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PULSE

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Scrambler Therapy Especially Effective for a “Paroxysmal” Subset of Neuropathic Pain

David Lee reviewing Min YG et al. Neuroimage 2022 May

A prospective open-label study of Scrambler therapy suggests noninvasive transcutaneous electrical stimulation may be preferentially favorable for the “paroxysmal” neuropathic pain phenotype.

Neuropathic pain is a prevalent condition affecting up to 10% of the general population, in which patients experience unpleasant sensations that can be attributed to the peripheral or central somatosensory nervous system. While tricyclic antidepressants and gabapentinoids have served as the first-line pharmacological agents for managing neuropathic pain, their efficacy and tolerance have been limited, with less than one third of patients experiencing 50% or greater relief. Scrambler therapy is an alternative approach for those with drug-resistant neuropathic pain that employs transcutaneous electrical

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stimulation to replace, or *scramble*, the endogenous pain signal carried by the C fibers with the synthetic non-pain information.

In a prospective, open-label, single-arm trial of 25 patients with chronic neuropathic pain unresponsive to conventional pharmacological management, participants received Scrambler therapy for two weeks. Each week consisted of five days with a single session each followed by two days of interruption, with each session consisting of 30 minutes of electrical stimulation administered through a pair of electrodes placed on the skin above where the patient has been experiencing the pain. The response to the Scrambler therapy was assessed using a patient-reported numerical rating scale (NRS) of pain ranging 0-10 across the 10 sessions. Investigators also subdivided participants' pain ratings into five subcategories as defined by the Neuropathic Pain Symptom Inventory (NPSI): superficial (burning), deep (squeezing), paroxysmal (stabbing), evoked (by brushing), and paresthesia (pins and needles). Following completion of the therapy sessions, researchers performed post-hoc hierarchical clustering analysis of NPSI pain profiles across all participants, which produced three distinct clusters of pain phenotypes, regardless of pain etiology: 1) "evoked pain," 2) "paroxysmal pain," and 3) "spontaneous pain."

Linear mixed-effects modeling of the NRS after two weeks of Scrambler treatment showed a 15% neuropathic pain reduction compared to baseline ($p<0.001$). The model further showed significant differential effects of Scrambler therapy on three distinct clusters of pain phenotypes ($p<0.002$), with a marked decrease in pain for cluster 2 ("paroxysmal pain," 23% decrease) compared to the other two clusters (18% and 3.7% decrease for "evoked pain" and "spontaneous pain," respectively). The authors suggest that the preferential effect of Scrambler therapy on "paroxysmal pain" may be attributed to the well-preserved C-fibers through which the therapy is theorized to exert its pain-modulating effects.

Impact: This prospective, open-label study demonstrated the efficacy of a two-week course of Scrambler therapy in reducing drug-resistant neuropathic pain. Using hierarchical clustering, the researchers identified three broad patterns of neuropathic pain, characterized as "evoked," "paroxysmal," and "spontaneous." The treatment outcome was found to differ across the three clusters, with the most favorable outcomes in the "paroxysmal" neuropathic pain cluster. The results of this study should be replicated in a larger population of subjects.

Min YG, Baek HS, Lee KM, Hong YH. Differential response to scrambler therapy by neuropathic pain phenotypes. Sci Rep. 2021;11(1):10148. Published 2021 May 12. doi:10.1038/s41598-021-89667-6

A Review of Potential Transdiagnostic Benefits with rTMS to DLPFC in MDD and AUD

Tiana J Raphel, MD reviewing Tang et al. Brain Sciences 2021 Dec

This review of selected literature on rTMS for MDD and AUD summarizes the outcomes in both disorders, highlighting the DLPFC as an important target. The authors also discuss how symptoms such as executive dysfunction may be transdiagnostic and could mediate the improvements observed in both disorders after rTMS.

MDD and AUD are commonly comorbid and lead to more severe illness by increasing suicide risk, length of depressive episodes, and healthcare utilization. Current treatments for comorbid MDD and AUD (MDD+AUD) are limited as alcohol use can increase safety risks of some antidepressants (i.e., bupropion) and outcomes show modest effects of antidepressants. Current approaches to MDD+AUD treatment rarely address both disorders at the same time. In this "narrative review," the authors summarize selected rTMS clinical trials results for the two disorders independently as well as the available literature for rTMS treatment of MDD+AUD. Though the exact method of study selection was not described, they summarize roughly 25 trials of rTMS for MDD, 17 trials of rTMS for AUD, and three trials of rTMS for MDD or dysthymia with comorbid AUD. The authors reported no quantitative results from their review of the literature.

