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Transcranial Magnetic Stimulation in the Treatment of Chronic Widespread Pain: A Randomized, Controlled Study

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Abstract

Objective—Our objective was to assess transcranial magnetic stimulation (TMS) in the treatment of chronic widespread pain (CWP).

Methods—Nineteen participants were randomized to two groups: one receiving active TMS (N=7) and another receiving sham stimulation (N=11) applied to the left dorsolateral prefrontal cortex. During sham stimulation, subjects heard a sound similar to the sound heard by those receiving the active treatment and received an active electrical stimulus to the scalp. The stimulation protocol consisted of 15 sessions completed within a 4-week period. Blind assessments were done at baseline and after each 5 sessions followed by blind assessments at 1 week, 1 month and 3 months after the last TMS sessions. The primary outcome variable was a pain measure, the Gracely Box Intensity Scale (BIRS).

Results—The percentage of subjects who guessed that they were receiving TMS was similar in the two groups. Both the TMS group and the sham group showed a statistically significant

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reduction in the BIRS scores from baseline during the acute phase of treatment and the follow-up phase. However, the TMS and sham groups did not differ in the change in the BIRS scores.

Discussion—Although some previous clinical studies and basic science studies of TMS in treating pain are promising, this study found no difference in the analgesic effect of TMS and sham stimulation. Future studies should utilize a sham condition that attempts to simulate the sound and sensation of the TMS stimulation. Stimulus location and other stimulus parameters should be explored in future studies.

Keywords

Transcranial magnetic stimulation; chronic widespread pain; fibromyalgia

Introduction

Chronic widespread pain (CWP) is a disorder that affects about 4–13% of the general population and causes much suffering and disability and has significant economic impact¹. Fibromyalgia (FM) patients lie at the more severe end of the CWP syndrome and comprise about 20% of the CWP population.² Patients with chronic pain are 3.6 times more likely to be depressed than patients without chronic pain; patients with depression are more 4 times more likely to have chronic pain than non-depressed patients.³ In addition, several treatments for major depression have been found to reduce levels of pain. In meta-analyses of placebo-controlled studies, antidepressants have been found effective for reducing pain in depressed patients and in patients with chronic non-malignant pain.⁴ Although some treatments, such as antidepressant treatments, may lessen symptoms, there is a need for improved treatments for this disorder.^{5,6}

Transcranial magnetic stimulation has been shown effective in treating major depressive disorder.^{7–10} TMS has been used in a variety of pain syndromes with varying degrees of success.^{11,12} Compared to sham treatment, TMS to the dorsolateral prefrontal cortex was found to have an analgesic effect in patients with major depression.¹³ However, most previous studies of TMS in pain syndromes used sham conditions that did not sound or feel like the real TMS. The sound and sensation of the real TMS could have unblinded the participants and biased the outcome of the studies; it is important that the TMS condition and the sham condition differ only in the presence or absence of the magnetic stimulation.

Previous TMS studies of pain have targeted different brain regions, including the dorsolateral prefrontal cortex and the motor cortex. CWP is associated with altered brain processing of sensory signals in various brain regions.^{14,15} In fMRI studies in which subjects receive a similar pressure on a finger, chronic pain patients have shown increased activation of several brain regions compared with controls.¹⁴ These regions include the anterior cingulate, medial prefrontal gyrus and the insula. Further, a scale assessing the catastrophizing of the pain correlated significantly with increased activation of the dorsal anterior cingulate, the dorsolateral prefrontal cortex, and the medial frontal cortex.¹⁶

In patients with FM, the level of depression correlated with fMRI activation of insula and amygdalae when pain was induced by pressure to a finger.¹⁴ The clinical pain intensity

correlated with fMRI activations of the insula, the contralateral anterior cingulate, and the prefrontal cortex. A review of functional imaging studies of major depression indicates involvement of the dorsolateral prefrontal cortex, medial prefrontal cortex, orbital prefrontal cortex, anterior cingulate, thalamus, and hippocampus.¹⁷ In particular, decreased activity in the dorsolateral prefrontal cortex is one of the more common findings in major depression. In addition, changes in the activity of the insula are often associated with recovery from depression.^{18,19} TMS to the prefrontal cortex has effects on the dorsolateral, medial and orbital prefrontal cortex, anterior cingulate cortex, insula and thalamus.^{20,21} Thus, there is not only clinical overlap between chronic pain and depression, but also neuroanatomical overlap, including alterations in function in several neuroanatomical sites: prefrontal cortex, anterior cingulate, insula, and thalamus. Because of the probable role of the dorsolateral prefrontal cortex in pain and the analgesic effect of TMS to the dorsolateral prefrontal cortex in depressed patients,¹³ we chose the dorsolateral prefrontal cortex as the site of stimulation.

