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PULSE

A Monthly Update on Advances in Neuromodulation

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TMS FOR THE TREATMENT OF INSOMNIA

Emily Wood, MD, PhD reviewing Sun et al. Sleep Med 2021 Jan

In this systematic review and meta-analysis, repetitive transcranial magnetic stimulation (rTMS) treatment was associated with improved sleep outcomes when compared to sham rTMS or to other treatments.

Insomnia is highly prevalent and is associated with negative physical and mental health outcomes, reduced quality of life, and an economic burden exceeding $100 billion USD annually. Cognitive behavioral therapy for insomnia (CBTi) is the first-line treatment, followed by pharmacological treatments, but both techniques have limitations. Repetitive transcranial magnetic stimulation (rTMS) is a safe and non-invasive neuromodulation strategy that can be used to increase or decrease cortical excitability; insomnia patients demonstrate abnormal cortical excitability. Might rTMS have a role in the treatment of insomnia?

Researchers searched multiple English and Chinese language databases, including Cochrane, PubMed, and others for controlled trials *(cont'd.)*

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involving adults with primary or comorbid insomnia who received active rTMS compared with sham rTMS, other treatment, or no intervention. The primary outcomes were sleep parameters as assessed by the Pittsburgh Sleep Quality Index (PSQI) and Polysomnography (PSG). Secondary outcome measures included other sleep-related scales, sleep parameters measured by actigraphy, and adverse events.

A total of 28 studies (with 2,357 adult participants) met inclusion criteria. All were carried out in China and published between 2012-2019. Twenty-one studies treated patients with primary insomnia; the remaining 7 studies treated patients with comorbid insomnia (with anxiety, depression, stroke, or drug-dependency). Most trials stimulated the dorsolateral prefrontal cortex (DLPFC) with frequencies ranging from 0.5 Hz to 20 Hz (most commonly, right DLPFC at 1 Hz).

Pulse numbers ranged between 800 and 2400, and total number of sessions varied between 7 and 30. Based on the included treatment arms, three different comparisons were made: rTMS versus sham TMS, rTMS versus other treatment, and other treatment with and without adjunctive rTMS.

In all comparisons, rTMS was associated with superior improvement in PSQI total scores and greater improvement in stage 3 and REM sleep on PSG. When compared to sham TMS or as an adjunctive, active rTMS led to greater improvement in all seven subscale scores on the PSQI (sleep latency, sleep disturbance, use of hypnotics, sleep quality, sleep time, sleep efficiency, and daytime dysfunction). When compared to other treatment, rTMS was associated only with improvement on PSQI subscale scores for sleep latency, sleep disturbance, and use of hypnotics. No severe adverse effects related to rTMS were reported. The most common side effect was mild headache; this was more common with active rTMS versus control groups. Differences in the occurrence of dizziness, nausea, and fatigue were not significantly different.

Impact: When compared to sham rTMS, other treatment alone, or as an adjunctive, rTMS was associated with significantly improved sleep as measured by decrease in PSQI total score and some PSG measures. Limitations of this analysis include high heterogeneity, low quality of some evidence, and limited external validity (all included studies were conducted in China). The results of this analysis are consistent with those of one prior meta-analysis of rTMS for insomnia, and together suggest that rTMS may be a safe and effective option for insomnia as monotherapy or as an adjunctive treatment.

Sun N, He Y, Wang Z, Zou W, Liu X. The effect of repetitive transcranial magnetic stimulation for insomnia: a systematic review and meta-analysis. Sleep Med. 2021;77:226-237 doi:10.1016/j.sleep.2020.05.020

TMS FOR THE TREATMENT OF DEPRESSION IN PARKINSON'S DISEASE

Andrew K Corse, MD reviewing Hai-jiao et al. Int J Neuroscience 2020 Jan

This meta-analysis examining the use of repetitive transcranial magnetic stimulation in patients with Parkinson's Disease provides evidence that rTMS can improve depression, but not motor function or cognition.

