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PULSE

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rTMS to Primary Motor Cortex Provides Superior Relief of Neuropathic Pain Intensity Compared to Prefrontal Cortex and Sham

Collin M Price, MD reviewing Attal et al. Brain 2021 Nov

A multi-center, randomized, double-blind, placebo-controlled trial comparing the efficacy of rTMS to M1 or DLPFC in the treatment of peripheral neuropathic pain found stimulation of M1 but not DLPFC was more effective than sham in reducing pain intensity.

Repetitive Transcranial Magnetic Stimulation (rTMS) has shown efficacy in the treatment of chronic neuropathic pain, with most effective trials targeting the primary motor cortex (M1) contralateral to the site of pain, or left M1 if pain is bilateral. Prior studies have been limited by small sample sizes, and no prior study has directly compared two different stimulation targets for the treatment of neuropathic pain.

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In this double-blind placebo-controlled trial, the modified intention-to-treat sample included 149 patients at four treatment centers, randomized to M1-rTMS (n=49), DLPFC-rTMS (n=52), or sham-rTMS (n=48). Inclusion criteria included adults aged 18-75 years, with continuous peripheral neuropathic pain for at least 6 months at an intensity of ≥4/10. Patients underwent a total of 15 rTMS sessions over 22 weeks, starting with once a day for five consecutive days, followed by a gradual taper over the following 21 weeks. The stimulation target (M1 or DLPFC) was identified using MRI-guided neuronavigation, with a robotic system used during each session to ensure optimal coil placement. Stimulation intensity was 80% of resting motor threshold and was delivered at 10 Hz over 15 minutes for a total of 3000 pulses per session. Sham stimulation targeting was split equally between M1 and DLPFC, and a MagVenture dual-sided active-sham coil and scalp electrical stimulation were used to maintain double-blinding.

The primary outcome was the mean change from baseline on a 0-10 pain scale after 25 weeks, with secondary outcomes assessing affect, mood and quality of life that included pain intensity, relief, and interference scores and global impression of change scales (GIC).

On the primary outcome, M1-rTMS showed a significantly greater reduction in average pain intensity from baseline to Week 25 (7.0 to 5.5 = 1.5 ± 1.8) compared to sham-rTMS (6.9 to 6.1 = 0.8 ± 1.5; p=0.04). Notably, there was a significant effect of time on M1-rTMS efficacy, with no difference from sham-rTMS on Days 1 to 5 but a significant difference from Day 8 onward. In contrast, the average change in pain from baseline to Week 25 for DLPFC-rTMS (6.5 to 5.6 = 0.9 ± 2.2) was not statistically different from sham-rTMS (p=1.0). M1-rTMS was also noted to be more effective than sham-rTMS on multiple secondary measures including percentage of pain relief and significant improvement on self-report and clinician GIC. DLPFC-rTMS, on the other hand, had no significant effect on secondary outcomes, except for a modest improvement on the pain relief scale. Neither active rTMS treatment separated from sham on measures of affect or pain interference. The NNT for ≥50% pain relief at Week 25 was 3.1-7.7 for M1-rTMS (depending on the scale) compared to 8.2-19.1 for DLFPC-rTMS. The location and etiology of chronic pain did not predict response to M1-rTMS.

Impact: The positive findings in this large, multi-center, double-blind, randomized placebo-controlled trial suggest that 15 sessions of 10 Hz rTMS to the M1 cortex, but not the DLPFC, is a safe and effective treatment for chronic peripheral neuropathy. Efficacy of M1 stimulation was not related to etiology or location of chronic pain, suggesting a diffuse analgesic effect despite a relatively focal neuromodulatory technique. Future work may yield further improvements through optimizing treatment parameters and trials of multifocal stimulation.

Attal, N., Poindessous-Jazat, F., De Chauvigny, E., Quesada, C., Mhalla, A., Ayache, S., Fermanian, C., Nizard, J., Peyron, R., Lefaucheur, J. and Bouhassira, D., 2021. Repetitive transcranial magnetic stimulation for neuropathic pain: a randomized multicentre sham-controlled trial. Brain, 144(11), pp.3328-3339.

Higher Frequency and Pulse-Count Associated with Greater Efficacy of rTMS for Neuropathic Pain

Mengdong He, MHS reviewing Mori et al. Neuromodulation 2021 Jan

In this single-blind, crossover, randomized controlled trial, high-dose rTMS (10 Hz with 2000 pulses) was shown to produce a greater analgesic effect than lower-dose rTMS (5 or 10 Hz with 500 pulses) in adults with neuropathic pain.