To address the possibility that inadequate blinding confounded previous studies, we compared TMS to the dorsolateral prefrontal cortex with an “active” sham condition; the participants who were randomized to sham heard a sound similar to the sound heard by those receiving the active TMS treatment, received an electrical stimulus which created a sensation at the site of stimulation on the scalp, but did not receive the magnetic pulses. Our study was designed to determine whether 15 TMS sessions had a greater analgesic effect than 15 sessions of sham TMS in participants with CWP with or without depression.

Materials and Methods

Overall design

Women with CWP were randomized using urn randomization into one of 2 conditions: 1) TMS at 120% of the estimated prefrontal cortex threshold intensity with high frequency (10 Hz with 4-second trains) to the left dorsolateral prefrontal cortex and 2) Sham stimulation. Each participant was to receive 15 sessions with 75 trains per session over a period of 4 weeks. Blind assessments of pain and depression took place before the 1st session, after the 5th, the 10th, and 15th sessions and 1 week after the 15th session. In a second phase of the study, we assessed the subjects in naturalistic follow-ups 1 month and 3 months after the last session at which time the blind was broken. Non-responders to sham at the end of the 3 month follow-up were offered 15 TMS sessions and assessed in an open-label manner after the real TMS sessions.

Subjects

Subjects were recruited through advertising, through publicity on television, and from a hospital clinic that specializes in the treatment of fibromyalgia. A research coordinator screened potential participants by telephone to determine who were likely to meet entry criteria for the study. If the subjects were considered likely to qualify, they came for the baseline assessment and interview.

The subjects were non-pregnant, non-breast feeding females between 18 and 65 years of age and had CWP as defined by the 1990 American College of Rheumatology guidelines.¹ This

definition requires musculoskeletal pain ≥ 3 months; pain above and below the waist, on both right and left sides, and at 1 axial site (e.g. head, neck, spine or back). The subjects had to have a global pain score of at least 4 on the Pain Intensity Numerical Rating Scale (PI-NRS) prior to treatment, and at least an 8 on the Gracely Box Intensity Scale at screening. They were willing to undergo randomization and regularly come for treatments. Participants were allowed to continue their current medicines as usual at stable doses for 4 weeks before and then during the acute phase of the study. Psychotherapy was allowed if it has been ongoing for ≥ 3 months before the treatment starts.

Potential participants were excluded if the screening history or physical exam revealed: 1) a concurrent medical condition associated with substantial pain such as diabetic neuropathy, systemic lupus erythematosus or severe degenerative joint disease or a condition that might increase the risk of seizures from the TMS, 2) a history of a seizure disorder or a first-degree blood relative with a seizure disorder, 3) previous use of TMS, 4) involvement in litigation or compensation related to FM, CWP or depression, 5) current use of proconvulsant medications such as bupropion, 6) metal in the body that is a contraindication to an MRI or TMS, 7) a history of head injury associated with loss of consciousness, brain surgery or lithium toxicity, 8) a history of a current or past major psychiatric disorder (other than major depression) including bipolar disorder, schizophrenia, obsessive compulsive disorder, and current substance abuse or dependence, 9) active suicidal intent or plan, 10) severe claustrophobia resulting in an inability to tolerate confinement in the MRI scanner. Patients with a current major depression were not excluded except for those with psychotic features or a major depressive episode that has lasted ≥ 5 years. Using DSM-IV criteria to define remission, we required that patients have not been in an episode of major depression for at least 2 months within the past 5 years. Initially in the study, patients taking opiates were excluded. However, because of the widespread use of opiates in this population and difficulty recruiting subjects, a stable dose of opiate was allowed.

The University of Washington Human Subjects Committee approved this study and all patients provided written informed consent before inclusion.

Clinical Assessments and Timing of Assessments

At the screening visit, the subject was interviewed by a psychiatrist and had a physical examination, including a neurological exam and a tender point exam,²² basic blood assessment and urinalysis, including a drug toxicology screen. The subjects had no major medical problems. Subjects were asked to complete questionnaires that assess pain, functional status, depression ratings, fatigue, sleep, and other measures of health. The research coordinator blind to the randomization repeated the baseline assessments of pain, functional status, depression, fatigue, and sleep before the 1st and after the 5th, the 10th, and the 15th TMS sessions as well as 1 week, 1 month, and 3 months after the last TMS treatment except for the SF-36, neuropsychological tests, audiometry and the dolorimetry which were only done at baseline and one week after the 15th TMS session. The tenderpoint exam and laser evoked potentials were only done at baseline and after the 15th session.

Measures of Pain

Gracely Box Intensity Scale (BIRS) and the Gracely Box Unpleasantness Rating Scales (BURS). The BIRS is a reliable, valid, and sensitive measure that has been used in a number of studies of analgesics and studies of changes of pain intensity over time^{15,16,23–29} and was selected as the primary outcome variable. Each scale is a 20-point scale that has clear anchor points. Patients were classified as responders if they had a 4-point drop or more on the BIRS. In order to be randomized, subjects were to have had a BIRS score of at least 8.

Pain Intensity Numerical Rating Scale (PI-NRS). The PI-NRS is an 11-point (0–10) simple rating scale for pain that was recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials Committee.³⁰ We also categorized patients as responders if they had a 30% or more reduction in pain intensity, based on the Committee's recommendations.

