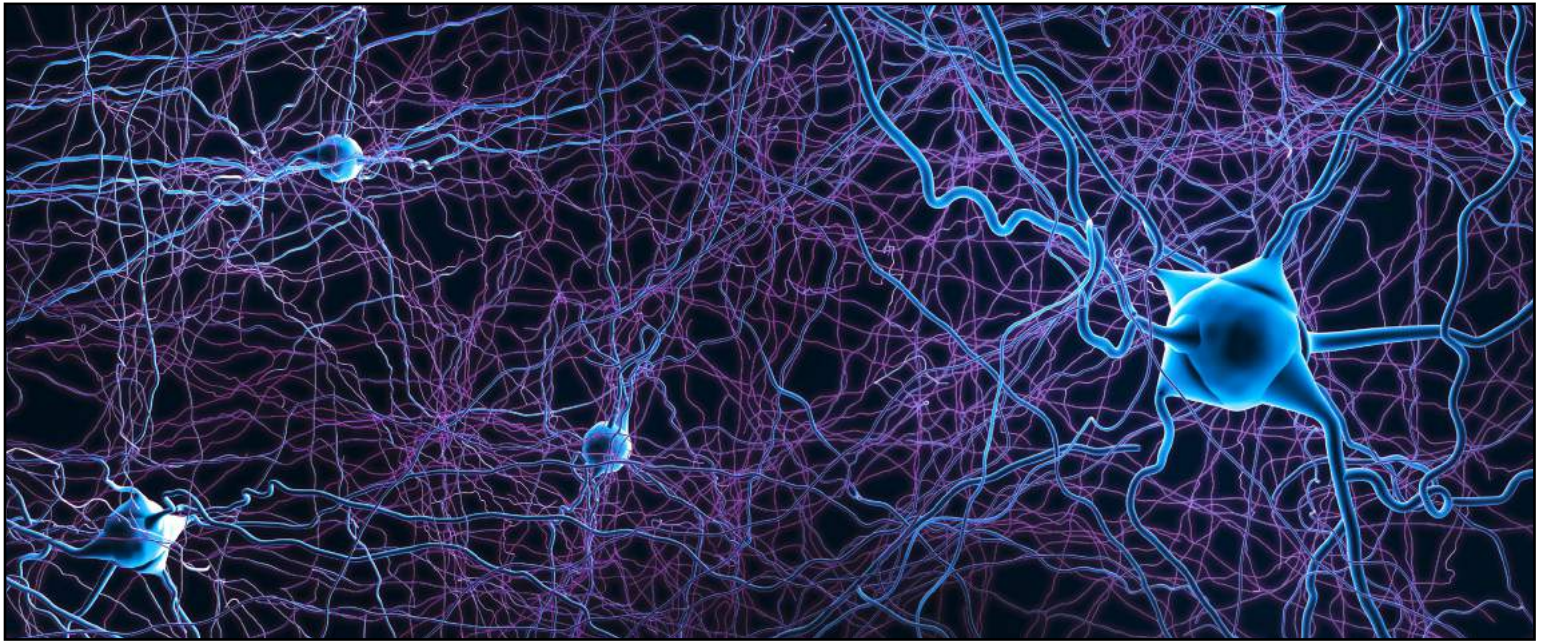




A Monthly Update on Advances in Neuromodulation



Produced by the Neuromodulation Division of the Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA

Note from the Editors

We are pleased to bring you this latest edition of the Pulse newsletter, which for the first time is being distributed to a national audience. Our goal is to update clinicians on the latest developments in the use of repetitive Transcranial Magnetic Stimulation (rTMS) and other neuromodulation interventions in an accessible and high-yield format. This edition of the newsletter focuses on the use of rTMS to treat Major Depressive Disorder (MDD) that is comorbid with Obsessive Compulsive Disorder (OCD), chronic pain, Post-traumatic Stress Disorder (PTSD), and other challenging conditions. Future issues will also review use of other neuromodulation methods including Transcranial Direct Current Stimulation (tDCS), Deep Brain Stimulation (DBS), and other invasive and non-invasive methods. We hope you enjoy the newsletter, and you can subscribe to receive future editions on our website at neuromodulation.ucla.edu/newsletter. There you also can view previous editions and learn more about our clinical, research, and academic programs. If you have questions, comments, or suggestions for future editions, please feel free to drop us a line at our email addresses listed above.

Thanks for reading.

