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PULSE

A Monthly Update on Advances in Neuromodulation

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A NATURALISTIC STUDY OF rTMS IN UNIPOLAR AND BIPOLAR DEPRESSION

Michael K. Leuchter, MD reviewing Yang Y et al. Can J Psychiatry 2021 March 1

In this naturalistic study, high-frequency rTMS delivered to left dorsolateral prefrontal cortex (HF LDLPFC) demonstrated efficacy in treating unipolar depression, but was far less efficacious in treating bipolar depression.

Repetitive Transcranial Magnetic Stimulation (rTMS) is primarily utilized as a treatment for unipolar depression, and is clearly effective for this indication. However, its role in the treatment of bipolar depression is less clear. The current evidence suggests some efficacy of right-sided rTMS protocols, but overall, trials of rTMS for bipolar depression have yielded mixed results. How effective is traditional HF LDLPFC rTMS in the treatment of bipolar depression compared to unipolar depression?

Researchers performed a retrospective chart review of 76 patients with

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depression (7 with bipolar I disorder, 6 with bipolar II disorder, and 63 with unipolar depression) treated with 10 Hz rTMS delivered to LDLPFC for 2-6 weeks (with treatment duration depending on unspecified patient factors). Clinician-rated Hamilton Depression Rating Scale (HDRS) scores were collected before and after the course of treatment. The primary outcome examined was clinical response, defined as improvement of at least 50% in the HDRS score from before to after treatment. The secondary outcome was percent change in HDRS score.

Significantly more unipolar than bipolar patients met criteria for response (39.3% vs 7.7%, p=0.024). The unipolar depression group achieved a greater reduction in symptoms (37.6% reduction in HDRS) compared to the bipolar depression group (25.5%) on a trend level (p=0.10). Examining demographics and other baseline factors, the only significant demographic and clinical difference between groups was more frequent use of concomitant anticonvulsant agents in the bipolar group (4/13 vs 5/61, p=0.024).

Impact: While this study is limited by unequal group sizes and its naturalistic, retrospective approach, its findings suggest that HF LDLPFC rTMS, the standard rTMS protocol for unipolar depression, is less effective for bipolar depression. This finding is line with previous work and highlights the need to explore other rTMS protocols for treating bipolar depression.

Yang YB, Chan P, Rayani K, McGirr A. Comparative Effectiveness of Repetitive Transcranial Magnetic Stimulation in Unipolar and Bipolar Depression. Can J Psychiatry. 2021;66(3):313-315. doi:10.1177/0706743720950938

INTERMITTENT THETA BURST STIMULATION IS NO MORE EFFECTIVE THAN SHAM FOR BIPOLAR DEPRESSION

Katharine G Marder, MD reviewing MicGirr A et al., JAMA Network Open 2021 Mar 1

This randomized controlled trial was terminated early after active intermittent Theta Burst Stimulation failed to demonstrate superiority over sham in the treatment of bipolar depression.

The efficacy of intermittent Theta Burst Stimulation (iTBS) has been well-established for the treatment of unipolar depression, and the protocol is FDA cleared for this indication. In the treatment of bipolar depression, the efficacy of rTMS in general, and iTBS in particular, is less clear. New treatments for bipolar depression are urgently needed given the disease burden of bipolar depression and the limited available treatment options. Is iTBS effective in treatment of bipolar depression?

Researchers conducted a 4 week, randomized, double-blinded, controlled trial comparing iTBS to sham in the treatment of bipolar depression. Thirty-seven patients with bipolar I disorder or bipolar II disorder in a current depressive episode were randomized to iTBS (n=18) or to sham (n=19). Participants continued psychotropic medications and all participants were taking concomitant mood stabilizers or antipsychotics. The active iTBS protocol delivered 600 pulses to the left dorsolateral prefrontal cortex (using neuronavigation) at an intensity of 120% of the resting motor threshold; the sham protocol utilized a sham coil. The primary outcome was the change in depressive symptoms on the Montgomery-Asberg Depression Rating Scale (MADRS) from baseline to endpoint; secondary outcomes included response rates, remission rates, and affective switch.

There was no significant difference in MADRS score change between the active and sham groups. Response rates were low in both groups (17% in active versus 16% in sham) and there were no significant differences in clinical response or remission rates between the two groups. The trial was terminated early due to futility. There was no differential efficacy in bipolar I versus bipolar II disorder, or according to concomitant medication use. One participant receiving active iTBS experienced treatment-emergent hypomania; no other affective switching or serious adverse events occurred.