Other measures included the McGill Pain Questionnaire- Short Form,^{31,32} the Brief Pain Inventory-Revised,³³ the Medical Outcomes Study Short Form-36 General Health Survey,³⁴ the Multidimensional Fatigue Inventory,³⁵ and visual analog scales of fatigue, sleep, pain and overall well-being.

Pain Thresholds Using a Dolorimeter. Blinded assessments were made by the research coordinator, measuring sensitivity to pain by using a dolorimeter (pressure gauge) on the thumbnail. The dolorimeter was applied to the thumbnail and then pressure was slowly increased by 1kg/second up to 12 kg. The subject was asked when she began to sense pain (pain threshold) and when it became intolerable (pain tolerance). We chose the Multiple Random Staircase (MRS) paradigm, in which the dolorimeter is applied only to the right thumb and pressure stimuli are applied in a random fashion.²⁹ We chose MRS pressure method because the ascending ramp used with other standard methods of assessing pain pressure stimuli may be influenced by participant distress.

Depression and Neuropsychological Measures

The psychiatrist diagnosed patients according to DSM-IV criteria. The research coordinator used the Structured Clinical Interview for DSM-IV Disorders-Research Version, version 2.0.³⁶ The research coordinator administered the Hamilton Depression Rating Scale-17 item³⁷ to assess the level of depression. The subjects completed the Beck Depression Inventory.³⁸

The research coordinator who was blind to the randomization conducted neuropsychological testing before the 1st TMS session and after the 15th TMS session. These cognitive tests included: the Rey Auditory Verbal Learning Test, Logical Memory (Wechsler Memory Scale), Digit Symbol Test, Digit Span (WAIS-R), the Mini-Mental State Exam, Trails A and B, Stroop, and the Controlled Oral Word Association Test (COWAT).³⁹

Other Measures

The subjects completed visual analog scales of fatigue, sleep, pain, and overall well-being. Additionally, the Multidimensional Fatigue Inventory was used to assess the severity of fatigue along several domains. The Patient Clinical Global Improvement (PGI) was

assessed: 1=very much improved, 2=much improved, 3=minimally improved, 4= no change, 5=minimally worse, 6= much worse, 7= very much worse. Adverse events (AEs) were collected by open report of emergent symptoms or illness during the study. This form was filled out during baseline, daily before each TMS session by the trained physician administering the TMS, and at each follow-up visit.

TMS Procedures

Determination of TMS Stimulation Site—We used the Neuronetics 2100 CRS Stimulator produced by Neuronetics, Inc. on loan from the manufacturer. Subjects placed earplugs in their ears. Using single pulse TMS, we determined the site of stimulation for TMS or sham sessions. We determined the point of optimal stimulation for the right abductor pollicis brevis in the left motor cortex. At that point, for all subjects, we found the motor threshold (MT), the lowest stimulation intensity capable of inducing a small twitch in the thumb muscle, detectable with an electromyography or EMG electrode, using the PEST program.⁴⁰ The location of the stimulation site was defined as a point 5 cm anterior to the point of the motor threshold determination for the treatment sessions.

Magnetic Resonance Imaging—Following this initial visit, subjects had a 3T magnetic resonance imaging (MRI) with vitamin E capsules (which are visible on the MRI) placed over the motor cortex and treatment stimulation site marked on a swim cap. In most previous TMS studies, scalp-cortex distances (SCDs) were assumed to be identical at the prefrontal cortex and the motor cortex. However, these distances may differ, resulting in TMS stimulus not reaching the prefrontal cortex in some patients with SCDs that were greater in the prefrontal cortex than in the motor cortex. To correct for these differences, the neuroradiologist measured the SCD at the site of prefrontal stimulation and the motor cortex using visualization of vitamin E capsules on the MRI. This allowed us to correct for the differences in the SCD and estimate the threshold for stimulating the prefrontal cortex, the corrected motor threshold (MTc) as we did in our previous study of TMS in major depression.^{7,13} The MRI also allowed us to screen for intracranial pathology that might be causing the chronic pain/depression or might pose a seizure risk and to verify the determination of the TMS stimulation site.

Randomization—At the completion of the baseline assessment, patients were randomly assigned to either real TMS or sham stimulation using a computerized urn randomization program that uses an adaptive randomization and stratification strategy. The urns included.⁴¹ 1. The presence or absence of major depression. 2. The presence or absence of FM. 3. The severity of pain (less than 14 on the BIRS, 14 or greater). Based on the randomization, a “smart card” which determined whether the real TMS or sham coil would be administered was assigned to a particular patient. The card had only a code number that did not reveal the randomization.

