show better response or remission rates or more rapid action than once daily treatment.

Treatment of depression with repetitive Transcranial Magnetic Stimulation (rTMS) can involve adjustment of a large number of parameters including pulses per treatment, stimulation frequency, and number of treatments per day, among other variables. Under many circumstances, more pulses per treatment and more treatments per day enhance response, but it is unclear whether the number of pulses, the number of treatment sessions per day, or both contribute to greater clinical improvement. This study examined the effect of the number of sessions per day while controlling for the number of pulses.

The CARTBIND consortium performed a multi-center double-blind randomized-controlled trial of 208 patients undergoing rTMS for Major Depressive Disorder (MDD) without co-morbid psychiatric conditions. All patients received 1200 pulses of intermittent theta burst stimulation (iTBS; 3 bursts at 50 Hz repeated at a frequency of 5 Hz) at 120% of resting motor threshold, delivered to both the left dorsolateral prefrontal cortex (LDLPFC) and Pz EEG electrode site (functioning as a sham site, with a shielded coil). Each group had two sessions of rTMS per day separated by 54 minutes. Those in the once-daily group (Daily; n=105) received 1200 pulses to the sham site followed by 1200 pulses to the LDLPFC. Those in the twice-daily group (BID; n=103) received 600 pulses to DLPFC and 600 pulses to Pz during each session. This design controlled for a number of factors including time spent undergoing treatment, time spent interacting with staff, and pulse number. The primary measure was the Hamilton Rating Scale for Depression (HRSD), with secondary measures of depression, side effects, and adverse events, all obtained during treatment (Day 10 and 30) and post-treatment (Week 1, 4, and 12). The primary outcome was between-group difference of changes in HRSD score from baseline to Day 10.

There was no significant difference between groups on the primary outcome at day 10 or 30 ($p<0.001$), with no significant between-group differences at day 10 (Daily: 20.0%; BID: 12.8%) or 30 (Daily: 41.1%; BID: 44.3%) in response or remission (Daily: 4.2%; BID: 5.3%; Daily: 23.3%; BID: 22.7%, day 10 and 30, respectively) rates. Post-treatment HRSD scores also showed no significant between-group differences at Weeks 1 ($t(158.0)=0.53$, $p=0.60$) and 4 ($t(102.86)=1.90$, $p=0.06$). However, there was a between-group difference favoring twice-daily treatment noted at 12 weeks after treatment ($t(133.44)=2.45$, $p=0.015$), though effect size was not reported. No significant between-group difference in adverse events was observed.

Impact: This large, multi-center, randomized controlled trial found no significant difference in response, remission, or speed of symptom relief for rTMS treatment delivered in one consolidated session vs. split between two sessions, up to four weeks post treatment, although twice-daily treatment was slightly favored twelve weeks after treatment. These results suggest once daily and twice daily treatments are largely equivalent, although a slight benefit to twice daily therapy may be evident in prolonged follow-up; future studies should investigate this possible benefit, and whether certain populations may benefit from each modality.

Blumberger DM, Vila-Rodriguez F, Wang W, et al. A randomized sham-controlled comparison of once vs twice-daily intermittent theta burst stimulation in depression: A Canadian rTMS treatment and biomarker network in depression (CARTBIND) study [published online ahead of print, 2021 Sep 21]. Brain Stimul. 2021;14(6):1447-1455.

Closed-Loop DBS Alleviates Intractable Depression in Proof-of-Concept Case Study

Collin M. Price, MD reviewing Scangos et al. Nat Med 2021 Oct

In a proof-of-concept, n=1, personalized clinical trial, investigators employed a two-stage process to identify a unique biomarker of depression that was deployed to create a closed-loop neurostimulation system. This method yielded rapid and sustained clinical improvement in one patient's intractable depression.

Deep Brain Stimulation (DBS) is an invasive neuromodulation modality that has proven safe and effective in the treatment of movement disorders. However, despite decades of research, this modality remains a rarely used intervention in psychiatry. Multiple small-scale clinical trials of DBS for refractory Major Depressive Disorder (MDD) have shown equivocal results. These trials typically employ a fixed, tonic stimulation with occasional tuning by the clinician. Advances in DBS technology now allow for so-called closed-loop systems, in which sensors within the brain monitor for triggers and deliver stimulation only when activated. Here, investigators developed such a closed-loop DBS system and asked whether it could treat one patient's intractable MDD.

The single patient was a 36-year-old woman with severe MDD (MADRS=36) refractory to multiple medications and electroconvulsive therapy. Investigators initially employed clinical mapping with ten stereoelectroencephalography (SEEG) electrodes implanted in the cortex and limbic system; these included the orbitofrontal cortex (OFC), subgenual cingulate cortex (SGC), ventral capsule/ventral striatum (VC/VS), amygdala, and hippocampus. Neural activity was recorded during stimulation and at rest, while the patient completed repeated measures of depression and anxiety. After identifying a personalized SEEG biomarker of worsened depression, the team removed those electrodes and implanted a NeuroPace Responsive Neurostimulation (RNS) system. The RNS device was programed to: 1) detect the previously identified and replicated biomarker, then 2) deliver the appropriate stimulation, creating a closed-loop system.

During SEEG mapping, bilateral amygdala gamma power differentiated high vs. low depression symptoms (AUC: 0.82), with VC/VS stimulation yielding both optimal symptom reduction and significant changes in amygdala gamma power. These findings guided implantation of the RNS device in the right hemisphere amygdala and VC/VS. Recording with the RNS device replicated the amygdala gamma power biomarker. The optimal stimulation paradigm was determined to be 6s of intermittent 1 mA stimulation, resulting in symptom improvement without exceeding the patient's perceptual threshold. Starting the first day with the closed-loop system on, the patient experienced rapid improvements on both the VAS-D (77 to 23) and HAMD-6 (12.0 to 1.0). These improvements persisted for months, with a change in MADRS from 33 at baseline to 14 at day 12 to below 10 (remission) after several months. A non-linear analysis of daily VAS-D and biomarker detection over two months suggested that the biomarker successfully detected changes in symptom severity better than random chance ($p = 2.8 \times 10^{-4}$).

Impact: This proof-of-concept,n=1, personalized clinical trial demonstrates successful use of clinical electrocorti-cography mapping and responsive neuromodulation to treat a neuro-psychiatric disorder. Though this method will require validation through larger, rigorously designed trials, the investigators have shown the impressive potential of advanced neuroscientific tools to treat intractable psychiatric disease.

Scangos, K.W., Khambhati, A.N., Daly, P.M. et al. Closed-loop neuromodulation in an individual with treatment-resistant depression. Nat Med 27, 1696–1700 (2021