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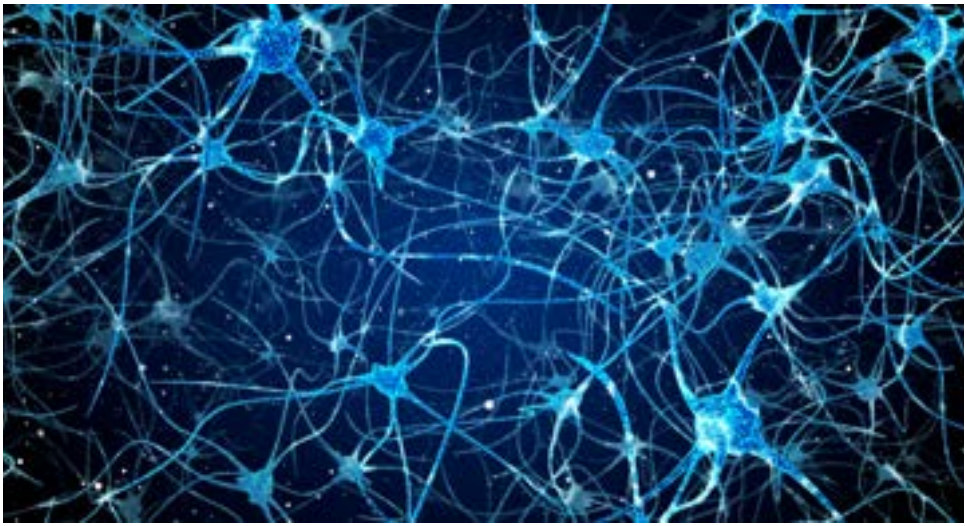
PULSE

A Monthly Update on Advances in Neuromodulation



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rTMS and Sham Treatment Both Improve Cognitive Function in Alzheimer's Disease

Kaleab Tessema, MD PhD, reviewing Moussavi et al., Neurotherapeutics, 2024 Apr

In this large, multicenter, double-blind RCT, HF-rTMS (20 Hz) to bilateral DLPFC demonstrated both short- and long-term improvement in cognitive function in patients with mild-moderate Alzheimer's disease. Notably, sham coil treatment showed comparable efficacy.

Alzheimer's disease (AD) continues to cause significant morbidity and mortality despite decades of research spanning numerous diagnostic and therapeutic techniques. Given that part of AD pathophysiology involves decreased neuronal/synaptic function and cell death in the cortex, increasing cortical excitability and synaptic plasticity via HF-rTMS has been proposed as a possible approach to address cognitive decline in AD. In this context, rTMS is often delivered

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to DLPFC given its importance in executive function and memory. While pilot studies have been encouraging, they have thus far been limited by small sample sizes and inconsistent treatment parameters (e.g., target area, stimulation frequency, treatment duration). In this study, the authors report on the largest (n=156) documented trial of rTMS for AD, with goals of definitively investigating whether HF-rTMS to bilateral DLPFC is superior to sham, the impact of treatment duration (2 weeks or 4 weeks), and how long the treatment benefits last.

This double-blind, sham-controlled RCT was conducted across three sites (Winnipeg, Canada; Montreal, Canada; and Melbourne, Australia) and included 156 patients with mild-moderate AD. Patients were all over 55 years old, had a physician-confirmed diagnosis, and did not have changes in acetylcholinesterase inhibitor dose for 3 months prior to entering the study. Patients were assigned via stratified block randomization to 2 weeks of active treatment, 4 weeks of active treatment, or 4 weeks of sham treatment. Active treatment was HF-rTMS (20 Hz, 1500 pulses, 1.5-second trains, inter-train interval of 10 seconds) targeting bilateral DLPFC via MRI-based neuronavigation. Sham treatment was the same protocol except using a Magstim sham coil. The primary outcome was change in cognitive function from pre-treatment to 3-28 weeks after start of treatment. This was measured via the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). Secondary outcomes were change in neuropsychiatric symptoms (measured via Neuropsychiatric Inventory Questionnaire, or NPI-Q) and change in activities of daily living (measured by Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory, or ADCS-ADL). Group differences were evaluated at baseline (via ANOVA) and longitudinally (via a mixed effects model), with additional post-hoc tests as appropriate.