Motor Threshold Determination. Before the 1st, 6th, and 11th sessions, each patient's MT was determined

Treatment Sessions. Based on randomization, the patients were given one of two stimulations to the left dorsolateral prefrontal cortex: 1) TMS at 120% of the MTc at 10 Hz

with 75 4-second “trains” or 2) sham stimulation with the electromagnet blocked within the coil by a piece of metal so the cortex was not stimulated. The coils appeared identical. Electrodes were attached to the left side of the forehead for each subject for each session. Those receiving the sham stimulation received an electrical stimulus to the forehead during the sham stimulation. Those receiving the real TMS received no electrical stimulation to the electrodes. Both groups experienced a sensation in the area of the left forehead. In addition, all subjects were given special earplugs and received an audible noise during the stimulation to mask any possible sound differences between the TMS and sham conditions. This system developed by James Long, is described in more detail elsewhere.^{9,42}

A TMS train refers to a continuous production of TMS pulses over a given time period. In this study, the TMS trains lasted 4 seconds at 10 Hz. Each subject was given 15 sessions with 75 trains per session with an intertrain interval of 26 seconds (10 Hz x 4 sec = 40 stimulations/train x 75 trains = 3,000 stimulations/session x 15 sessions = 45,000 total 10-Hz stimulations). The 15 sessions were completed within a 4-week period. Blinding of the physicians administering the TMS or sham stimulation was also attempted as the TMS machine acted and sounded the same when giving real and sham TMS stimulations; the physicians wore ear inserts producing white noise, and there were two identical treatment coils and randomization “smart cards” assigned to each patient. The treater was never a rater of the outcome measures. If a patient was unable to tolerate the stimulation at 120%, the intensity was lowered by 5% until the subject was able to tolerate the stimulation.

Statistical Analysis

Our primary aim was to determine whether TMS is superior to sham stimulation in reducing pain in patients with CWP. To examine differences in changes in outcomes over time between TMS and comparison group subjects, we estimated random coefficient models⁴³ following the intent-to-treat principle. Random coefficient analysis has a number of advantages when longitudinal data are available. One, the approach recognizes that repeated measures are dependent within study participants. Two, the number and temporal spacing of observations can vary across participants. Three, the approach allows for differences across study participants with subject-specific intercept and slope regression coefficients.

To assess the impact of the intervention, we estimated random coefficient models that included measures of time (visits 1, 5, 10, 15, 16), group, and time by group interactions. We specified time as a set of indicator variables with baseline as the reference category. Similarly, the group variable used the comparison group as the reference category. To avoid restrictive assumptions, we left the covariance of the outcomes at assessment unstructured. We estimated the models with a restricted maximum likelihood approach, which produces valid estimates under the missing-at-random assumption.⁴⁴ This approach correctly handles the additional uncertainty arising from missing data and uses all available data to obtain unbiased estimates for model parameters.⁴⁵ We conducted analyses with Stata SE version 12 (StataCorp LP, College Station, TX, USA). All p-values are 2-tailed. Dr. Joesch conducted the analyses for the primary outcome variables.

For data involving baseline and only one post treatment assessments, general linear model repeated measures was used to compare groups. For categorical data, we used Fisher's Exact tests. When the word "significant" is used, it refers to statistical significance.

Results

Subjects

Telephone screening was conducted for 493 potential subjects. The top two reasons for exclusion were recent opiate use and a concurrent medical condition that causes pain except CWP. Twelve of the enrolled 31 patients were screen failures, one because of comorbid alcohol use, two because of fatigue too severe to meet the time commitment of the study, one because of a neurological disorder, one because of head trauma, one because of a motor threshold that was too high, one because of a neurological problem (essential tremor of the head), one who no longer met criteria for CWP just before the planned randomization, one had comorbid medical conditions, one could not meet the time commitment of the study, one because of disability litigation and one abnormal MRI. Nineteen patients met entry criteria for inclusion in the study. 11 were randomized to the sham group and 8 were randomized to the TMS group. However, one subject randomized to the TMS had a baseline BIRS score of 4 which was well below the BIRS score of 8 required for randomization. Because of this incorrect randomization, this subject was excluded from the efficacy analyses, but was included in the analysis of side effects. The clinical characteristics of those correctly randomized are in Table 1. One subject in the TMS dropped out after the 10th session because of lack of response and is included in the analyses. The study was conducted between January, 2008 and November, 2010.

Blinding

After the first session, the percentage of subjects who guessed that they were receiving TMS was similar in each group: in the TMS group, 37.5%, in the sham group 36.4% (Fisher's exact test, NS). After the 15th session, in the TMS group, 57% of the subjects guessed that they were receiving TMS; within the sham group, 30% (Fisher's exact test, NS). After the first session, the physician administrators of the treatment guessed that the subjects were receiving TMS in 86% of the TMS and in 22% of the sham group (Fisher's exact test, $p < 0.05$). After the 15th session, the physicians guessed that the subjects were receiving TMS in 67% of the TMS group and in 10% of the sham group (Fisher's exact test, $p < 0.05$).

Efficacy Data

Table 2 summarizes the random coefficient analysis estimates for assessments done at baseline, after 5 sessions, after 10 sessions, after 15 sessions and one week, one month and 3 months after the last session. Table 3 summarizes assessments done only at baseline and after the 15 sessions. Table 4 summarizes the open-label cross-over data on patients who received sham stimulation during the blind phase and then received 15 TMS sessions.