Impact: Increasing evidence suggests that the rTMS protocols typically employed in the treatment of unipolar depression may be less effective in the treatment of bipolar depression. This randomized, controlled trial provides compelling evidence that iTBS to the left DLPFC is not an effective treatment for bipolar depression, and highlights the need to investigate alternative rTMS approaches for this indication.

McGirr A, Vila-Rodriguez F, Cole J, et al. Efficacy of Active vs Sham Intermittent Theta Burst Transcranial Magnetic Stimulation for Patients With Bipolar Depression: A Randomized Clinical Trial. JAMA Netw Open. 2021;4(3):e210963. doi: 10.1001/jamanetworkopen.2021.0963

IMPROVED rTMS OUTCOMES IN DEPRESSION WHEN STIMULATING A PERSONALIZED fMRI-BASED TARGET

Collin Price, MD reviewing Cash RFH et al., JAMA Psychiatry 2020 Nov 25

This retrospective study analyzed fMRI data from a clinical trial of rTMS for major depressive disorder. Proximity to a personalized fMRI-based target derived post-hoc was associated with improved outcomes compared to a standardized fMRI-based target.

Repetitive transcranial magnetic stimulation (rTMS) has been established as a safe and effective treatment for treatment-resistant major depressive disorder (TRD). Maximizing efficacy of rTMS treatment is an area of active investigation, with particular interest in optimizing target localization. Stimulating regions of the dorsolateral prefrontal cortex (DLPFC) that show anti-correlated functional connectivity with the subgenual cingulate cortex (SGC) has been associated with improved outcomes. Given the inter-subject variability of functional connectivity between these regions, would a personalized fMRI target outperform a standardized fMRI target within the DLPFC?

Researchers analyzed retrospective data from a clinical trial investigating the predictors of response to rTMS in TRD. Twenty-six patients received 15 treatments of 10-Hz rTMS (5 days a week for 3 weeks targeted to the left DLPFC using the Beam F3 method. Each patient also underwent resting-state fMRI before and after the rTMS course. Each patient's fMRI scans were used to retrospectively identify the cluster within the DLPFC that was most anti-correlated with SGC activity. The Euclidian distance between this personalized target and the actual stimulation location was then calculated for each patient. A standardized fMRI target was generated using resting-state fMRI data from 1000 participants in the Human Connectome Project (HCP). Coordinates for this target and 11 other standardized targets were then used to calculate distances from the actual stimulation target. These distances were then correlated with the percentage improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) score for the 3-week timepoint.

The median distance between the personalized target and the actual stimulation location was 30mm. Shorter distance between these locations was associated with improved antidepressant response ($R= -0.60$, $p<0.001$), even after controlling for proximity between the standardized HCP target and the actual stimulation location (partial $R= -0.54$, $p=0.002$). There were no significant associations with clinical outcomes when the distances were calculated between any of the 12 standardized targets and the actual stimulation location. Improved outcomes were additionally associated with a stronger anticorrelation between the actual stimulation location and the SGC ($R= -0.57$, $p=0.001$).

Impact: Symptoms of depression improved more when rTMS happened to stimulate closer to a post-hoc personalized fMRI-based region of DLPFC-SGC connectivity. Standardized DLPFC targets, including a group average of maximal DLPFC-SGC anticorrelation, showed no association with symptom improvement. This study lends support to the idea that individualized targeting may improve TMS outcomes. However, well-designed prospective studies are still necessary to justify the increased resource requirements of these approaches.

Cash RFH, Cocchi L, Lv J, Fitzgerald PB, Zalesky A. Functional Magnetic Resonance Imaging–Guided Personalization of Transcranial Magnetic Stimulation Treatment for Depression. JAMA Psychiatry. 2021;78(3):337–339. doi:10.1001/jamapsychiatry.2020.3794

FROM THE ARCHIVES: AN EXTENDED COURSE OF DEEP TMS TREATMENT YIELDS HIGHER RESPONSE RATES

Katharine G Marder, MD reviewing Yip et al. Brain Stimulation 2017 Mar 10

In this extension of a randomized, controlled trial of deep TMS for treatment of depression, patients who did not respond to 20 sessions of deep TMS continued to receive active, double blind treatment twice weekly for up to 12 additional weeks. Most patients eventually responded with continued treatment.

There is a pressing need to improve response rates to TMS treatment for depression. Early trials of TMS for depression significantly underdosed TMS in terms of treatment intensity, pulse number, and duration of the treatment course, and subsequent lengthening of the treatment increased clinical efficacy. Currently, an acute course of standard TMS treatment typically involves 5 sessions per week for 6 weeks, while an acute course of deep TMS treatment typically involves 5 sessions per week for 4 weeks. Can extending the duration of treatment beyond 4-6 weeks help more patients respond?

