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PULSE

A Monthly Update on Advances in Neuromodulation

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Subthreshold Priming Associated with Improved Outcomes in rTMS for MDD

Joseph Kaizer, MD reviewing Lee JC et al. Brain Stim 2021

In this retrospective review of patients who underwent iTBS priming before undergoing rTMS, those who received subthreshold intensity therapy showed superior clinical outcomes compared with those who received suprathreshold therapy.

Repetitive Transcranial Magnetic Stimulation (rTMS) directed at the dorsolateral prefrontal cortex (DLPFC) is an effective treatment for major depressive disorder (MDD). When predicting the efficacy of rTMS, initial response to high-frequency left-sided (HFL) stimulation of the DLPFC is an important indicator of long-term outcomes. When patients show no early signs of benefiting from HFL stimulation of the DLPFC, intermittent theta-burst stimulation priming (iTBS-P) can improve clinical efficacy. However, it has yet to be determined how the intensity of the priming stimulus and number of priming pulses affects clinical outcomes. Are intensity and pulse number of iTBS-P before rTMS associated with improved response?

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Researchers at UCLA conducted a retrospective review of 71 patients diagnosed with MDD who received iTBS-P augmentation after receiving at least five sessions of HFL and showing little clinical benefit. Weekly self-ratings on the Inventory of Depressive Symptomatology Self Report (IDS-SR) were obtained after every five treatments to direct treatment parameters. All patients received a total of 30 HFL rTMS treatments to the left DLPFC. iTBS-P augmentation was offered to most patients after 10 treatments if IDS-SR scores indicated <20% improvement, although augmentation could be offered earlier during treatment based on clinical judgment. Augmentation consisted of iTBS delivered with 600-1800 pulses at 80-120% of motor threshold (MT) immediately before receiving standard HFL rTMS. Participants maintained their outpatient psychotropic medication regimen during rTMS treatment. For data analysis, participants were dichotomized by MT intensity (< or > 100% MT) and pulse number (< or > 1200 pulses), using the mean for each across a participant's priming sessions. A linear model was fit to the data, with change in IDS-SR as the primary outcome variable, and intensity (subthreshold or suprathreshold), number of pulses (<1200 or >1200), gender, age, and the number of iTBS-P treatments as predictors.

Fifty-nine participants (83%) received 10 or more sessions of HFL stimulation prior to being offered priming augmentation. The mean number of iTBS-P sessions was 16.5 , and the overall group mean percent improvement in IDS-SR score from baseline to treatment #30 was 31.8 %. The linear model indicated a significant effect of stimulus intensity, with subthreshold stimulation associated with lower IDS-SR score at treatment #30 (p=0.005); no other significant effects were noted. Twenty-seven participants (38%) received subthreshold stimulation. This group also received significantly fewer pulses compared to the suprathreshold group (775 vs. 962, p=0.022) and had significantly lower IDS-SR scores at treatment #30 (24.6 vs. 32.6), though there was not a statistically significant difference between groups in response (33% vs. 18%) or remission (19% vs. 5%) rates. All patients offered iTBS-P elected to proceed with the augmentation strategy, and no subjects were forced to discontinue therapy due to adverse effects.

Impact: The findings here suggest a superior response to iTBS-priming of rTMS treatment when exposed to subthreshold vs. suprathreshold priming stimulation. Keeping in mind the limitations of this study, most notably the lack of randomization or experimental control of priming intensity and pulse number, these results are nonetheless an important signal suggesting the value of subthreshold iTBS priming. The field would benefit from future prospective randomized controlled trials assessing this question.

Lee JC, Corlier J, Wilson AC, et al. Subthreshold stimulation intensity is associated with greater clinical efficacy of intermittent theta-burst stimulation priming for Major Depressive Disorder. Brain Stimul. 2021;14(4):1015-1021. doi:10.1016/j.brs.2021.06.008

Acute Improvements Found with rTMS for Cocaine Use Disorder

Collin M. Price, MD reviewing Garza-Villarreal et al. Biol Psychiatry Cogn Neurosci Neuroimaging 2021

A 2-week randomized, double-blind, sham-controlled study of rTMS in cocaine use disorder yielded significant reductions in cravings and impulsivity, though these effects were not fully maintained during a subsequent 6 month open-label phase.

There are few effective treatments for most substance use disorders (SUD), with disorders associated with stimulants such as cocaine proving particularly difficult to treat. As repetitive transcranial magnetic stimulation (rTMS) has shown effectiveness in a variety of psychiatric conditions, interest has grown in applying this novel treatment to SUD. Can the addition of rTMS to standard treatment of cocaine use disorder (CUD) improve treatment outcomes?