The analyses of the variables in Table 2 and Table 4 are summarized in the following paragraphs:

Gracely Box Intensity Rating Scale (BIRS)

The random coefficient analysis showed a significant decrease in the primary outcome variable, the BIRS, with TMS at V10 and subsequent visits compared to baseline. However, the sham group also had significant decreases compared to baseline, and there were no significant differences between the TMS and sham groups at any visit. In the open-label, cross-over phase, there were significant decreases in the BIRS at Visits 10, 15, and 16 compared to baseline. Within the TMS group, 3/7 (43%) met criteria for response. Within the sham group, 5/11 (46%) met criteria for response. Within the sham group who then received real TMS in the open-label cross-over phase, 4/8 (50%) met response criteria.

Gracely Box Unpleasantness Rating Scale (BURS)

The random coefficient analyses showed no significant differences in changes over time between the TMS and sham groups. In the open-label, cross-over phase, there were significant decreases in the BURS at Visits 15 and 16 compared to baseline.

Pain Intensity Numerical Rating Scale (PI-NRS)

The random coefficient analyses showed no significant difference between the TMS and sham groups. The response rates were similar: 40% (4/10) in the sham group and 43% (3/7) in the TMS group. In the open-label, cross-over phase, there were significant decrease in the PI-NRS at Visits 15 and 16 compared to baseline.

McGill Pain Questionnaire-Short Form

The random coefficient analyses showed no significant differences between the TMS and sham groups on any of the total score measures. However, on the sensory subscale the sham group had a greater reduction than the TMS group at visits 10, 15, and 17. On the affective subscale, the TMS group had a greater reduction than the sham group at Visits 15,16,17, and 18. However, taking into account the multiple measures in this study and applying a Bonferroni correction to the p values, even these findings become non-significant. In the open-label, cross-over phase, there were significant decreases in all three measures at Visits 10, 15, and 16 compared to baseline.

Brief Pain Inventory-Short Form

The random coefficient analyses showed no significant differences between the TMS and sham groups in either the severity scores or interference scores. In the open-label, cross-over phase there were significant decreases in the BPI Interference scores and the BPI Severity Scores at Visits 15 and 16 compared to baseline.

Hamilton Depression Rating Scale- 17 Item

The random coefficient analysis showed no differences between groups. In the open-label, cross-over phase, there were significant differences at Visits 10 and 15 from baseline.

Beck Depression Inventory

The random coefficient analysis showed no differences between groups. In the open-label, cross-over phase, there were significant differences from baseline at Visits 10 and 15 compared to baseline.

Multidimensional Fatigue Inventory

The random coefficient analysis showed no differences between groups. In the open-label, cross-over phase, there were significant differences at Visits 10 and 16 compared to baseline.

Visual Analog Scales for Fatigue, Sleep, Pain, and Overall Well-Being

The random coefficient analysis showed no differences between groups for any of the scales. In the open-label, cross-over phase, the pain scale showed significant differences from baseline at Visits 10, 15, and 16 and the well-being scale showed significant differences from baseline at Visits 10 and 16. The fatigue and sleep scales showed no significant changes from baseline.

Patient Clinical Global Improvement (PGI)

The random coefficient analysis showed no difference between groups. In the open-label, cross-over phase, there were significant differences from baseline at Visits 15 and 16.

The analyses of the variables in Table 3 are summarized in the following paragraphs:

SF-36

The functional status was assessed using the Medical Outcomes Study Short Form-36 General Health Survey (SF-36). The SF-36 results are summarized in Table 3. With the general linear model with repeated measures, there were no significant differences between groups in any of the 8 domains of the SF-36.

Tender Point Exam

The tender point exam data are summarized in Table 3. All the subjects met criteria for fibromyalgia at baseline. After 15 sessions, all in the sham group and 5 of 6 in the TMS group still met criteria. With the general linear model with repeated measures, there were no significant differences between groups.

Pain Thresholds Using a Dolorimeter

The dolorimetry data are summarized in Table 3. The MRS threshold pressures (kilograms/cm²) at which subjects reported low, medium, and high ratings on the Gracely Box Intensity Scale were recorded. With the general linear model with repeated measures, for the random pressures, there were no significant differences between groups. However, for each of the analyses, low, medium and high, the mean pain threshold increased for the TMS group and decreased for the sham group. (See Table 3.)

Side Effects

The side effects experienced by the subjects are summarized in Table 5. Neuropsychological tests and audiometry data showed no significant differences between groups and no significant pre-post changes.

Discussion

In both the double-blind phase and in the open-label phase, the TMS was associated with a significant lowering of the pain measures. However, the sham condition also was associated with a similar pain reduction. TMS did not differ from sham in analgesic effects. The active sham condition was successful in blinding the patients; patients in the sham group were just as likely to guess that they had received TMS as those in the TMS group. The active sham condition in which the subjects experienced both a sound and an electrical sensation on the scalp may have contributed to the sham response. In most other studies of TMS and pain, the lack of an active sham condition created the potential for participants to be unblinded and biased in their assessments of pain.