Approximately 35% of Parkinson's Disease (PD) patients suffer from persistent and treatment-resistant depression. Repetitive transcranial magnetic stimulation (rTMS) delivered to the left dorsolateral prefrontal cortex (DLPFC) has proven effective for the treatment of depression in PD. Some studies have suggested that rTMS treatment may also improve motor function in these patients. Should rTMS be given greater consideration for the treatment of depression associated with Parkinson's Disease?

Researchers searched PubMed, Embase, Cochrane Online Library, and Clinicaltrials.gov with the terms "Parkinson's Disease", "transcranial magnetic stimulation," and "depression." Included studies were randomized, double-blinded, and placebo-controlled, and involved subjects with clinical diagnoses of both idiopathic Parkinson's Disease and Major Depressive Disorder. Of the 528 search results, 6 trials (including a total of 92 participants) met inclusion criteria. Three trials used sham-rTMS in the control group and three trials used SSRI treatment in the control group. In this meta-analysis, the primary outcome measure for depression was the Beck Depression Inventory (BDI). Other outcome measures included the Unified Parkinson's Disease Rating Scale Part III (UPDRS III), the Mini-Mental State Examination (MMSE), and the Montreal Cognitive Assessment (MoCA).

The authors found that rTMS led to significantly greater reductions in BDI scores than sham-rTMS (SMD= -0.86; 95% CI: -1.29 to -0.43; p<0.0001). Change in BDI scores was not significantly different between rTMS and controls treated with SSRIs (SMD= -0.12; 95% CI: -0.86 to 0.62; p=0.75). Changes in motor function (UPDRS III scores) were not significantly different between rTMS and sham-rTMS (SMD =-0.30; 95% CI: -0.71 to 0.11; p=0.15), or between rTMS and controls treated with SSRIs (SMD= -0.50, 95% CI: -1.57 to 0.57; p=0.36). Two studies examined MMSE scores and found no

significant difference between rTMS and sham-rTMS (SMD = -0.07, CI: -0.56 to 0.41; p=0.68). Another two studies examined MoCA scores; again, there was no significant difference between rTMS and sham-rTMS groups (SMD=-0.29, 95% CI : -1.43 to 0.85; p=0.62).

Hai-jiao W, Ge T, Li-na Z, et al. The efficacy of repetitive transcranial magnetic stimulation for Parkinson disease patients with depression. International Journal of Neuroscience. 2020; 130:1, 19-27, doi: 10.1080/00207454.2018.1495632.

Impact: This meta-analysis demonstrates that rTMS over the left DLPFC is superior to sham—but not to SSRIs—for the treatment of depression in patients with Parkinson's Disease. Although rTMS is not superior to SSRIs, it is a valuable treatment option in PD patients, who are generally elderly and therefore vulnerable to serious side effects from SSRIs, including falls, bleeding, and hyponatremia. Contrary to previous studies, this meta-analysis did not demonstrate that rTMS led to significant changes in motor or neurocognitive function. Additional studies with greater number of participants and more standardized stimulation parameters and follow-up periods are required.

TMS TREATMENT OF COMORBID DEPRESSION AND OBSESSIVE-COMPULSIVE DISORDER

Katharine G Marder, MD reviewing Tadayonnejad R et al. Brain Stimulation 2020 Oct 13

In this case series, excitatory transcranial magnetic stimulation of left dorsolateral prefrontal cortex followed by inhibitory stimulation of supplementary motor area led to meaningful response in both depression and OCD symptoms.

Obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) are frequently comorbid; this comorbidity is associated with lower quality of life and higher treatment-resistance. TMS is established as an effective treatment for both MDD and OCD when the conditions occur independently. Can stimulating multiple targets in a sequential fashion effectively treat comorbid MDD and OCD?

Researchers retrospectively analyzed treatment outcomes of seven patients with refractory and comorbid MDD and OCD. The participants had severe symptoms, with an average baseline Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of 24.2 and an average baseline Inventory of Depressive Symptomatology Self-Report (IDS-SR) score of 45.1. Participants had on average tried 6.8 different psychotropic medications and 2.4 courses of psychotherapy. Participants received 36 TMS treatment sessions of excitatory treatment at left dorsolateral prefrontal cortex (LDLPFC) with either 3,000 pulses of 10 Hz or 600 pulses of intermittent theta burst stimulation at a goal intensity of 120% motor threshold, followed by 1,200 pulses of 1 Hz inhibitory TMS over the bilateral supplementary motor area (SMA) at a goal intensity of 130% motor threshold.