Researchers recruited 44 participants who were identified as having high-consumption of cocaine for at least one year. The study designed involved two phases: an acute phase, which was a double-blind, parallel-group, two-week randomized controlled trial; and a maintenance phase, which was a 6-month open-label trial. rTMS was delivered at 100% of motor threshold to the left dorsolateral prefrontal cortex (l-DLPFC). During the acute phase, treatments were given once-daily, 5 days a week, for two weeks, with 5000 pulses delivered per day at 5 Hz. During the maintenance phase, similar sessions were delivered two times per week. Data were acquired at baseline, 2 weeks, 3 months, and 6 months, and included clinical outcomes as well as structural and functional magnetic resonance imaging (MRI) data. Primary outcomes measures were craving (measured via visual analog scale [VAS] and questionnaire) and cocaine-positive urine, with secondary outcomes including impulsivity, depression, anxiety, and sleep quality. A modified Timeline Followback method was used to assess self-reported frequency and amount of cocaine use. MRI data was used to analyze resting-state functional connectivity (rs-FC) between l-DLFPC and ventromedial prefrontal cortex (vmPFC).

After the 2-week acute phase, active rTMS was more effective than sham at reducing cravings based on VAS (p=0.013, d=0.77), though not via questionnaire (p=0.11, d=0.48). Impulsivity also showed a greater reduction after two weeks of active rTMS (p=0.011, d=0.79), but anxiety, depression, sleep, and cocaine-positive urine results did not differ significantly between groups. During the maintenance phase, rTMS treatment reduced cravings at 3 months compared to baseline, based on VAS and questionnaire, and at 6 months based on questionnaire only (p<0.01). Impulsivity, anxiety, and depression also showed significant reductions from baseline at 3 months, but not 6 months (p<0.01). Timeline Followback analysis revealed a significant reduction in both frequency and amount of cocaine use from pre-enrollment levels, which was maintained for 6 months. rs-FC between l-DLPFC and vmPFC was significantly increased after the acute phase of treatment, though this finding was not maintained at 3- and 6-month follow-ups. Functional connectivity between these regions did not correlate with craving or impulsivity measures. Attrition rates were high in this study, with 17% dropout at 2 weeks, 63% at 3 months, and 72% at 6 months.

Garza-Villarreal EA, Alcala-Lozano R, Fernandez-Lozano S, et al. Clinical and Functional Connectivity Outcomes of 5-Hz Repetitive Transcranial Magnetic Stimulation as an Add-on Treatment in Cocaine Use Disorder: A Double-Blind Randomized Controlled Trial. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021;6(7):745-757. doi:10.1016/j.bpsc.2021.01.003

Impact: This study provides RCT-level evidence of effectiveness for 5-Hz rTMS to the left DLPFC in the acute reduction of cravings and impulsivity in cocaine use disorder. The additional open-label phase of the study indicates some persistent benefits in these outcomes up to 3 months out, and maintenance of reduced self-reported cocaine use up to 6 months out. Acute effects of rTMS were observed on rs-FC in a key neural circuit related to substance use disorders, though these changes were not associated with the clinical findings. Although limited by the significant dropout rates that are common to SUD studies, this work nonetheless provides strong support for continued investigation of rTMS in the treatment of CUD.

rTMS Treatment of MDD May Be Less Affected by Borderline Personality Traits than ECT

Michael K. Leuchter, MD reviewing Ward H. et al. Journal of Affective Disorders 2020

In this retrospective naturalistic study, investigators found that while the presence of borderline personality disorder (BPD) traits diminished the efficacy of Electroconvulsive Therapy (ECT), no reduction was found in the response to repetitive Transcranial Magnetic Stimulation (rTMS).

Comorbid personality disorders are extraordinarily common in major depressive disorder, and generally predict a decreased response to antidepressant pharmacotherapy and psychotherapy. This is even true for ECT, an FDA-approved therapy for treatment resistant depression. rTMS has been established as effective for treatment-resistant depression, but it has been studied little in those with co-morbid personality disorders. Does the presence or lack of BPD traits influence someone's response to rTMS or ECT?

Researchers performed a retrospective chart review of 1790 treatment-seeking patients receiving TMS (n=356) or ECT (n=1434) at McLean Hospital between 2011-2018. All subjects completed the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD) self-report inventory at baseline, with scores of at least 5 serving as a proxy for a BPD diagnosis. Subjects also completed the self-report 16-item Quick Inventory of Depression Screening (QIDS-SR) at baseline, every 5 ECT treatments or 10 TMS treatments, and at the end of the course of treatment. Subjects receiving TMS underwent treatment with the Brainsway system using a H1 coil stimulating left dorsolateral prefrontal cortex (1980 pulses, 18Hz delivered over 20 minutes at 120% resting motor threshold for 20 to 36 sessions). Subjects receiving ECT underwent treatment with the Mecta Spectrum 5000Q starting with unilateral stimulation, followed by progression to increased intensity or bilateral stimulation if needed (6 to 12 sessions). The outcome measure was change in QIDS-SR score from baseline at each measured timepoint; rates of response and remission were neither calculated nor examined for either group. MSI-BPD scores and number of treatments were examined as covariates in a two-way repeated measures ANOVA.