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IN THIS ISSUE:

Note from the Editors

TMS Updates

- *Outcome of TMS treatment of Major Depressive Disorder and Comorbid Chronic Pain Associated with Neurophysiologic Biomarkers*
- *Promising Early Data for TMS in Treatment of Comorbid MDD and OCD*
- *rTMS to Dorsomedial Prefrontal Cortex Effective for Treatment of Anorexia Nervosa with Comorbid MDD*

Review Article

- *Approaches to Use of rTMS for Treatment of MDD with Comorbid Psychiatric Illnesses*

Outcome of TMS treatment of Major Depressive Disorder and Comorbid Chronic Pain Associated with Neurophysiologic Biomarkers

Don Wei, MD, PhD reviewing Corlier et al. *Psychological Medicine* 2021 June

In this naturalistic study of 162 patients with depression and comorbid chronic pain, rTMS targeting of the left dorsolateral prefrontal cortex (DLPFC) resulted in improved pain and depression scores after 30 sessions of treatment. More severe comorbid pain was associated with worse treatment response and lower alpha phase coherence.

Major depressive disorder (MDD) is comorbid with a variety of conditions, including chronic pain. Comorbid pain significantly worsens quality of life in patients with MDD and is associated with greater refractoriness to medication treatment, which underscores the need for novel treatment approaches. While repetitive transcranial magnetic stimulation (rTMS) has been shown to be efficacious for several comorbidities of MDD, and rTMS can ameliorate pain syndromes such as neuropathic pain, headache, and fibromyalgia, it is unclear whether rTMS is effective for comorbid MDD with chronic pain. The authors ask if severity of chronic pain comorbid with MDD is associated with worse rTMS outcomes and propose that activity within overlapping functional neural pathways in the two diseases may predict response to treatment.

In a naturalistic clinical setting, 162 patients diagnosed with MDD were categorized into moderate/severe or no/minor chronic pain groups, each of which was subcategorized to receive EEG or not. Patients were

stably maintained on antidepressant medications. Patients received 10 Hz rTMS treatment administered to the left DLPFC and depression and pain symptoms were assessed before treatment, mid-way through treatment (session 15), and at the end of treatment (session 30). Main MDD outcomes were assessed using the Hamilton Depression Scale (HAM-D17) and Depressive Symptomatology Self Report (IDS-SR). Pain outcomes were assessed with the eight-question Visual Analog Scale (VAS). Results were compared across timepoints (baseline, mid-treatment, and after treatment) and among MDD outcome, pain severity, and peak alpha frequency (PAF) coherence in the EEG (a functional connectivity biomarker that has been related to pain syndromes and response to rTMS).

Both depression and pain symptoms were significantly reduced after rTMS treatment. For patients in the MDD + pain group, the IDS-SR decreased from 46.0 at baseline to 32.6, and the VAS decreased from 383.8

to 312.9 – both statistically significant differences. Patients with severe pain were 27% less likely to respond to MDD treatment than pain-free individuals – 19% of pain-free patients remitted vs. 3% of severe pain patients. Greater PAF phase coherence in the somatosensory and default mode networks was associated with greater response to treatment.

Impact: This study found that rTMS targeting the left DLPFC improved outcomes overall in patients with MDD and comorbid chronic pain. More severe pain was found to be associated with poorer response rates. Treatment response may be related to engagement of default-mode and somatosensory networks via alpha coherence. These results emphasize conceptualization of common network neurophysiology between MDD and chronic pain, which supports future investigation of circuit-, population-, or condition-specific interventions.

Corlier J, Tadayonnejad R, Wilson AC, et al. Repetitive transcranial magnetic stimulation treatment of major depressive disorder and comorbid chronic pain: response rates and neurophysiologic biomarkers. *Psychological Medicine*. 2021;1-10.

Promising Early Data for TMS in Treatment of Comorbid MDD and OCD

Collin M. Price, MD reviewing Tadayonnejad et al. *Brain Stim* 2020 Oct

In this small open-label case series, excitatory TMS to the left DLPFC followed by inhibitory rTMS to the SMA led to robust improvements in both MDD and OCD symptoms.

Major depressive disorder (MDD) responds very well to conventional transcranial magnetic stimulation (TMS) treatments, but cooccurring psychiatric illnesses like obsessive compulsive disorder (OCD) are frequent and may impact treatment outcomes. Comorbid MDD and OCD can lead to more severe disease courses and suicide deaths, underscoring the need for

effective treatments in this population. In this study, the authors report on an effective TMS protocol in a treatment-refractory population, and postulate how underlying neural circuits may explain the therapeutic effects.