Data from a total of 135 patients were analyzed, as 21 of the 156 enrolled patients withdrew without enough useful data. Analysis of ADAS-Cog scores showed no significant difference in baseline scores across treatment groups. Over time, there was a trend of improvement in ADAS-Cog scores after treatment, maintenance of this improvement for 2 months, and return to baseline after 6 months. Notably, this trend was demonstrated in all 3 treatment groups, with no significant differences between the rTMS groups or between rTMS and sham. Mixed effect model analysis revealed a significant effect of time ($F=21.4$, $p<0.00001$) but not group ($F=0.63$, $p=0.53$) or time*group ($F=1.59$, $p=0.13$), indicating that scores varied significantly over time but that this effect was similar across treatment groups. Post-hoc tests at each time point also showed no significant differences in change in ADAS-Cog score (from baseline) across treatment groups.

Impact: This study suggests that HF-rTMS and sham coil treatment to bilateral DLPFC both improve cognitive function in mild-moderate AD. While the positive benefit of rTMS is encouraging, the lack of efficacy compared to sham suggests that effects may largely reflect nonspecific or placebo-related mechanisms. The authors raise the possibility that the Magstim Sham coil produces a significant perpendicular magnetic field that may induce a weak electrical current akin to tACS, which may explain some of its effects. In the absence of more rigorous sham controls, the current findings demonstrate a lack of evidence supporting the efficacy of bilateral DLPFC rTMS for the treatment of Alzheimer's disease.

Moussavi Z, Uehara M, Rutherford G, et al. Repetitive transcranial magnetic stimulation as a treatment for Alzheimer's disease: A randomized placebo-controlled double-blind clinical trial. Neurotherapeutics. 2024;21(3):e00331-e00331. doi:10.1016/j.neurot.2024.e00331

rTMS Reduces Pain and Enhances Quality of Life in Patients with Fibromyalgia

Kaleab Tessema, MD PhD, reviewing Sun et al., Pain Med., 2021 Sept

In this systematic review and meta-analysis of 14 RCTs (n=433 participants total) that enrolled patients with fibromyalgia, rTMS demonstrated efficacy in improving pain and quality of life, with no significant effects on depression, anxiety, fatigue, or catastrophizing of pain. Based on subgroup analyses, the authors recommend low frequency (1 Hz) rTMS to DLPFC as the standard protocol for fibromyalgia.

Fibromyalgia is a chronic condition primarily characterized by significant pain, with secondary symptoms including insomnia, fatigue, depression, and anxiety. Research efforts have thus far not definitively revealed the mechanistic drivers of fibromyalgia pathophysiology and

consequent symptoms. As a result, clinical management is limited to controlling symptoms and improving quality of life. Past work has identified abnormal central pain processing as a possible driver of fibromyalgia pathophysiology based on neuroimaging studies that implicate limbic hyperactivity. Given the specific brain regions and circuitry implicated in fibromyalgia and its associated mental health conditions (e.g., insomnia, depression, anxiety), direct brain stimulation delivered to critical brain regions has emerged as a possible treatment approach for fibromyalgia. In particular, rTMS (for example, to DLPFC, which is linked to central pain processing) has been investigated as a noninvasive treatment option for fibromyalgia. While some studies have suggested positive benefits of rTMS, there have been conflicting findings across reviews and meta-analysis. Notably, a recent systematic review was encouraging but did not include quantitative analyses and was not fully based on RCTs. Thus, the authors aimed to robustly investigate the efficacy of rTMS in fibromyalgia via systematic review and meta-analysis with only RCTs included.

