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PULSE

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Concomitant Stimulant Medications May Improve Outcomes of rTMS for MDD

Collin M Price reviewing Wilke et al. Depress Anxiety 2022 Apr 7

In this retrospective analysis of patients treated with a standard course of rTMS for MDD, patients taking psychostimulants showed a significantly greater decrease in the IDS-SR30 compared to those not taking these medications.

In a clinical population seeking rTMS treatment for MDD, concomitant pharmacotherapy is common. Prior work has suggested that these medications can influence outcomes, with some medications potentially improving rTMS efficacy and others reducing it. This study used a retrospective analysis to compare rTMS outcomes in patients with MDD taking psychostimulants compared to those not taking these medications.

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From a clinical cohort treated with rTMS for MDD between September 2009 and January 2017, researchers identified 37 patients taking known dosages of one or more psychostimulant medications (dextroamphetamine/ lisdexamfetamine, methylphenidate/ dexmethylphenidate, and/or modafinil/armodafinil) and compared them with a control group of 53 patients who were taking neither stimulants nor benzodiazepines (benzodiazepine users were excluded given prior work suggesting they may reduce rTMS efficacy). Each patient received a course of 30 rTMS treatments over six weeks, delivered initially as 3000 pulses at 10 Hz and at the maximally-tolerated intensity up to 120% MT. After 10 sessions, the rTMS therapy could be augmented based on clinician judgement. Patients completed the 30-item Inventory of Depressive Symptomatology Self Report (IDS-SR30) at the start of treatment and after 10, 20, and 30 rTMS sessions.

An ANOVA revealed a significant main effect of treatment number ($p<0.001$) as well as a significant treatment number x psychostimulant user interaction ($p=0.001$), with patients who received stimulants demonstrating significantly greater reductions in IDS-SR30 score compared to those not taking stimulants. Effect sizes favoring the stimulant group were small at $d=0.32$ after session 10 and $d=0.35$ after session 30. An ANOVA analyzing the three classes of stimulants separately did not yield any significant results, except for a main effect of treatment number ($p<0.001$). In analyses of IDS-SR30 subscales the combined stimulant group also showed significantly greater improvement compared to the control group on measures of sleep ($p=0.024$) and mood/cognition ($p=0.004$), but not anxiety/arousal ($p=0.311$). Wilke et al. also evaluated the effect of stimulant dose, finding that lower doses of lisdexamfetamine/dextroamphetmine were associated with significantly greater improvement ($r=-0.44$, $p=0.038$), though this remained at trend level after correction for false discovery rate ($p=0.069$). Sample sizes for the other two stimulant classes were too small to calculate accurate correlation coefficients.

Impact: This retrospective study of patients with MDD seeking rTMS in a clinical setting revealed an association between taking a psychostimulant and greater improvements on a measure of depression. Although limited by the retrospective nature and small sample size, these intriguing results suggest that low dose stimulant medications may enhance clinical efficacy of rTMS treatment for depression, and warrant follow-up with well-controlled prospective studies.

Wilke SA, Johnson CL, Corlier J, et al. Psychostimulant use and clinical outcome of repetitive transcranial magnetic stimulation treatment of major depressive disorder [published online ahead of print, 2022 Apr 7]. Depress Anxiety. 2022;10.1002/da.23255. doi:10.1002/da.23255

rTMS Shows Promise for Treating Suicidal Ideation in Patients with Treatment Resistant Depression

Nicole Wong reviewing Mehta et al. J Clin Psychiatry Jan 2022

A meta-analysis of 16 studies, comprised of both RCTs and uncontrolled trials, suggests that rTMS may be an effective treatment for suicidal ideation (SI) in treatment-resistant depression (TRD), although more investigation is needed.

Over 15 years of research has shown rTMS to be an effective treatment for TRD, but there are no meta-analyses summarizing its efficacy in reducing SI in these patients. Collectively, what do 15 years of studies show about how rTMS affects SI in patients with TRD?

Researchers identified studies that: 1) used rTMS as a treatment in patients ages ≥ 16 years with either bipolar or unipolar depression; 2) reported SI scores as an outcome measure; and 3) were available in English. Abstracts, individual case reports, reviews, and editorials were excluded. The Hedges' *g* was computed as a marker of effect size for each study, an approach that allowed the authors to compute study weights using sample size and compare study outcomes on a single scale. RCTs that met inclusion criteria were included in a primary quantitative analysis, while the active arms of randomized trials as well as uncontrolled trials (i.e., an "all trials" group) were included in a secondary quantitative analysis. A third exploratory analysis was performed using the uncontrolled trials only.