Researchers recruited 7 patients (2 females) with treatment refractory comorbid MDD

and OCD who had failed an average of 6.8 medications and 2.4 psychotherapy courses prior to initiating TMS therapy. Each patient received 36 TMS sessions which included excitatory TMS to the left dorsolateral prefrontal cortex (DLPFC) and inhibitory TMS to the bilateral supplementary motor area (SMA). Excitatory TMS was delivered as either 10 Hz repetitive TMS (rTMS; 3000

pulses) or intermittent theta burst stimulation (iTBS; 600 pulses), while inhibitory TMS involved 1 Hz rTMS (1200 pulses). Outcomes were measured using the Inventory of Depressive Symptomatology – Self Report (IDS-SR) and Yale-Brown Obsessive Compulsive Scale (Y-BOCS) collected before and after the treatment course; response was defined as $\geq 35\%$ reduction in Y-BOCS and $\geq 50\%$ reduction in IDS-SR scores.

Patients showed significant improvements in both depressive and obsessive-compulsive symptoms after treatment 36. IDS-SR scores improved from a mean of

45.1 at baseline to 19.3 ($p=0.0017$), while the Y-BOCS scores improved from a mean of 24.2 to 12.7 ($p=0.0013$). Five of the seven patients (71%) showed full response on both the IDS-SR and Y-BOCS, while the remaining 2 showed partial responses on both. No serious adverse events were noted, and no patients returned for re-treatment. Based on their results, the authors suggest that targeting of the DLPFC with excitatory TMS modulates network activity that is both specific to MDD, via the default mode network (DMN), as well as shared between MDD and OCD, via downstream effects on the pregenual anterior cingulate cortex.

Tadayonnejad R, Wilson AC, Cortier J, et al. Sequential multi-locus transcranial magnetic stimulation for treatment of obsessive-compulsive disorder with comorbid major depression: A case series. *Brain Stimul.* 2020;13(6):1600-1602.

rTMS to Dorsomedial Prefrontal Cortex Effective for Treatment of Anorexia Nervosa with Comorbid MDD

Shawna Chan, MD reviewing Woodside DB et al. *J Eat Disord* 2021 Apr

In this open-label study, rTMS was associated with reduction of core anorexia nervosa psychopathology and correlated with relevant functional imaging changes.

Anorexia nervosa (AN) is a serious condition with one of the highest mortality rates among psychiatric disorders, yet it is an illness for which there are no reliably effective treatments. While existing data for repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex (DLPFC) in AN are limited, these authors have previously found that rTMS to the dorsomedial prefrontal cortex (DMPFC) demonstrated significant symptom reduction in bulimia nervosa and obsessive-compulsive disorder, conditions that share overlapping psychopathology with AN. Furthermore, the observed clinical improvement in those studies was correlated with changes in brain activity on functional magnetic resonance imaging (fMRI). Can DMPFC-rTMS lead to reduction of key symptoms of comorbid AN and demonstrate similar functional imaging correlates?

Researchers analyzed a subset of 19 female patients who underwent TMS for treatment of major depressive disorder or post-traumatic stress disorder and who concurrently met criteria for AN based on a full clinical review. Participants received an initial course of 20-30 sessions of once daily bilateral (left then right) DMPFC-rTMS (6000 pulses total, 10 Hz frequency, goal intensity of 120% of

motor threshold) over 4-6 weeks. Subjects completed the Eating Disorders Examination (EDE), Beck Depression Inventory (BDI), Hamilton Depression Inventory (HAM-D), Beck Anxiety Inventory (BAI), and Difficulties with Emotional Regulation Scale (DERS) before and after treatment. Additionally, baseline structural and resting-state fMRI with regions of interest (ROI) in the bilateral DMPFC and dorsal anterior cingulate cortex (dACC) were available in 16 subjects; associations were tested between this data and improvement in EDE score at first follow-up (0-4 weeks; $n=12$) or end-of-treatment ($n=4$).

Following DMPFC-rTMS, statistically significant improvements were noted in the EDE global scale ($p=0.01$) and the BAI measure of anxiety ($p<0.001$) after correction for multiple comparisons. Uncorrected comparisons were also significant for the EDE subscales Shape Concerns ($p=0.042$) and Weight Concerns ($p=0.024$), as well as the BDI measure of depression ($p=0.041$). The EDE subscale Eating Concerns and the HAM-D trended toward improvement. Percent EDE global score improvement was significantly correlated with decreased pre-treatment resting-state functional connectivity between the DMPFC to the right frontal pole and left

angular gyrus. In contrast, no correlation was found between improvement of global EDE scores and pre-treatment resting-state functional connectivity from the dACC to any area of the brain.