This study identified RCTs from four medical databases (PubMed, Cochrane Library, Excerpta Medica Database, and Web of Science) and one physiotherapy database (Physiotherapy Evidence Database) that focused on rTMS for fibromyalgia. Systematic review and meta-analysis were performed according to the PRISMA statement and Cochrane Handbook. Study quality was assessed using the Physiotherapy Evidence Database and manual review. Outcome measures included Numerical Pain Rating Scale (NPRS) score, BDI, Hospital Anxiety and Depression Scale (HADS) anxiety score, Pain Catastrophizing Scale (PCS) score, Fatigue Severity Scale (FSS) score, Short Form-36 General Health Survey mental score, and Fibromyalgia Impact Questionnaire (FIQ) score. Statistical analysis was done via a fixed effects model when no significant heterogeneity was observed or a random effects model otherwise.

Data from a total of 14 RCTs (n=433 participants total) were used for meta-analysis, with an additional 2 studies (16 total) used for systematic review. Studies ranged in size from 15-90 participants and were conducted in 7 countries. All studies compared active rTMS to sham treatment. The quality of evidence was acceptable based on a PEDro score of 8.5 (cutoff was 6). In terms of outcome measures, rTMS significantly decreased pain (assessed via NPRS score) (SMD=-0.49, 95% CI [-0.86, -0.13], p=0.008) and fibromyalgia's impact on quality of life (assessed via FIQ) (SMD=-0.5, 95% CI [-0.75, -0.25], p=0.0001) compared to control. There were no significant differences in depression (p=0.33), mood (p=0.69), anxiety (p=0.67), fatigue (p=0.71), or catastrophizing of pain (p=0.20), assessed via BDI, Short Form-36 General Health Survey mental score, HADS anxiety score, FSS score, and PCS score, respectively. Subgroup analyses examining stimulation frequency (high vs low) and cortical target (DLPFC vs M1) revealed a significant interaction between these parameters. Of the four resulting subgroups (high-frequency M1, low-frequency M1, high-frequency DLPFC, and low-frequency DLPFC) only low-frequency stimulation of the DLPFC was associated with significant pain relief, with no observed heterogeneity across studies ($P < 0.05$; $I^2 = 0$).

Impact: This study suggests that rTMS can effectively target pain and quality of life in patients with fibromyalgia. Although no significant effects were observed in other symptom domains (depression, anxiety, fatigue, or pain catastrophizing), the observed improvement in quality of life suggests that the clinical benefits of rTMS may be heterogeneous and patient-specific, and therefore less likely to be captured by group-level analyses. Notably, while limited by sensitivity and sample size, the authors successfully performed a subgroup analysis that was clinically meaningful: they identified low frequency (1 Hz) rTMS to DLPFC as the most effective in treating pain, possibly due to this protocol's ability to increase pain tolerance. These findings would be bolstered by future investigation with larger sample sizes, consistent protocols across studies, and more robust blinding via sham control (the authors note that some studies rotated the TMS coil to simulate a control condition, which can potentially un-blind physicians).

Sun P, Fang L, Zhang J, Liu Y, Wang G, Qi R. Repetitive transcranial magnetic stimulation for fibromyalgia patients: A Systematic Review with Meta-Analysis. Pain Medicine. Published online September 20, 2021. doi:10.1093/pm/pnab276

High-Frequency rTMS With Rehabilitation Shows Inconclusive Effects on Lower Limb Motor Recovery After Spinal Cord Injury in a Sham-Controlled RCT

Praveen P. Rajaguru MD, MPH reviewing Krogh et al., Spinal Cord, 2022 Sep

In this sham-controlled RCT, high-frequency rTMS applied over the leg motor cortex (M1) along with standard rehabilitation did not produce a significant improvement in lower-limb maximal voluntary contraction (MVC); however, patients exhibited a significant improvement in the clinician-rated Lower Extremity Motor Score (LEMS) from admission to discharge.