Both groups demonstrated a similar prevalence of BPD, while the ECT group had a higher baseline QIDS-SR score (21.4 vs 20.3, p<0.05). In both treatment groups, subjects' QIDS-SR scores improved with more treatment sessions. In ECT, there was a significant interaction between BPD status and number of treatment sessions, indicating that those with BPD traits, while improved with ECT, improved less than those without BPD traits (p=0.02). This interaction between BPD status and number of sessions was not present with TMS, indicating that the presence of BPD traits had no bearing on response to TMS (p=0.18). Further analysis utilizing a single linear mixed-effects model including both sets of treatment data did not show a significant interaction between treatment modality, BPD trait status, and number of sessions.

Impact: ECT and rTMS are both effective treatment options for treatment-resistant depression.However, while the efficacy of ECT is generally diminished in the presence of co-morbid BPD, this large-sample study suggests that rTMS has similar efficacy regardless of the presence of BPD traits. This result, while not conclusive given its retrospective naturalistic nature, suggests that further study may more conclusively demonstrate the efficacy of rTMS in depression with co-morbid BPD, and possibly other personality disorders.

Ward HB, Yip A, Siddiqui R, Morales OG, Seiner SJ, Siddiqi SH. Borderline personality traits do not influence response to TMS. J Affect Disord. 2021;281:834-838. doi:10.1016/j.jad.2020.11.054

Improved Negative Symptoms in Schizophrenia with High-Frequency Transcranial Random Noise Stimulation

Collin M. Price, MD reviewing Chang et al. J Psychiatr Res 2021

In a double-blind, randomized, sham-controlled study, high-frequency transcranial random noise stimulation targeted to the prefrontal cortex led to significant improvements in the negative symptoms of schizophrenia. Effect sizes were large, and improvements persisted up to one-month.

The negative symptoms associated with schizophrenia are notoriously difficult to treat, though various neuromodulatory techniques have shown some promise in recent years. One such technique, high-frequency transcranial random noise stimulation (hf-tRNS), utilizes alternating current stimulation delivered in a randomized pattern at varying intensities and frequencies. Such stimulation is hypothesized to optimize signal-to-noise ratios in affected neural networks, and has been shown to improve cognitive tasks as well as symptoms of schizophrenia in limited case reports. Can hf-tRNS improve the negative symptoms of schizophrenia in a randomized controlled trial?

Researchers in Taipei, Taiwan recruited 36 participants to take part in a randomized, double-blind, sham-controlled study of hf-tRNS. Participants were included if they carried a diagnosis of schizophrenia or schizoaffective disorder, were stable on an antipsychotic, and had a Positive and Negative Syndrome Scale (PANSS)-Total <120. After randomization to active (n=18) or sham (n=18) conditions, participants received treatments twice a day for 5 consecutive days, with >2h between each treatment. Five electrodes were placed in a 4x1 configuration, with the single anode placed over 10-10 EEG-position AF3 (left lateral prefrontal cortex), while the four cathodes were placed over positions AF4, F2, F6, and FC4 (right lateral prefrontal cortex). Active hf-tRNS was delivered using a variable intensity between -1mA and 3mA, with a variable frequency between 100 to 640 Hz, for 20min each treatment including a 15s ramp-in/ramp-out. Sham hf-tRNS involved 40s of 2mA stimulation followed by a 110microA, 15ms pulse delivered at a frequency of 1.81 Hz for 20min. The primary outcome was the change over time in the PANSS Factor Score for Negative Symptoms (PANSS-FSNS) between baseline and end-of-treatment (10 sessions), one-week follow-up, and one-month follow-up. Response rates, tolerability, and cognitive measures were among the secondary outcome measures. Data were analyzed in an intention-to-treat analysis, using Bonferroni correction for multiple comparisons.

Thirty-five participants completed the study, with one participant in the active group dropping out after 4 stimulations, for non-medical reasons. The primary outcome of percent-change in PANSS-FSNS was significantly greater in the treatment group compared to the sham group, at all timepoints (-17.11 % vs. -1.68 % at end-of-treatment; -16.47 % vs. -0.10 at 1 week; and -16.82 % vs. -0.15 % at 1 month). The end-of-treatment effect sizes for active hf-tRNS were large for PANSS-FSNS (Cohen's d = 2.16) and PANSS-Total (d=1.69). Active treatment also showed improvements in awareness of negative symptoms (d=1.37), subjective response to taking medication (d=1.85), and extrapyramidal symptoms severity (d=1.26). Negative symptoms awareness showed persistent improvements at 1 month. Blinding assessments indicated adequate blinding, and no significant difference was noted in mean total side effect score.

Impact: This randomized, double-blind, sham-controlled study shows that hf-tRNS can provide rapid and enduring improvements in the negative symptoms of schizophrenia. Although results were modest in absolute terms, effect sizes were large. With a paucity of effective treatments for negative symptoms in schizophrenia, positive findings like this are encouraging. Future work optimizing delivery and patient selection may show even further advances with this promising new technology.

Chang CC, Lin YY, Tzeng NS, Kao YC, Chang HA. Adjunct high-frequency transcranial random noise stimulation over the lateral prefrontal cortex improves negative symptoms of schizophrenia: A randomized, double-blind, sham-controlled pilot study. J Psychiatr Res. 2021;132:151-160. doi:10.1016/j.jpsychires.2020.10.008