Of the 16 studies that met inclusion criteria, six were RCTs, four were open-label trials, three were retrospective analyses of primary studies, two were case series, and one was a single-blind trial. The RCTs included a sum of 506 patients, while the "all trials" group included a sum of 833 patients. In the six RCTs analyzed, the cumulative effect size was 0.158 (95% CI = -0.078 to 0.393), and the total change in SI scores for rTMS treatment was not significantly greater than for sham ($p=0.191$). For the 15 studies included in the all trials" analysis (one study could not

be used because it did not report post-treatment SI scores for the active treatment arm alone), the cumulative effect size was moderate at 0.692 (95% CI = 0.463 to 0.922), with a significant decrease in SI scores after rTMS treatment ($p < 0.001$). For the 10 studies included in the uncontrolled trials analysis, the cumulative effect size was moderate at 0.565 (95% CI = 0.322 to 0.807) and significant ($p < 0.001$).

Impact: In this meta-analysis of 16 studies examining the effect of rTMS on SI in TRD, an analysis of both controlled and uncontrolled trials demonstrated a statistically significant improvement in SI scores with moderate/large effect sizes. An analysis of six RCTs comparing rTMS to sham showed a similar trend but did not reach statistical significance. The wide variability of baseline SI (e.g., ranging from inpatients with acute suicidality to those with only mild SI) and large differences in rTMS protocols among the RCTs may partially account for the non-significant effect size. Inclusion of SI as an outcome measure in future studies of rTMS for TRD may allow future analyses to more clearly elucidate the effects of this therapy on SI in these patients.

Mehta S, Konstantinou G, Weissman CR, Daskalakis ZJ, Voineskos D, Downar J, Mulsant, BH, Blumberger DM. The Effect of Repetitive Transcranial Magnetic Stimulation on Suicidal Ideation in Treatment-Resistant Depression: A Meta-Analysis. J Clin Psychiatry. 2022 Jan 18;83(2):21r13969. doi: 10.4088/JCP.21r13969. PMID: 35044731.

Scrambler Therapy Proves Effective in Treating Central Neuropathic Pain when Compared to Sham

Mengdong He, MHS reviewing Mori N et al. Neuromodulation 2020 May 5

In this single-blind, randomized, sham-controlled trial, Scrambler therapy was shown to be a feasible, acceptable, effective, and safe intervention for central neuropathic pain in patients with neuromyelitis optica spectrum disorder (NMOSD).

Central neuropathic pain associated with neuromyelitis optica spectrum disorder (NMOSD) is a rare debilitating condition marked by inflammation of the optic nerve (optic neuritis) and inflammation of the spinal cord (myelitis). It can lead to diffuse pain of central origin and treatment options are limited. Scrambler therapy, a form of peripheral nerve stimulation approved by the FDA for treating pain, has been proposed as a potential treatment for persistent central neuropathic pain. The aim of this study is to determine the feasibility, acceptability, effectiveness, and safety of Scrambler therapy for treating central neuropathic pain in NMOSD and its effects on co-occurring symptoms.

Twenty-two adult patients with self-reported neuropathic pain caused by MRI-confirmed NMOSD were enrolled in this single-blind, randomized, sham-controlled trial. Patients were required to have pain at a level of ≥4 on an 11-point numeric rating scale (NRS) and persistent for >3 months, and they were allowed to use pain medications. Participants were 1:1 randomized to Scrambler vs. sham treatment for 10 consecutive weekdays. Scrambler electrodes were placed in dermatomes surrounding the level of spinal cord injury and pain, and stimulation was delivered at an intensity of maximum tolerable level for 35 minutes per session. In sham treatment, electrodes were connected to small motors producing vibratory sensation, with similar placement. The primary outcomes were feasibility (adherence to visit schedule) and acceptability (whether the patient wants to continue treatment in clinic if available). Secondary outcomes included safety and effectiveness. Patients' pain severity and interference, anxiety, depression, and sleep disturbance were also measured using surveys. All outcomes were assessed at baseline, the end of the 10-day treatment period, and 30 and 60 days after the treatment period.

The median NRS pain score decreased from 5.0 to 1.5 after 10-day Scrambler therapy ($p < 0.001$), while the median NRS score did not significantly decrease in the sham group (5.0 to 4.0; $p = 0.42$). Eight of 11 (73%) patients in the Scrambler group had a clinically meaningful improvement in pain (≥1.8 point decrease in NRS pain scores from baseline to the end of treatment), and 4 patients (36%) achieved complete pain free status immediately. The NRS pain scores in the Scrambler group remained significantly decreased at 30 days ($p = 0.0195$), but the effect was not sustained at 60 days ($p = 0.0518$). After treatment with Scrambler therapy, the median depression score also significantly decreased ($p = 0.03$) and the change of median anxiety scores was significant in responders of Scrambler therapy ($p = 0.02$). However, in the sham group, no significant change in the median anxiety, depression, or sleep disturbance scores were found. No significant difference was observed between the two groups in acceptability or feasibility, and no severe adverse events were reported during the 10-day treatment period in either group.