Spinal cord injury (SCI) may lead to significant disability and decrease quality of life, and numerous interventions have been explored to restore lower limb strength and gait after SCI although few exist that demonstrably increase muscle strength. Preliminary evidence suggests that rTMS combined with skill-based training may enhance motor recovery after SCI. This RCT explored whether rTMS would be more effective than sham stimulation as an adjuvant therapy combined with lower limb resistance training & physical therapy (LL-RT, LL-PT) to improve recovery of lower limb muscle strength.

Twenty adults with motor-incomplete SCI admitted for initial rehabilitation were randomized to receive real (n = 11) or sham (n = 9) rTMS combined with LL-RT and LL-PT over 4 weeks. rTMS was delivered daily before LL-RT or LL-PT on weekdays. Stimulation was delivered with a Magstim double-cone coil over the bilateral leg motor cortex by targeting an area 0–2 cm anterior to the cranial vertex. The stimulation protocol was 1800 pulses over 22 minutes (45 trains of 40 pulses @ 20 Hz @ 100% resting motor threshold (RMT) with 28 s between trains). For sham rTMS, the treatment coil was positioned identically but disconnected, while a second active figure-of-eight coil, using the same stimulation parameters, was placed beneath the pillow and oriented away from the head to mimic treatment effects. The primary outcomes were the lower limb maximal voluntary contraction (MVC) and Lower Extremity Motor Score (LEMS) to assess muscle strength. MVC was measured before and after the 4-week rTMS protocol, while LEMS was measured on admission and within one week of discharge (71.2 ± 47.2 days after completing the rTMS protocol). The secondary outcome was gait performance as measured by the 10-minute walking test (10MWT) and Timed Up-and-Go (TUG) test in all ambulatory patients (n=8 in each group). Safety and adverse effects were monitored.

N=19 subjects completed the study. Baseline characteristics across demographics and injury characteristics were similar across groups and masking was successful. After 4 weeks, the rTMS group demonstrated a qualitative but non-significant ($p>0.15$) increase in MVC than sham; effect sizes were 0.40 for total leg MVC, 0.34 for knee flexor MVC, and 0.29 for knee extensor MVC. There was a statistically significant ($p = 0.014$) iimprovement in LEMS for patients receiving rTMS (mean difference +12.5) relative to sham (mean difference -3). Both groups demonstrated improvement in gait performance across both measures ($p < 0.05$) with no significant group difference (all $p > 0.05$). Regarding adverse effects, one rTMS patient withdrew due to a seizure during stimulation. Occasional transient side effects were observed in the rTMS group (drowsiness, facial twitching, scalp tingling), and two sham participants reported mild headache.

Impact: This sham-controlled RCT suggests that high-frequency rTMS with resistance training may be beneficial for lower-limb motor outcomes, although the overall findings were inconclusive. While rTMS was associated with greater improvements in clinician-rated motor function at hospital discharge when compared to sham, it did not significantly enhance objective measures of muscle strength or gait performance. Further studies consisting of greater sample size, exploring different stimulation parameters, and exploring longer courses of treatment are necessary to establish the utility of rTMS for lower-limb motor recovery following SCI.

Krogh S, Aagaard P, Jønsson AB, Figlewski K, Kasch H. Effects of repetitive transcranial magnetic stimulation on recovery in lower limb muscle strength and gait function following spinal cord injury: a randomized controlled trial. Spinal Cord. 2022;60(2):135-141. doi:10.1038/s41393-021-00703-8

Scrambler Therapy Significantly Reduces Chronic Neuropathic Pain After Burn Injuries

Praveen P. Rajaguru MD, MPH reviewing Lee et al., Journal of Clinical Medicine, 2022 Jul

This double-blinded, sham-controlled RCT found that Scrambler therapy (ST) produced significant reductions in chronic post-burn injury neuropathic pain relative to sham stimulation with no serious adverse effects. Average pain intensity decreased by 50% in the ST group, with changes observed in cerebral blood volume (CBV) in central pain networks.