Over the course of treatment, there were significant decreases in average YBOCS scores (from 24.2 at baseline to 12.71, 47% decrease, p=0.0013) and IDS-SR scores (from 45.1 at baseline to 19.29, 57% decrease, p=0.0017). Five of seven participants showed a full response of OCD symptoms (defined as >35% reduction in YBOCS score), and the remaining two participants showed a partial response (20-34% reduction in YBOCS score). Five of seven participants showed a full response of depressive symptoms (defined as a >50% reduction in IDS-SR score), and the remaining two participants showed a partial response (30-50% reduction in IDS-SR score). There were no adverse events leading to treatment discontinuation.

Impact: This study suggests a sequential TMS treatment protocol targeting both LDLPFC and SMA can effectively treat comorbid MDD and OCD. The results from this retrospective case series are promising, but should be interpreted with caution; a larger, prospective, sham-controlled study of this novel treatment approach is warranted.

Tadayonnejad, R, Wilson, AC, Corlier, J et al. Sequential multi-locus transcranial magnetic stimulation for treatment of obsessive-compulsive disorder with comorbid major depression: A case series. Brain Stimulation. 2020; 13(6): 1600-1602. doi: 10.1016/j.brs.2020.10.003.

FROM THE ARCHIVES: PRIMING ENHANCES THE EFFICACY OF LOW-FREQUENCY RIGHT-SIDED STIMULATION FOR DEPRESSION

Michael K. Leuchter, MD reviewing Fitzgerald PB et al. Journal of Clinical Psychopharmacology 2007 September 19

This study found that administering a brief "priming" stimulation protocol prior to 1 Hz stimulation increased the efficacy of the 1 Hz treatment for reducing symptoms of depression. This study was the first to examine the clinical use of TMS priming in depression, and set the foundation for its use in clinical practice.

When treating major depressive disorder (MDD) with repetitive transcranial magnetic stimulation (rTMS), both high-frequency (excitatory) stimulation to the left dorsolateral prefrontal cortex (DLPFC) and low-frequency (inhibitory) stimulation to the right DLPFC have proven effective. There is a pressing clinical need to enhance the efficacy of these two treatment strategies. Some research indicates that applying high-frequency (excitatory) stimulation at a low-intensity immediately prior to low-frequency (inhibitory) stimulation can "prime" the neurons and enhance their response to the subsequent low-frequency (inhibitory) train. Can "priming" the right DLPFC in this manner enhance the efficacy of low-frequency, right-sided rTMS for the treatment of depression?

Researchers performed a randomized, double-blind, sham-controlled study comparing the efficacy of priming stimulation to sham priming stimulation during a course of low-frequency right-sided TMS treatment. 60 participants with treatment-resistant depression were randomized to two groups: a priming group and a sham priming group. Both groups (all participants) received 10 sessions of 1 Hz rTMS treatment to the right DLPFC (900 pulses, continuous, 15 minutes, 110% RMT). The priming group (30 participants) received priming stimulation (6 Hz, 600 pulses, 25-second inter-train interval, 10 minutes, 90% RMT) immediately prior to each session of 1 Hz. The sham group (30 participants) received the same stimulation with the coil angled away from the scalp. Partial responders (>20% improvement) could receive an additional 10 treatment sessions. The primary outcome was the change in the 10-item Montgomery-Asberg Depression Rating Scale (MADRS) score; secondary outcomes included remission and response rates, and change in the Brief Psychiatric Rating Scale (BPRS), Beck Depression inventory (BDI), CORE Assessment of Psychomotor Change, Global Assessment of Functioning Scale (GAF), and Clinical Global Improvement Scale (CGI) scores. Assessments were collected at baseline, 2 weeks, and 4 weeks.