Repetitive Transcranial Magnetic Stimulation (rTMS) of the primary motor cortex (M1) has previously shown efficacy in the treatment of neuropathic pain. However, the optimal stimulation conditions for treating neuropathic pain remain unclear. This study compared the analgesic effects of three different rTMS stimulation parameters.

Twenty-two adult patients with medically intractable neuropathic pain lasting at least 6 months were enrolled in this randomized, single-blind, sham-controlled, crossover trial. Participants experienced pain in the face (n=2), upper limb (n=10), and lower limb (n=10), with a variety of etiologies including central and peripheral nervous system lesions. Each patient received rTMS during one sham session and three active sessions with varied stimulation parameters. The order of the stimulation conditions was randomized, and consecutive sessions were at least two weeks apart to avoid carry over effects. Patients were encouraged to continue their existing pain medications during the study. A figure-8 coil was used for the active stimulation and a sham coil (visually and audibly identical to the active coil) was used for the sham stimulation. The coil was positioned perpendicular to the central sulcus to target the M1 hand area contralateral to the painful side. With a stimulation intensity of 90% of resting motor

threshold, active rTMS was delivered at either 5 Hz with 500 pulses, 10 Hz with 500 pulses, or 10 Hz with 2000 pulses during the active stimulation sessions; sham rTMS was designed to mimic the 5 Hz, 500 pulse session. Prior to the first stimulation, baseline scales were administered for depression, anxiety, and pain. The primary outcomes included changes in Visual Analog Scale (VAS) pain intensity, the Japanese version of the Short-Form McGill Pain Questionnaire 2 (SF-MPQ2), and the Global Impression of Change (PGIC).

All four stimulation conditions led to reduction of VAS pain intensity immediately after the intervention. However, 10 Hz rTMS with 2000 pulses produced the greatest analgesic effect. The mean (95% CI) VAS reduction was 7.8 (2.8 - 12.9) for 5 Hz rTMS with 500 pulses, 4.3 (−0.7 - 9.3) for 10 Hz rTMS with 500 pulses, 11.0 (6.1 - 15.9) for 10 Hz rTMS with 2000 pulses, and 2.8 (−2.1 - 7.7) for sham stimulation. Similar results were found for SF-MPQ2. Among the three active simulation conditions, only 10 Hz rTMS with 2000 pulses reduced VAS pain intensity and SF-MPQ2 significantly more than the sham intervention ($p = 0.03$ for VAS and $p = 0.01$ for SF-MPQ2). The level of PGIC was not significantly different across the stimulation conditions.

Impact: This single-blind, crossover, randomized controlled trial aimed to identify the optimal stimulus parameters for rTMS in the treatment of neuropathic pain. The only parameter combination that produced significantly greater pain reduction than sham was 10 Hz rTMS with 2000 pulses. The efficacy of low frequency (1 Hz) or newer pulse sequences (such as intermittent or continuous theta burst) was not assessed. Despite limitations of small sample size, single-blind design, heterogeneous pain etiology, and short-term intervention and follow-up, the findings are clinically useful and support future larger-scale investigation.

Mori N, Hosomi K, Nishi A, Oshino S, Kishima H, Saitoh Y. Analgesic Effects of Repetitive Transcranial Magnetic Stimulation at Different Stimulus Parameters for Neuropathic Pain: A Randomized Study [published online ahead of print, 2021 Jan 21]. Neuromodulation. 2021;10.1111/ner.13328. doi:10.1111/ner.13328

Primary Motor Cortex rTMS Stimulation Effective for Neuropathic Pain in Upper Limb but Not Lower Limb or Face

David M Carlson, MD reviewing Mori et al. Front Hum Neurosci 2021 Nov

In this "mini meta-analysis" of data from three prior studies, rTMS to M1 was found to be effective at reducing neuropathic pain in the upper limb, but not the lower limb or face.

Since the first report in 1995 of the effectiveness of rTMS for neuropathic pain, the M1 area of the motor cortex, corresponding to the hand, has emerged as one of the most promising targets. A previous large, multi-center clinical trial failed to show a positive primary outcome, but subgroup analyses suggested that the response to rTMS varies by the site of pain. The authors thus conducted a "mini meta-analysis" to assess for differential effects of rTMS on neuropathic pain in different body regions.

The authors identified two studies from other investigators examining the effects of rTMS on pain, however those studies did not report the amount or rate of decrease in pain. Thus, only three previous trials by the authors met inclusion criteria for this analysis. Each study used 10 daily sessions of rTMS to the M1 area of the primary motor cortex with a sham control and assessed response using the decrease in mean visual analog scale (VAS) between pre- and post-treatment assessments. In two of the studies, stimulation consisted of 500 pulses at 10 Hz. In one study where multiple rTMS parameters were used, only the results from the condition providing the most effective pain relief (2000 pulses at 10 Hz) were included in this analysis. Chi squared and I2 (a measure of heterogeneity) were used to quantify heterogeneity between the two groups.