Impact: DMPFC-rTMS yielded some improvement in core domains of AN pathology, a notable finding in the context of a brief treatment course and the absence of additional therapeutic interventions such as psychotherapy and medication management. Neuro-imaging findings identified regions of the brain associated with cognitive and impulse control, and the authors suggest that a subgroup of AN patients with prominent symptoms of impulsivity, negative self-referential thinking, and/or mood dysregulation may experience greater benefit from treatment with rTMS. These preliminary results should be interpreted with caution due to the open-label design and small sample size.

Woodside DB, Dunlop K, Sathi C, Lam E, McDonald B, Downar J. A pilot trial of repetitive transcranial magnetic stimulation of the dorsomedial prefrontal cortex in anorexia nervosa: resting fMRI correlates of response. *J Eat Disord.* 2021;9(1):52. Published 2021 Apr 17.

Approaches to Use of rTMS for Treatment of MDD with Comorbid Psychiatric Illnesses

Joseph Kaizer, MD reviewing Chou PH et al. *Clin Psychopharmacol Neurosci* 2021 May

This review paper summarizes the use of repetitive transcranial magnetic stimulation (rTMS) and intermittent theta burst stimulation (iTBS) in the treatment of major depressive disorder (MDD) with PTSD, Substance Use Disorder, and other comorbid psychiatric illnesses.

High-frequency rTMS (HF-rTMS) to the left dorsolateral prefrontal cortex (DLPFC), low-frequency rTMS (LF-rTMS) to the right DLPFC, and iTBS of the left DLPFC have all been shown in extensive research to be effective treatments for depression. However, many of these studies excluded psychiatric comorbidities, and comparatively few studies have examined the most effective treatments for MDD with comorbid psychiatric illnesses. This review explores the evidence for the most effective TMS treatments of MDD with comorbid anxiety, PTSD, and substance use disorders, and discusses the biomarkers which might inform treatment decisions in these populations.

Among patients with MDD there is a high prevalence of anxiety and post-traumatic stress (PTSD) disorders, with rates as high as 20-25%. The authors found the most robust literature for TMS treatment of MDD with comorbid anxiety disorders. In multiple open-label and sham-controlled studies, sequential bilateral rTMS and right-sided LF-rTMS were effective in reducing symptoms of both depression and anxiety. Comorbid anxiety disorders did not appear to reduce

effectiveness of TMS for depression, in contrast to some prior literature on the effectiveness of antidepressant medications in this population.

There was sparse literature on the treatment of MDD with comorbid PTSD and substance use disorders (SUD). A handful of retrospective, open-label, and sham-controlled studies suggested 5 Hz rTMS to the left DLPFC and 1 Hz rTMS to the right DLPFC were effective in treating both depressive and PTSD symptoms. The authors also report on literature suggesting 20 Hz rTMS to either left or right DLPFC and right-sided iTBS are effective for isolated PTSD, and may have efficacy with comorbid MDD. The authors found no studies focused specifically on comorbid MDD and SUD. However, they do report on literature showing left-sided HF-rTMS is effective in reducing craving and use of multiple substances, and one study showed significant reductions in depression scales while treating cocaine use disorder. Because left-sided HF-rTMS is a main-stream treatment option for patients with MDD, it should also be effective in MDD with comorbid SUD.

In a review of the biomarkers associated with these illnesses, the authors note significant overlap between the biomarkers of depression and anxiety, particularly hyperactivity of the right frontal cortex; they also note overlap between depression and SUD through hypoactivity of the left frontal cortex. Important biomarkers in PTSD include excessive frontal theta activity, providing theoretical support for the 5Hz rTMS treatment, as well as hypoactivity of the right frontal cortex.

Impact: Although extensive literature has shown the efficacy of rTMS and iTBS in the treatment of MDD, relatively few studies have focused on the comorbidities that frequently present with MDD. This review summarizes the nascent literature, providing tentative treatment recommendations and appropriately calling for more rigorous study of these important intersections of psychiatric illnesses.

Chou PH, Lin YF, Lu MK, et al. Personalization of Repetitive Transcranial Magnetic Stimulation for the Treatment of Major Depressive Disorder According to the Existing Psychiatric Comorbidity. *Clin Psychopharmacol Neurosci*. 2021;19(2):190-205.

