BRIEF RESEARCH REPORT

Slow-Frequency rTMS Reduces Fibromyalgia Pain

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ABSTRACT

Objective. Evidence suggests that fibromyalgia (FM) is a centrally mediated pain disorder. Antidepressants, including electroconvulsive therapy, provide some symptomatic relief in FM and other pain disorders. Repetitive transcranial magnetic stimulation (rTMS) is a new antidepressant treatment, which may also be useful in treating chronic pain.

Design. As part of a larger study, four women with depression, FM, and borderline personality disorder received 1-Hz rTMS applied to the right dorsolateral prefrontal cortex. Subjects rated pain using an 11-point Likert scale.

Results. Pretreatment pain averaged 8.2 (7–9.5) and reduced to 1.5 (0–3.5) after treatment ($P < 0.009$). All had improvement in pain, and two had complete resolution of pain. Only one of the four subjects had an antidepressant response.

Conclusions. These preliminary findings suggest a possible role for rTMS in treating FM.

Key Words. Fibromyalgia; Repetitive Transcranial Magnetic Stimulation; Depression; Chronic Pain; Borderline Personality Disorder

Introduction

Fibromyalgia (FM) is a generalized chronic pain disorder of unknown etiology. Characteristic symptoms include widespread pain and muscle tenderness typically accompanied by sleep disturbance, fatigue, depressive symptoms, and cognitive complaints. The American College of Rheumatology delineated case-finding criteria in 1990, which include pain of at least 3 months duration above and below the waist bilaterally, axial skeletal pain, and 11 of 18 discrete tender points [1].

Although FM is characterized by musculoskeletal pain, evidence suggests that it is not a primary muscle disorder [2]. Thus far, the search for peripheral, systemic, or psychiatric causes for FM has not uncovered a specific etiology. In the ongoing investigation of FM, increasing attention has been directed to central (spinal and supraspinal) nociceptive regulatory processes [3]. Functional neuroimaging research has identified some of the specific brain structures (thalamus, anterior cingulate cortex, somatosensory cortices, limbic structures) that appear to be involved in the experience of pain [4], and the sensory-discriminative and affective-motivational components of pain appear as anatomically distinct brain regions [5]. Neuroplastic changes induced by noxious stimulation can produce aberrant function (sensitization) in these brain regions, suggesting a possible locus and mechanism to explain the phenomenology of persistent, multifaceted pain syndromes such as FM, which have no apparent explanatory peripheral pathology [6].

FM is an illness that is difficult to treat frequently resulting in chronic symptoms, impaired...
functioning, and reduced quality of life. Treatment is frequently multidisciplinary, employing education, medications, physical therapies, and cognitive behavioral therapy [7,8]. Although antidepressants are known to improve the symptoms of FM [8,9], resolution is uncommon. In the context of treatment-resistant illness, the search for novel and more effective interventions is active.

Repetitive transcranial magnetic stimulation (rTMS) is a novel, noninvasive method of brain stimulation using brief magnetic pulses to stimulate the brain [10]. Magnetic pulses pass unimpeded through the scalp and skull, and produce an electrical current in the underlying cortex. There is evidence to suggest a potential therapeutic response to rTMS in depression [11], and it may be as effective as electroconvulsive therapy (ECT) [12]. Both high-frequency rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) and low-frequency rTMS applied to the right DLPFC (R-DLPFC) have an antidepressant effect [11].