The evidence base for rTMS in MDD is very strong, with FDA approval over the past 15 years achieved for HFL targeting the DLPFC, dTMS targeting much of the prefrontal cortex and deeper midline structures, and iTBS targeting DLPFC. Other protocols found to be effective with high quality evidence for MDD include low frequency (~1-5 Hz) stimulation to the right DLPFC and bilateral rTMS (low frequency right DLPFC followed by high frequency left DLPFC). No convincing evidence indicates that one protocol is better than another, although low frequency stimulation may be more tolerable.

Studies of rTMS in AUD are fewer and less robust than those available for MDD. The right DLPFC is targeted in AUD

treatment protocols rather than the left due to better results in studies of cocaine cravings, and early studies implicating the right DLPFC in cognitive processes related to craving and drug seeking. In line with this thinking, a small study of inhibitory continuous theta-burst (cTBS) to the right DLPFC led to increased ad libitum alcohol consumption and worse performance on inhibition tests (stop-signal reaction time task). Positive results have also been found using dTMS (with an H1 coil) and bilateral stimulation with the H8 coil (which specifically targets the insula rather than the anterior prefrontal area).

A challenge to synthesizing study results of rTMS for MDD+AUD is that AUD studies often measured cravings after just one session and focused on cravings as the primary outcome rather than effects on actual alcohol consumption. Very few studies looked at the effects of rTMS on comorbid MDD+AUD. Synthesizing findings from various study protocols for MDD and AUD suggests that excitatory stimulation to bilateral DLPFC could be effective, addressing MDD with left sided stimulation and AUD on the right. The benefits of bilateral stimulation were corroborated by positive effects seen in MDD+AUD with the H1 coil used in dTMS. Another important challenge to applying rTMS to MDD+AUD is that rTMS is known to decrease the seizure threshold and AUD patients may be at increased risk of seizures depending on stage of alcohol cessation. However, seizures with rTMS are quite rare, and seizure rates measured are lower than for other psychotropic medications that are already prescribed (e.g., antidepressants, antipsychotics).

Impact: This selected review summarized protocols found beneficial in rTMS for MDD and AUD separately and extrapolated to suggest the potential transdiagnostic benefit of bilateral DLPFC stimulation. The authors theorize that executive functioning deficits in both disorders could support the proposed transdiagnostic benefits of bilateral rTMS. A significant limitation of this study was a lack of any description regarding study selection, or the number of studies reviewed in the generation of this "narrative" review. Future work that incorporates quantitative information on the literature base (e.g., through use of a PRISMA flow chart) and meta-analytic results would add significantly to the descriptive findings.

Tang VM, Le Foll B, Blumberger DM, Voineskos D. Repetitive Transcranial Magnetic Stimulation for Comorbid Major Depressive Disorder and Alcohol Use Disorder. Brain Sci. 2021;12(1):48. Published 2021 Dec 30. doi:10.3390/brainsci12010048

Theta Burst Stimulation of the Orbitofrontal Cortex May Modulate Compulsive Behavior

Nicole Wong reviewing Price et al. Am J Psychiatry 2021 Mar

A double-blind, between-subjects randomized trial of individuals with compulsive behavior disorders showed that continuous theta-burst stimulation (cTBS) of the OFC reduced compulsive behaviors in the laboratory setting.

Neuroimaging studies in patients with OCD have implicated the OFC in compulsive behaviors, showing hyperactivity of the OFC at rest and during symptom provocation, and hypoactivity of the OFC during cognitive tasks related to goal-directed behavior. This study explored the role of OFC in a laboratory model of compulsive behavior in human subjects.

Sixty-nine participants performed a habit acquisition task involving shocks delivered to the left and right feet and then were assigned in a double-blind design to a single session of one of two conditions targeting the left OFC: iTBS, expected to increase OFC activity, or cTBS, expected to decrease OFC activity. Ninety minutes after TBS, participants performed a habit override task in which they were directed to maintain one of the learned habits (e.g., continue to avoid shocks to the left foot) but resist the second learned habit (e.g., stop trying to avoid shocks to the right foot). Immediately after the habit override task, participants were scanned using fMRI, which was compared to baseline fMRI scans performed after sham TBS.

The TBS conditions were equally well tolerated, without adverse events in either group. Functional MRI confirmed that cerebral blood flow to the OFC decreased relative to sham with cTBS ($p = 0.038$) and increased with iTBS ($p = 0.004$). Immediately after treatment, active cTBS relative to baseline sham resulted in decreased urge strength to complete compulsive behaviors in the habit override task ($r = 0.39$, $p = 0.006$), and decreased effort needed to resist compulsive behaviors ($r = 0.30$, $p = 0.026$), but had no significant effect on time spent in compulsive behaviors ($r = 0.22$, $p = 0.093$). At 1-week follow-up, active cTBS relative to baseline sham showed persistent decreased urge strength ($d = 0.76$, $p = 0.006$) and decreased effort to resist ($d = 0.51$, $p = 0.03$), and new reduction in time spent in compulsive behaviors ($d = 0.46$, $p = 0.027$).