There were significantly greater reductions in MADRS score in the verum priming group compared to the sham priming group at both week 2 (21.7 vs 7.3 percent change, $p < 0.005$) and at week 4 (30.5 vs 13.2 percent change, $p < 0.05$). Secondary outcomes demonstrated similar trends, except for the change in CORE scores (a time effect was noted, though no group effect was observed). There was a trend towards higher rates of clinical response in the active priming group compared to sham group (33% vs 14% of participants). Stimulation site discomfort and mild headache occurred in both groups, and were reported in greater numbers in the active group, though no statistical comparison was noted. One patient in the active group reported nausea during a single session.

Impact: This study demonstrated that an active priming protocol administered prior to 1 Hz stimulation of the right DLPFC was superior to a sham priming protocol in reducing depressive symptoms. More broadly, this pivotal study supported the notion that "priming" a target by delivering low-intensity, high-frequency stimulation prior to low-frequency stimulation can enhance clinical benefit. This important result informed the clinical use of priming prior to low-frequency rTMS and inspired research into the role of priming stimulation in other rTMS treatment protocols.

Fitzgerald PB, Hoy K, McQueen S, et al. Priming Stimulation Enhances the Effectiveness of Low-Frequency Right Prefrontal Cortex Transcranial Magnetic Stimulation in Major Depression. J Clin Psychopharmacol. 2008;28(1):52-58. doi:10.1097/jcp.0b013e3181603f7c

TRIGEMINAL NERVE STIMULATION FOR PEDIATRIC ADHD

Katharine Marder, MD reviewing McGough et al. J Am Acad Child Adolesc Psychiatry 2019 Apr

In this randomized, double-blinded, sham-controlled trial, non-invasive electrical stimulation with a portable device was superior to sham for reducing ADHD symptoms in pediatric patients.

While stimulant medications are the mainstay of ADHD treatment, many patients and families prefer non-pharmacological approaches due to concerns about side effects or social stigma. The trigeminal nerve conveys sensory information to brain regions involved in ADHD, such as the nucleus tractus solitarius, locus coeruleus, reticular activating system, anterior cingulate, and insula. Trigeminal nerve stimulation is a non-invasive neuromodulation treatment modality in which a small, portable stimulator produces an electrical current to stimulate the trigeminal nerve via an adhesive electrode worn on the forehead. Can trigeminal nerve stimulation provide clinical benefit for ADHD?

Researchers performed a randomized,

double-blinded, sham-controlled trial in which children aged 8 to 12 years with ADHD by DSM-5 criteria (n=62) were randomized to receive active trigeminal nerve stimulation (rate of 120 Hz, pulse width of 250-μs, strength of 2 to 4 milli-Amperes, and duty cycle of 30 seconds on/30 seconds off) or sham stimulation via identical-appearing stimulators (the Monarch eTNS System™, NeuroSigma, Inc., Los Angeles CA) for 8 hours nightly over a 4-week period, followed by one blinded week without intervention. The primary outcome was change in the clinician completed ADHD-RS Total Score; secondary outcomes included clinician-scored CGI-Improvement (CGI-I) and several parent- and teacher-completed scales. Scales were collected weekly over the 5 week study period. Participants underwent quantitative electroencephalography (EEG) at baseline and weeks 1 and 4. Participants were randomized to active treatment (n=32) or sham (n=30).

In the first week, both groups demonstrated improvement (with greater improvement in the active TNS group). The active group demonstrated gradual ongoing improvement for the remainder of the trial, while the sham group did not. A significant group-by-time interaction was found. The effect size of active treatment at week 4 was 0.50, indicating a medium effect size. The number-needed-to-treat for improvement on the CGI-I scale was 3. Quantitative EEG demonstrated increased broadband power with active TNS. Power changes in right frontal and frontal midline regions were significantly associated with decreases in ADHD-RS scores, particularly for hyperactive and impulsive symptoms. The active TNS group showed increased weight and blood pressure, as well as fatigue, headache, increased appetite, and temporary skin discoloration from patch removal. There were no serious adverse events.