However, the experienced TMS administrators (who were not raters) were much more likely to guess the treatment assignment than by chance alone. The reason most commonly cited by the physicians for guessing TMS was the intensity of the subject's pain experience during the treatment sessions; more intense pain experience during the treatment sessions made a guess of TMS more likely.

A study of fibromyalgia by Short et al⁴⁶ compared TMS (10 hz at 120% of MT for 10 sessions) with an active sham control; the active sham condition produced not only a sound, but also a sensation near the sham coil. Both that study and the current study found that TMS was associated with a reduction in pain measures, but there were no differences between the TMS group and the active sham group. However, in the Short study there was a non-significant trend toward TMS being superior to sham.

In two other studies of TMS in fibromyalgia, no attempt was made to create a sensation on the scalp near the sham coil and the blinding of the conditions was not assessed. One study⁴⁷ found that in fibromyalgia, TMS to the left motor cortex (10 hz, 110% of MT, 14 sessions) was superior to sham stimulation after 5 days and during the 25-week maintenance phase. In a study of patients with both fibromyalgia and major depression, TMS (1 hz at 110% of MT, 20 sessions) to the right dorsolateral prefrontal cortex was found to be not significantly different from sham stimulation.⁴⁸

The current study has several limitations: First, the current study was limited by the small sample size due to difficulties recruiting participants who met our strict entry criteria. The small sample size limited our ability to detect possible true differences between groups. Second, concomitant medications may have confounded the results. Third, we only used one site of stimulation. The current study attempted to stimulate the left dorsolateral prefrontal cortex; some other studies of TMS in the treatment of pain have stimulated other areas, especially the motor cortex. In addition, the current study used the "5 cm rule" to determine

the site of stimulation at the left dorsolateral prefrontal cortex; this technique sometimes results in stimulation of areas posterior to the prefrontal cortex.⁹

In spite of these negative results of the current study, TMS should continue to be studied in the treatment of CWP and other pain disorders. TMS has biological effects on brain circuits involved in pain perception. TMS can have acute analgesic effects.^{49–51} Naloxone reduces TMS-induced analgesia, suggesting that TMS may drive top-down opiodergic analgesia.⁵² Future studies may clarify whether different stimulus parameters or other sites of stimulation, including deeper structures, may have a better analgesic response.^{53,54} Attention should be given to whether the pain reduction is with the sensory or affective component of pain. It is of interest that TMS to the dorsolateral prefrontal cortex in the current study was associated with a greater reduction in the affective component of pain compared to the sham condition. The sham condition had greater reduction in the sensory component to pain compared to the TMS condition. However, these findings are only suggestive given the small sample size and the multiple measures. Nonetheless, stimulation of the dorsolateral prefrontal cortex might be expected to have a greater effect on the affective component of pain compared to the sensory component; anterior structures such as the anterior cingulate may be more closely associated with the affective component of pain compared to the somatosensory cortex.^{55–57} Given the potential for participants being unblinded and biased when an inactive sham is used, a sham condition that produces a sound and sensation similar to real TMS is important for future studies.

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Table 1

Demographic and Clinical Characteristics of Patients. Means (Standard deviations) and Percentages.

	Sham Group (n=11)		TMS Group (n=7)	
Age	52.09	(10.02)	54.86	(7.65)
Age of Onset of Pain	36.45	(10.72)	43.86	(9.92)
Duration of Illness (Years)	15.64	(6.93)	11	(4.26)
% with Major Depression	5/11	(45%)	3/7	(43%)
Medications:				
Antidepressant %	36%		43%	
Anticonvulsants %	45%		0%	
Opiates %	18%		14%	
NSAIDS%	55%		57%	
Benzodiazepines%	55%		47%	
Muscle Relaxants %	0		14%	
Mean # of Medications	2.04		1.71	

Table 2

Random Coefficient Analysis Estimates of Predicted Means (SE) over Time in the TMS and Sham Groups. V5 are the scores after 5 sessions; V10, after 10 sessions; V15, after 15 sessions; V16, one week after the last TMS session; V17, one month after the last TMS session, and V18, three months after the last TMS session.