Impact: This single-blind, randomized, sham-controlled trial showed that Scrambler therapy is a feasible, acceptable, effective, and safe intervention for central neuropathic pain in patients with NMOSD. Significantly greater pain reduction was reported by patients who received Scrambler therapy compared to sham, and the effect was sustained for 30 days after the end of treatment. Scrambler therapy also improved depression and anxiety in a subset of patients who responded to the treatment. Despite limitations of single-blind design and small sample size, the findings warrant a larger study to further assess the effect of Scrambler on pain, reduction of pain medication use, co-occurring symptoms, and quality of life in patient with NMOSD.

Mealy MA, Kozachik SL, Cook LJ, Totonis L, Salazar RA, Allen JK, Nolan MT, Smith TJ, Levy M. Scrambler therapy improves pain in neuromyelitis optica: A randomized controlled trial. Neurology. 2020 May 5;94(18):e1900-e1907. doi: 10.1212/WNL.0000000000009370. Epub 2020 Apr 8. PMID: 32269109; PMCID: PMC7274926.

Tractography-Guided TMS Demonstrates Indirect, Dose-Dependent Stimulation of a Deep Brain Structure

David Lee reviewing Luber B et al. Neuroimage 2022 Apr 1

TMS of a cortical site guided by diffusion tractography facilitates dose-dependent modulation of the fMRI BOLD signal in a deep brain structure.

Recent advances in TMS coil placement using fMRI and stereotactic robotics have allowed for precise and reliable targeting of cortical regions of interest. Conventional wisdom holds that the effects of TMS are limited to the superficial cortex of ~3 cm in depth; however, recent evidence has suggested that functional and structural connectivity among brain regions allows TMS of cortical areas to modulate deep brain structures. In this study, the authors ask whether diffusion tractography can be used to facilitate modulation of a deep brain structure by applying TMS to a cortical site identified via structural connectivity.

In this work involving 10 healthy subjects, the researchers selected the right subcallosal cingulate gyrus (BA25) as a target deep brain structure for evaluation of tractography-guided TMS. BA25 has been identified as an important subcortical structure implicated in the pathophysiology of MDD, and therefore, a therapeutic target for DBS. Here, researchers identified a site on the scalp overlying a cortical region structurally connected to BA25 based on a diffusion tractography model of white matter fibers. Then, while stimulating with single pulses at this tractography-derived site, the researchers obtained interleaved TMS-fMRI scans, where TMS pulses were applied and the BOLD signal was measured as a marker of modulated functional activity. The TMS session consisted of 160 pulses, with four intensity levels (80%, 100%, 120%, and 140% of MT). The fMRI data was analyzed by fitting a general linear model and identifying which brain regions were activated by the TMS pulses. Then, the degree of activation was compared for 100%, 120%, and 140% with the baseline of 80% MT levels.

Across all subjects, diffusion tractography reliably identified the medial frontal pole (BA10) on the superficial cortex as structurally connected to the deep brain structure BA25. Thus, the tractography-derived stimulation sites across all subjects were within a 5 cm diameter region on the forehead. In the whole-brain analysis, there was significantly increased activation in BA25 with 120% and 140% intensity compared to the 80% baseline. By employing an analysis technique called guided principal analysis, the researchers identified a monotonically increasing relationship between TMS intensity and BOLD signal activation magnitude.

Impact: This study demonstrates that TMS applied to a diffusion tractography-derived cortical target can induce dose-dependent functional changes in a structurally-connected deep brain structure. This potentially extends the utility of TMS by enabling researchers to target deeper brain areas which were previously thought beyond reach. Replication of these findings in a clinical sample could open up new avenues of treatment, particularly for conditions in which no effective cortical target has been established.

Luber B, Davis SW, Deng ZD, Murphy D, Martella A, Peterchev AV, Lisanby SH. Using diffusion tensor imaging to effectively target TMS to deep brain structures. NeuroImage. 2022 Apr 1;249 https://doi.org/10.1016/j.neuroimage.2021.

Abbrevations

DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent theta burst stimulation)
LIFUP (low intensity focused ultrasound pulsation)
TENS (transcutaneous electrical nerve stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tACS (transcranial alternating current stimulation)
tDCS (transcranial direct 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)

AUD (alcohol use disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
SUD (substance use disorder)
TRD (treatment resistant depression)

BDI (Beck Depression Inventory)
HAM-D (Hamilton Depression Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)
PANSS (Positive and Negative Symptom Scale)
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)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)

DLPFC (dorsolateral prefrontal cortex)
M1 (primary motor cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)