Researchers analyzed the outcomes of patients who were receiving active treatment, but did not respond to acute treatment in the Brainsway pivotal clinical trial. All patients had major depressive disorder and were free of medication. All patients underwent active deep TMS treatment (18 Hz, 1980 pulses, 120% resting motor threshold) five days per week for four weeks before entering a twelve-week continuation phase, where they continued to receive active versus sham treatment under blinded conditions. Eighty-nine subjects were randomized to active treatment and 81 of these patients completed the acute treatment phase. Response was defined as a greater than 50% reduction in the 21-item Hamilton Depression Rating Scale (HDRS-21). Of these 81 patients, 33 were non-responders.

During continuation treatment, twelve of the 33 non-responders dropped out before the end of the continuation phase. Twenty-four of the 33 non-responders (73%) achieved response during at least one time point during the continuation phase. Thirteen of the non-responders (39%) met response criteria for multiple consecutive weeks. Twenty of the non-responders achieved remission status at some point during the continuation phase; of these, seven maintained remission for the duration of the study.

Impact: Patients who failed to respond to a standard course of deep TMS could go on to achieve response or even remission when treatment was extended. This was true even though treatment frequency was reduced to twice weekly in the continuation phase. Patients were not compared to patients receiving sham treatment in the continuation phase, so these results should be interpreted with caution. However, this study provides compelling preliminary evidence that extending the duration of TMS treatment may improve response rates.

Yip AG, George MS, Tendler A, Roth Y, Zangen A, Carpenter LL. 61% of unmedicated treatment resistant depression patients who did not respond to acute TMS treatment responded after four weeks of twice weekly deep TMS in the Brainsway pivotal trial. Brain Stimul. 2017;10(4):847-849. doi: 10.1016/j.brs.2017.02.013

BRIGHT LIGHT THERAPY ACCELERATES AND ENHANCES rTMS RESPONSE

Katharine G Marder, MD reviewing Barbini et al. Int J Psychiat Clin 2021 Mar 18

In this pilot, randomized single-blind clinical trial, the addition of bright light therapy to TMS treatment accelerated response to TMS and enhanced treatment outcomes.

TMS and bright light therapy are both safe, effective, nonpharmacological approaches for the treatment of depression. Bright light therapy has been shown to accelerate response to pharmacotherapy. Increasing literature describes TMS in combination with psychotherapy and pharmacotherapy, but the combination of TMS and bright light therapy has only been described once before, by Mania and Kaur in 2019. In their small case series of six patients, all patients completed the course of treatment and tolerated treatment well, with response and remission rates of 100% and 50%, respectively. How does the addition of bright light therapy to TMS compare to TMS monotherapy? Can bright light therapy accelerate TMS response?

Researchers randomized 80 psychiatric inpatients with major depressive disorder or bipolar depression to TMS monotherapy or combination therapy with TMS and bright light therapy. All patients received TMS at noon each day, five days per week, for a total of three weeks. TMS was delivered to left DLPFC using a MagStim device. Patients in the combined treatment group also received bright light therapy for 30 minutes per day, upon awakening, with 10,000 lux intensity. Evaluators were blinded to group status but patients were not, as no sham bright light intervention was used. The 17-item Hamilton Depression Rating Scale (HDRS-17) score was the primary outcome.

Participants receiving combination treatment had significantly greater improvement in depressive symptoms after one week (30% reduction in HDRS-17 score compared to 15% reduction in the monotherapy group, $p<0.001$) and from baseline to endpoint (64% reduction compared to 53% reduction, $p=0.033$). There were no significant differences in response or remission rates. No participants dropped out, and mild headaches were the only side effect reported.

Impact: This pilot study shows remarkably promising efficacy of combination treatment with TMS and bright light therapy, though it is not clear if this is due to additive effects or true synergy between these modalities. Larger, double-blinded randomized controlled trials are needed to confirm these findings. However, because bright light therapy is exceptionally safe, well-tolerated, and affordable, clinicians might consider recommending bright light therapy for patients undergoing TMS.

Barbini B, Attanasio F, Manfredi E, Cavallini MC, Zanardi R, Colombo C. Bright light therapy accelerates the antidepressant effect of repetitive transcranial magnetic stimulation in treatment resistant depression: a pilot study. Int J Psychiatry Clin Pract. 2021 Mar 18:1-3. doi: 10.1080/13651501.2021.1894579.