	Baseline	V5		V10		V15		V16		V17		V18	
BIRS-Sham	13.18 (0.99)	10.64 (0.99)	10.27 (0.99)	8.45 (0.99)	8.89 (0.99)	10.30 (1.36)	7.67 (1.36)	10.30 (1.36)	7.67 (1.36)	10.30 (1.36)	7.67 (1.36)	10.30 (1.36)	7.67 (1.36)
BIRS-TMS	14.43 (1.20)	13.00 (1.20)	11.29 (1.20)	10.58 (1.36)	10.50 (1.36)	7.73 (0.78)	7.88 (1.05)	7.70 (0.78)	7.88 (1.05)	7.70 (0.78)	7.88 (1.05)	7.70 (0.78)	7.88 (1.05)
BURS-Sham	9.91 (0.78)	8.73 (0.78)	9.00 (0.78)	9.00 (0.78)	9.00 (0.78)	9.00 (0.78)	9.00 (0.78)	9.00 (0.78)	9.00 (0.78)	9.00 (0.78)	9.00 (0.78)	9.00 (0.78)	9.00 (0.78)
BURS-TMS	12.57 (1.26)	11.86 (1.26)	10.43 (1.26)	10.43 (1.26)	10.43 (1.26)	10.43 (1.26)	10.43 (1.26)	10.43 (1.26)	10.43 (1.26)	10.43 (1.26)	10.43 (1.26)	10.43 (1.26)	10.43 (1.26)
PI-NRS-Sham	5.91 (0.41)	4.91 (0.54)	4.55 (0.54)	3.86 (0.69)	4.16 (0.73)	4.62 (0.80)	4.69 (0.66)	4.16 (0.73)	4.62 (0.80)	4.16 (0.73)	4.62 (0.80)	4.16 (0.73)	4.62 (0.80)
PI-NRS-TMS	6.57 (0.35)	6.29 (0.59)	5.71 (0.84)	5.33 (1.02)	4.83 (1.04)	4.33 (0.79)	4.00 (1.04)	4.83 (1.04)	4.33 (0.79)	4.83 (1.04)	4.33 (0.79)	4.00 (1.04)	4.33 (0.79)
McGill PQ-Total-Sham	17.09 (0.75)	11.91 (0.75)	9.55 (0.75)	8.27 (0.75)	8.98 (0.75)	8.61 (1.00)	10.56 (0.82)	8.98 (0.75)	8.61 (1.00)	8.98 (0.75)	8.61 (1.00)	10.56 (0.82)	8.61 (1.00)
McGill PQ-Total-TMS	17.14 (2.11)	15.00 (2.11)	12.86 (2.11)	10.33 (2.49)	11.17 (2.49)	11.50 (2.49)	9.83 (2.49)	11.17 (2.49)	11.50 (2.49)	11.17 (2.49)	11.50 (2.49)	9.83 (2.49)	11.50 (2.49)
McGill PQ- Sensory-Sham	13.91 (1.28)	10.00 (0.86)	*8.18 (0.49)	*6.64 (1.06)	6.83 (1.22)	**7.18 (0.93)	8.27 (1.07)	6.83 (1.22)	**7.18 (0.93)	6.83 (1.22)	**7.18 (0.93)	8.27 (1.07)	6.83 (1.22)
McGill PQ- Sensory-TMS	11.86 (1.80)	11.14 (2.25)	10.14 (1.95)	8.50 (2.58)	9.33 (3.02)	9.67 (1.67)	7.83 (2.68)	9.33 (3.02)	9.67 (1.67)	9.33 (3.02)	9.67 (1.67)	7.83 (2.68)	9.33 (3.02)
McGill PQ-Affective-Sham	3.18 (0.25)	1.91 (0.25)	1.36 (0.25)	1.64 (0.25)	1.70 (0.25)	1.56 (0.32)	1.87 (0.27)	1.70 (0.25)	1.56 (0.32)	1.70 (0.25)	1.56 (0.32)	1.87 (0.27)	1.70 (0.25)
McGill PQ-Affective-TMS	++5.29 (0.43)	3.86 (0.43)	2.71 (0.43)	#1.83 (0.50)	#1.83 (0.50)	#1.83 (0.50)	#2.00 (0.50)	#1.83 (0.50)	#1.83 (0.50)	#1.83 (0.50)	#2.00 (0.50)	#2.00 (0.50)	#1.83 (0.50)
BPI-Severity-Sham	4.77 (0.24)	4.09 (0.48)	3.70 (0.54)	3.16 (0.59)	3.59 (0.72)	4.31 (0.85)	4.46 (0.54)	3.59 (0.72)	4.31 (0.85)	3.59 (0.72)	4.31 (0.85)	4.46 (0.54)	3.59 (0.72)
BPI-Severity-TMS	+6.29 (0.38)	5.25 (0.47)	5.02 (0.79)	4.67 (1.14)	5.21 (0.87)	4.29 (0.66)	#3.88 (0.97)	5.21 (0.87)	4.29 (0.66)	5.21 (0.87)	4.29 (0.66)	#3.88 (0.97)	5.21 (0.87)
BPI Interference-Sham	5.44 (0.61)	3.97 (0.61)	3.69 (0.61)	2.68 (0.61)	2.97 (0.61)	2.52 (0.76)	3.41 (0.66)	2.97 (0.61)	2.52 (0.76)	2.97 (0.61)	2.52 (0.76)	3.41 (0.66)	2.97 (0.61)
BPI Interference-TMS	5.37 (0.64)	4.43 (0.64)	4.71 (0.64)	3.40 (0.50)	2.83 (0.50)	2.55 (0.50)	2.07 (0.50)	2.83 (0.50)	2.55 (0.50)	2.83 (0.50)	2.55 (0.50)	2.07 (0.50)	2.83 (0.50)
Hamilton Depression Rating-Sham	14.64 (1.37)	*11.18 (1.37)	9.09 (1.37)	8.36 (1.37)	7.45 (1.37)	8.38 (1.74)	10.40 (1.45)	7.45 (1.37)	8.38 (1.74)	7.45 (1.37)	8.38 (1.74)	10.40 (1.45)	7.45 (1.37)
Hamilton Depression Rating-TMS	14.71 (1.84)	15.43 (1.84)	11.86 (1.84)	10.83 (1.89)	8.67 (1.89)	9.50 (1.89)	8.83 (1.89)	8.67 (1.89)	9.50 (1.89)	8.67 (1.89)	9.50 (1.89)	8.83 (1.89)	8.67 (1.89)
Beck Depression Inventory-Sham	15.64 (2.62)	12.27 (2.74)	9.82 (2.10)	8.55 (2.30)	7.18 (2.38)	7.83 (2.98)	8.95 (2.73)	7.18 (2.38)	7.83 (2.98)	7.18 (2.38)	7.83 (2.98)	8.95 (2.73)	7.18 (2.38)
Beck Depression Inventory-TMS	15.14 (2.03)	12.86 (2.65)	11.86 (2.63)	9.17 (3.86)	5.83 (3.10)	8.17 (2.87)	7.17 (3.17)	5.83 (3.10)	8.17 (2.87)	5.83 (3.10)	8.17 (2.87)	7.17 (3.17)	5.83 (3.10)
Multidimensional Fatigue Inventory-Sham	52.45 (3.84)	49.55 (3.84)	45.82 (3.84)	38.36 (3.84)	36.82 (3.84)	34.72 (4.94)	37.82 (4.08)	36.82 (3.84)	34.72 (4.94)	36.82 (3.84)	34.72 (4.94)	37.82 (4.08)	36.82 (3.84)
Multidimensional Fatigue Inventory-TMS	49.57 (4.14)	45.86 (4.14)	43.00 (4.14)	35.50 (3.88)	36.17 (3.88)	40.00 (3.88)	34.67 (3.88)	36.17 (3.88)	40.00 (3.88)	36.17 (3.88)	40.00 (3.88)	34.67 (3.88)	36.17 (3.88)
VAS-F-Fatigue-Sham	71.14 (6.76)	60.27 (6.76)	57.89 (6.76)	47.23 (6.76)	42.77 (6.76)	35.55 (9.34)	46.12 (7.39)	42.77 (6.76)	35.55 (9.34)	42.77 (6.76)	35.55 (9.34)	46.12 (7.39)	42.77 (6.76)
VAS-F-Fatigue-TMS	75.68 (6.44)	71.64 (6.44)	60.00 (6.44)	52.50 (6.74)	59.75 (6.74)	58.92 (6.74)	51.58 (6.74)	59.75 (6.74)	58.92 (6.74)	59.75 (6.74)	58.92 (6.74)	51.58 (6.74)	59.75 (6.74)