Direct stimulation of motor cortex with chronic electrical stimulation or rTMS is known to reduce chronic central pain [13–15]. A single session of high-frequency (10 Hz) rTMS applied to the motor cortex was able to reduce chronic pain for up to 8 days [14], and monthly sessions of rTMS were able to control neuropathic pain in a patient for more than 1 year [16]. Although most reports of rTMS applied to motor cortex used high-frequency stimulation, low-frequency (1 Hz) stimulation of the motor cortex reduces capsaicin-induced acute pain [17]. To date, most studies using rTMS to reduce pain have stimulated the motor cortex using a single session of treatment, while most studies using rTMS to treat depression have stimulated the DLPFC over multiple treatment sessions. In one study, high-frequency rTMS applied to the left DLPFC in pain-free treatment-resistant depressed patients altered acute pain perception [18]. Additionally, low-frequency rTMS (1 Hz) applied to the right DLPFC has also been shown to increase bilateral pain tolerance in healthy volunteers, and suggests there may be a right hemisphere preference in pain processing [19].

ECT is beneficial in refractory pain states [20]. Given that rTMS applied to the DLPFC has similar antidepressant effects, possibly, rTMS may be beneficial in treating centrally mediated FM pain.

Methods

A sham-controlled, double-blind study was performed to examine the effect of slow-frequency (1 Hz) rTMS in subjects with treatment-resistant depression and borderline personality disorder (BPD). Four subjects in this study also had a previous diagnosis of FM. The subjects met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for major depression and for BPD, were between 18 and 85 years of age, were capable of providing consent, and scored ≥20 on a 28-item Hamilton Rating Scale for Depression (HRSD). Exclusion criteria included the following: diagnosis of schizophrenia or schizoaffective disorder, substance abuse in the past year (except nicotine), an unprovoked seizure history or family history of treatment-resistant epilepsy, pregnancy, history of failure to respond to ECT, metal in the head (except dental fillings), any implanted devices, prior brain surgery, any significant change in psychotropic medication within the previous 4 weeks or any significant change in treaters in the previous 6 weeks, and any suicide attempt within the past 3 months. Institutional Review Board approval was obtained to perform this study. After complete description of the study to the subjects, written informed consent was obtained.

Clinical evaluations included a 28-item HRSD, the Montgomery Asberg Depression Rating Scale (MADRS), the Clinical Global Impression, and the Global Assessment of Function. These assessments were performed at baseline and every 2 weeks thereafter, as long as the patient remained in the study. Additionally, HRSD evaluations were performed on a twice-weekly basis. Clinical raters were blinded for the first 2 weeks of treatment only, as the sham condition was given for 2 weeks only. Pain ratings were subjective reports of pain based on a 0–10 scale, with 0 being no pain and 10 being the worst ever.

rTMS was produced using a Magstim Super Rapid repetitive stimulator and a 70-mm figure-of-eight coil. Single transcranial magnetic stimulation stimuli were used to identify the optimal site for production of a motor-evoked potential in the left abductor pollicis brevis and to determine motor threshold (MT). One-hertz rTMS was applied 5 cm anterior to the optimal motor cortex stimulation site to approximate localization of the R-DLPFC. rTMS was applied using a frequency of 1 Hz, intensity of 110% MT, and two 800-second trains with an intertrain interval of 60 seconds, for a total of 1,600 stimuli per session. One of the four subjects with FM received 10 sham rTMS treatments, using a 90-degree one-wing position, before receiving active rTMS. All subjects received daily Monday-to-Friday treat-
ments with active rTMS over 4 weeks, and one subject received an additional 12 treatments over 6 weeks as part of a taper protocol for those who had remission of depression (>50% decline and <10 on HRSD).

All subjects remained on their stable psychotropic medications, and no medication changes were permitted during this study.