Active iTBS showed unchanged or non-significantly worsened results across these 3 indices, with no significant effects at 1-week follow-up. Across participants, larger cerebral blood flow reductions in OFC from pre- to post-cTBS correlated with larger reductions in urge strength ($r = 0.32$, $p = 0.045$) and time spent in compulsive behaviors ($r = 0.32$, $p = 0.023$), but not effort ($r = -0.02$, $p = 0.88$).

Impact: This double-blind, between-subjects randomized trial showed that cTBS was associated with decreased blood flow to the OFC on fMRI and significant decreases in indices of compulsive behavior immediately after treatment and at 1 week follow-up, with medium to large effect sizes. Conversely, iTBS was associated with increased blood flow to the OFC on fMRI and non-significant changes to indices of compulsive behavior. This study is one of the first to demonstrate the role of OFC in mediating compulsive behaviors in humans and has implications for possible treatment interventions. The study was limited by a small sample and lack of sham control arm, which should be addressed in future RCTs.

Price RB, Gillan CM, Hanlon C, et al. Effect of Experimental Manipulation of the Orbitofrontal Cortex on Short-Term Markers of Compulsive Behavior: A Theta Burst Stimulation Study. Am J Psychiatry. 2021;178(5):459-468. doi:10.1176/appi.ajp.2020.20060821

A Single Sub-threshold HF-rTMS Session May Modulate Testosterone Levels

David M Carlson, MD reviewing Crewther B et al. Neurol Sci 2021 May

In a small pilot study, a single sub-maximal session of rTMS did not significantly alter testosterone or cortisol levels relative to sham, but within-person correlations between motivation and testosterone levels after DLPFC rTMS may be relevant to the efficacy of rTMS and variability in patient response.

Converging lines of evidence seem to indicate that the effect of rTMS may operate via several neurobiological mechanisms including hormones, neuro-transmitters, and neurotrophic factors. Previous studies have indicated that a single, maximal-intensity session of rTMS of the DLPFC can acutely lower cortisol concentration, and a mouse model found repeated HF-rTMS sessions attenuated baseline hypothalamic-pituitary-adrenal (HPA) axis activity and stress-reactivity. However, the roles of testosterone and the hypothalamic-pituitary-gonadal (HPG) axis in TMS have been under-explored.

This pilot study examined the effect of a single session of sub-maximal (90% of resting MT) HF-rTMS to the DLPFC and motor cortex on testosterone, cortisol, mood, anxiety, and motivation. Eleven healthy adults received two sessions of 20Hz, 250-pulse rTMS (DLPFC and motor cortex applications, respectively) and a sham rTMS session, each scheduled at least 2 days apart to avoid any carry-over effects. Participants' salivary testosterone and cortisol were collected before each session, and at 1, 5, and 30 minutes afterward. At each time point, participants rated their mood and motivation using a 10-cm visual analog scale, and rated anxiety using the 6-item State Trait Anxiety Inventory.

At baseline, an ANOVA across stimulation conditions was non-significant for all variables. Across the study population, two-way ANOVAs did not show any significant main effects or interactions for measures of testosterone, cortisol, mood, or motivation following any of the treatments. However, when multilevel (within-person) correlations were examined, significant effects were found. Following DLPFC stimulation, within-person fluctuations in testosterone were positively related to motivation ($r = 0.44$, $p = 0.018$), while mood variation was related to motivation ($r = -0.68$, $p < 0.001$) and anxiety ($r = 0.43$, $p = 0.018$). Motor cortex stimulation found fluctuations in anxiety correlated with mood ($r = 0.46$, $p = 0.012$) and motivation ($r = -0.62$, $p < 0.001$). No such correlations were identified following the sham condition.

Impact: This small pilot study in healthy individuals receiving sub-threshold HF-rTMS demonstrated changes in hormone dynamics that hint at a possible role of testosterone in the therapeutic efficacy of TMS. These findings may also serve as a model for understanding individual differences in response to this treatment. Larger studies, particularly those involving a longer treatment course, higher-intensity stimulation, and in a clinical population could help examine this topic further.

Crewther BT, Kasprzycka W, Cook CJ, Rola R. Impact of one HF-rTMS session over the DLPFC and motor cortex on acute hormone dynamics and emotional state in healthy adults: a sham-controlled pilot study. Neurol Sci. 2022;43:651-659 Published online 26 May 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)