A total of 227 patients from three clinical trials were included in the analysis. These participants had neuropathic pain in the upper limb (n=112), lower limb (n=91), or face (n=24). For the entire sample, rTMS provided a non-significant improvement in pain with an effect size of -0.33 (95% CI: -0.70 to 0.04). However, for upper limb pain, rTMS had a statistically significant, moderate effect size of -0.45 (95% CI: -0.77 to -0.13). The effect sizes for lower limb (0.04; 95% CI: -0.33 to 0.41; $p = 0.82$) and facial pain (-0.24; 95% CI -1.59 to 1.12; $p = 0.73$) were modest and did not meet statistical significance.

Impact: In this "mini meta-analysis" of three studies examining the efficacy of rTMS for neuropathic pain, stimulation of the M1 primary motor cortex yielded statistically significant pain improvement for upper limb pain but not for lower limb or facial pain. Of note, the patients in this study all received stimulation to the M1 area of the primary motor cortex, which corresponds with the hand, and it was a

"mini meta-analysis" that only included three previous studies, which were conducted by the authors. If these findings can be replicated in the hands of other investigators and in larger sample sizes, rTMS may prove to be a useful tool for neuropathic pain.

Mori N, Hosomi K, Nishi A, Dong D, Yanagisawa T, Khoo HM, Tani, N, Oshino S, Saitoh Y, Kishimi H. Difference in Analgesic Effects of Repetitive Transcranial Magnetic Stimulation According to the Site of Pain. Front Hum Neurosci. 2021; 15 (786225). Published Nov 26 2021

Scrambler Electroanalgesia Shows Promise for Chemotherapy-Induced Peripheral Neuropathy

David M Carlson, MD reviewing Childs D et al. J. Pain Symptom Manage 2021 Jun

In this crossover analysis from a randomized pilot trial, patients with chemotherapy-induced peripheral neuropathy (CIPN) receiving Scrambler therapy, a form of electroanalgesia, were more than twice as likely to experience a 50% or greater reduction in their primary pain symptom (pain or tingling) compared to those receiving self-administered TENS.

Cancer survivors report experiencing pain most or all days at a rate more than twice that of the general population. Whereas most treatments for CIPN attempt to inhibit pain signals, Scrambler therapy uses cutaneous electrode stimulation to "scramble" overactive pain signals into non-pain signals that are hypothesized to travel along somatosensory C fibers. Preliminary trials have found scrambler therapy to completely resolve CIPN symptoms, and lead to reduced usage of pharmacologic treatments in others. This study reports on the crossover portion of a trial in patients with CIPN treated with Scrambler therapy vs. a transcutaneous electrical nerve stimulation (TENS) unit.

In the initial treatment arm, 46 participants were randomized and completed two weeks of TENS or Scrambler therapy followed by an 8-week observation period with weekly reporting. Scrambler therapy involved the placement of up to five electrode pairs along the innervation path of the region of pain. The electrical impulse intensity was gradually increased to the maximum tolerated, with the goal of eliminating symptoms. Patients received one 30-minute treatment session per day for 10 consecutive weekdays. For TENS therapy, patients were given a new unit and counseling on how to use it, then were instructed to use it on their own for 30 minutes a day for 14 consecutive days. After the initial treatment arm, 22 patients were able to complete the crossover treatment, which consisted of two weeks of the other treatment modality followed by another eight-week observation period. Pain data were measured using a 10-point scale of severity of their primary symptom (pain or tingling); these were recorded daily during treatment and weekly during observation.

After the initial trial, nearly twice as many Scrambler-treated patients recorded a 50% reduction in their primary pain symptom (36-56% of patients) compared to TENS therapy (16-28%). After crossover, a similar ratio was observed with 60% (6 of 10) patients receiving Scrambler therapy experiencing 50% or greater reduction in their primary symptom, compared to only 25% (3 of 12) receiving TENS treatment, though the difference was not significant (p=0.11).

Impact: The data from this crossover portion of a pilot clinical trial suggests that Scrambler therapy may be more effective for chemotherapy-induced neuropathic pain than TENS therapy. Notable limitations of this study include the small sample size, a lack of blinding, and greater clinician contact in the Scrambler arm. Future studies including sham procedures for placebo control could lend further support to this novel neuromodulation technique.

Childs DS, Le-Rademacher JG, McMurray R, Bendel M, O'Neill C, Smith TJ, Loprinzi CL. Randomized Trial of Scrambler Therapy for Chemotherapy-Induced Peripheral Neuropathy: Crossover Analysis. J Pain Symptom Manage. 2021;62(6):1247. Published June 6 2021