Impact: This study demonstrates the safety and efficacy of TNS in the treatment of ADHD in this age group. The effect size is similar to that of non-stimulant medications, and the treatment is well tolerated and accepted by patients and parents. The Monarch eTNS System™ has since been FDA approved as monotherapy for ADHD in patients ages 7 to 12. Further study is needed to determine whether this portable device has a role in treating patients in other age groups or as an adjunct to psychotropic medication.

McGough JJ, Sturm A, Cowen J, et al. Double-Blind, Sham-Controlled, Pilot Study of Trigeminal Nerve Stimulation for Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry. 2019;58(4):403-411.e3. doi: 10.1016/j.jaac.2018.11.013.

BIMODAL ACOUSTIC AND ELECTRICAL SOMATOSENSORY STIMULATION FOR THE TREATMENT OF TINNITUS

Katharine G Marder, MD reviewing Conlon B et al. Sci Transl Med. 2020 Oct 7

Approximately 10-15% of the population suffers from chronic tinnitus, or the perception of sound in the absence of an external stimulus. The condition can be debilitating, and no adequate treatment options are currently available. Neuromodulation offers one promising approach. Neuromodulation strategies generally apply a magnetic or electrical stimulus to the brain, for example by stimulating a peripheral nerve or by applying a magnetic field or an electric current to the scalp, in order to modulate neuronal activity. Some strategies, including electrical somatosensory stimulation, achieve nonspecific activation of widespread areas of the brain. Paired stimulation is a neuromodulation approach that pairs broad electrical stimulation with a targeted input in order to achieve greater activation within a selected group of neurons. Animal studies and pilot human studies have shown that pairing sound (the targeted input) with electrical somatosensory stimulation (the broad input) can increase plasticity within the auditory system and improve tinnitus symptoms. More synchronized stimulation appears to drive greater increases in plasticity.

In this study, researchers investigated bimodal stimulation with the Lenire device (Neuromod Devices, Dublin, Ireland) for the treatment of tinnitus. A small battery-powered stimulator electrically stimulated the tongue via a wired connection to a small array of 32 electrodes placed on the anterior dorsal surface of the tongue. The same stimulator provided acoustic stimulation via a Bluetooth connection to a set of headphones. 326 participants with chronic, subjective tinnitus were randomized 1:1:1 into one of three treatment arms. Each arm paired sound and tongue stimulation with different frequencies, inter-stimulus delays, synchronization, and tone-to-tongue mapping. The volume of acoustic stimulation and the intensity of electrical tongue stimulation was customized to each participant's sensation thresholds. In each arm, patients used the device for 60 minutes daily for 12 weeks. The primary outcome was within-arm and between-arm change in the Tinnitus Handicap Inventory (THI) and Tinnitus Functional Index (TFI), where scores range from 0 (least severe) to 100 (highest severity).

Depending on the arm, 74.7 to 88.8% of participants experienced improvement. All within-arm comparisons demonstrated highly significant decreases in TFI and THI scores, with moderate to large effect sizes (ranging from -0.77 to -0.92). There was not a significant difference between the arms during the treatment phase. Arms 1 and 2 sustained benefits out to 12 months, while arm 3 did not; this finding was consistent with the notion that more synchronized stimulation (as in Arms 1 and 2) drives greater plasticity and therapeutic effect. Adverse effects included increase in tinnitus symptoms, discomfort in the head, ear, or mouth, and ulceration in the mouth. There were no serious adverse events.

Impact: This is one of the largest medical device trials for the treatment of tinnitus, and demonstrates that bimodal neuromodulation is feasible, safe, tolerable, and likely effective for the treatment of tinnitus. A significant limitation is the absence of a sham control. A sham-controlled study of this novel treatment approach is warranted to provide definitive evidence of efficacy.

Conlon B, Langguth B, Hamilton C, et al. Bimodal neuromodulation combining sound and tongue stimulation reduces tinnitus symptoms in a large randomized clinical study. Sci Transl Med. 2020 Oct 7;12(564):eabb2830. doi: 10.1126/scitranslmed.abb2830. PMID: 33028707.