Chronic neuropathic pain is a common and debilitating and treatment refractory complication of burn injuries. Scrambler therapy (ST) utilizes non-invasive electrocutaneous stimulation to send synthetized non-pain information in place of pain signaling through C-fibers and possibly other afferent neurons, leading to alterations of central pain networks. This RCT evaluated the efficacy of ST in post-burn neuropathic pain and explored mechanisms for its effect via CBV imaging.

This study utilized a prospective, double-blinded, randomized, sham-controlled design. Subjects included were adults with unilateral burn injuries and at least moderate chronic neuropathic pain as measured by Visual Analog Scale (VAS) pain scores of 5 or greater that lasted at least 3 months. Patients using extended-release morphine were excluded. Other pharmacological pain regimens were not excluded or controlled, but doses were not changed during the study. The sample (N=43) was randomized to either ST (therapeutic intensity of <70 U; n=20) or sham (ST w/ subtherapeutic intensity <10 U; N=23). Ten 45-minute sessions were delivered on weekdays over two weeks. The primary outcome was change in pain intensity using the VAS. CBV was also measured with post-gadolinium T1-weighted MRI to assess possible central network changes before and after treatment.

Six subjects from the ST group dropped out of the study prior to completion due to improvements in pain, and so the final included sample consisted of 37 patients (ST N=14; sham N=23). After completion of the protocol, the ST group had a statistically greater decrease in VAS pain score relative to the sham group (ST median change -3; sham median change -1; $p<0.001$), although both groups did have significant reductions in VAS pain score (ST median change 6 to 3, $p=0.004$; sham median change 7 to 6, $p=0.001$). The ST group demonstrated changes in anatomic regions associated with the pain network, with significant decreases in CBV in the right orbito-frontal gyrus, right middle frontal gyrus, right superior frontal gyrus, right gyrus rectus, left orbito-frontal gyrus, and the left superior frontal gyrus (all $p < 0.05$). When comparing the CBV between the experimental and sham groups, there were significant increases in CBV in the precentral and postcentral gyri of the hemisphere of the burned limb (all $p < 0.05$).

Impact: This double-blinded RCT demonstrates that ST has promise in treating chronic neuropathic pain after burn injury, with this study finding an average pain reduction over 50% and outperformance of sham stimulation. This effect may be attributable to changes in central sensitization via C-fibers and other neural afferents, as evidenced by the known mechanism of ST and this study's observations of changes in CBV within the cerebral pain network after ST.

Lee SY, Park CH, Cho YS, et al. Scrambler Therapy for Chronic Pain after Burns and Its Effect on the Cerebral Pain Network: A Prospective, Double-Blinded, Randomized Controlled Trial. J Clin Med. 2022;11(15):4255. Published 2022 Jul 22. doi:10.3390/jcm11154255

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
ECT (electroconvulsive therapy)
HFL (high frequency left, 10 Hz stimulation to left DLPFC)
HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent theta burst stimulation)
MST (magnetic seizure therapy)
TBS (theta-burst stimulation; TMS delivered as triplet burst pulses at 50 Hz, repeated at 5 Hz)
TENS (transcutaneous electrical nerve stimulation)
TMS (transcranial magnetic stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tDCS (transcranial direct current stimulation)
tACS (transcranial alternating current stimulation)
TPS (transcranial pulse 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)
RMT (resting MT)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
PTSD (post-traumatic stress disorder)
SUD (substance use disorder)
TRD (treatment resistant depression)

BAI (Beck Anxiety Inventory)
BDI (Beck Depression Inventory)
CGI (clinical global impression scale)
HAM-A (Hamilton Anxiety Rating Scale)
HAM-D / HDRS (Hamilton Depression Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)
MoCA (Montreal Cognitive Assessment)
PANSS (Positive and Negative Symptom Scale)
QIDS (Quick Inventory of Depressive Symptomatology)
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)
OR (odds ratio)
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)
SMD (standard mean difference)

BA (Brodmann area)
DLPFC (dorsolateral prefrontal cortex)
DMPFC (dorsomedial prefrontal cortex)
M1 (primary motor cortex)
mPFC (medial prefrontal cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)