**Results**

All four subjects with FM were female, ranging in age from 36 to 51 years (X = 43.5). Data for each subject is shown in Table 1. The length of time in which the subjects had a diagnosis of FM ranged from approximately 4 to 10 years. The actual duration of FM symptoms experienced by each subject is not known. Subjects A, C, and D were diagnosed by board-certified rheumatologists at our institution, and Subject B was diagnosed by a physician at an outside institution. Records for Subject B show that tender points were tested; however, the number of positive points was not listed. Psychiatric diagnoses were made by one or more board-certified psychiatrists at our institution. All subjects had chronic psychiatric illnesses with long-standing diagnoses of recurrent major depression and BPD and had a history of abuse. The subjects did not change their medications during the study. The following medications were used daily: Subject A, sertraline 200 mg, trazodone 150 mg, and clonazepam 0.5 mg; Subject B, fluoxetine 40 mg, bupropion SR 200 mg, and ziprasidone 100 mg; Subject C, nortriptyline 100 mg, clonazepam 2 mg, quetiapine 225 mg, gabapentin 600 mg, tramadol hydrochloride 100 mg, and cyclobenzaprine hydrochloride 20 mg; Subject D, bupropion SR 300 mg, clonazepam 2–6 mg, tramadol hydrochloride 100 mg, and rofecoxib 25 mg.

The subjects received a total of 18–20 active rTMS treatments. The two subjects who received 19 treatments missed one treatment due to scheduled national holidays. Only one subject missed two treatments; thus, compliance with the protocol was high.

Although improvement on HRSD ($P < 0.028$) and MADRS ($P < 0.005$) ratings were statistically significant, only one subject had a remission of depression (Subject C). All subjects noted an improvement in FM pain ($P < 0.009$), with two subjects reporting complete resolution of pain. Subject B received sham rTMS for 2 weeks with no pain improvement during that time. One subject noted improvement in pain during the first week of treatment, and two noted improvement during week 3 of treatment. Two subjects provided pain ratings during treatment (Subjects C and D), and two described changes in pain retrospectively when contacted after it was noted that rTMS might be altering pain (Subjects A and B). The subjects were contacted repeatedly after having completed the acute series of treatment to assess the recurrence of pain. The subjects were defined as having recurrence of pain when reported ratings increased by at least 1.5 points. The duration of pain improvement ranged from 15 to 27 weeks.

**Discussion**

This is the first report of pain reduction in FM patients with rTMS. Given that only one subject had a remission in depression and one subject had a limited decline in HRSD ratings with a significant decrease in pain, the reduction in FM pain cannot be explained by the treatment of depression alone. Notably, the subjects’ pain improvement was sustained for a number of weeks after rTMS, and raises the possibility that rTMS applied to the R-DLPFC may be clinically useful in reducing FM pain.

The findings in this study are the first to show reduction in chronic pain with rTMS applied to the DLPFC, and provide further evidence for a potential modulatory role of the DLPFC in the experience of pain. A recent functional neuroimaging study using positron emission tomography scanning also provides evidence for involvement of the DLPFC in modulating pain [21].

This study clearly has many limitations, the most obvious being the small number of patients. The potential confound from comorbid BPD is

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**Table 1** Age and pre/post depression and pain ratings for four subjects receiving active rTMS

<table>
<thead>
<tr>
<th>Subject</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.0</td>
<td>36.0</td>
<td>51.0</td>
<td>39.0</td>
</tr>
<tr>
<td>HRSD</td>
<td>Baseline</td>
<td>43.0</td>
<td>42.0</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>27.0</td>
<td>28.0</td>
<td>4.0</td>
</tr>
<tr>
<td>MADRS</td>
<td>Baseline</td>
<td>35.0</td>
<td>36.0</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>20.0</td>
<td>17.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Pain (0 = no pain)</td>
<td>Baseline</td>
<td>7.0</td>
<td>8.5</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>3.5</td>
<td>0.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Duration of pain improvement (weeks)</td>
<td>27.0</td>
<td>15.0</td>
<td>18.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

HRSD = Hamilton Rating Scale for Depression; MADRS = Montgomery Asberg Depression Rating Scale.
also problematic. However, as individuals with a diagnosis of FM [22] and those with a diagnosis of BPD [23] have a significant incidence of past abuse, this comorbidity may not be uncommon. Another problem is that monitoring pain was not the primary objective of this study. Further research with a prospective study design is required to examine if slow-frequency rTMS applied to the R-DLPFC may be effective in treating FM pain.

References