	Baseline	V5	V10	V15	V16	V17	V18
VAS-F-Sleep-Sham	61.30 (4.62)	53.27 (4.62)	57.80 (4.62)	42.45 (4.62)	43.82 (4.62)	38.76 (5.93)	45.05 (5.04)
VAS-F-Sleep-TMS	54.64 (7.29)	50.43 (7.29)	38.14 (7.29)	39.83 (8.62)	47.17 (8.62)	40.17 (8.62)	45.25 (8.62)
VAS-F-Pain-Sham	65.59 (5.27)	50.64 (5.27)	44.09 (5.27)	41.41 (5.27)	40.00 (5.27)	49.93 (7.22)	49.75 (5.83)
VAS-F-Pain-TMS	67.79 (5.41)	62.79 (5.41)	58.21 (5.41)	52.92 (6.19)	51.17 (6.19)	45.08 (6.19)	38.17 (6.19)
VAS-F-Overall Well Being-Sham	42.41 (5.51)	45.27 (5.22)	41.25 (6.35)	39.50 (7.18)	35.50 (5.27)	36.70 (9.38)	43.56 (8.75)
VAS-F-Overall Well Being-TMS	+64.50 (4.47)	64.11 (5.45)	51.21 (9.50)	43.17 (8.81)	40.67 (8.16)	41.58 (7.93)	37.42 (6.52)
Patient CGI-Sham	4.50 (0.18)	3.27 (0.30)	3.05 (0.30)	2.55 (0.36)	2.64 (0.44)	3.04 (0.57)	3.11 (0.29)
Patient CGI-TMS	4.71 (0.26)	3.71 (0.40)	3.43 (0.63)	2.50 (0.48)	3.17 (0.53)	3.00 (0.25)	2.33 (0.21)

TMS superior to Sham at the p<0.05 level: #

Sham Superior to TMS at the p<0.05 level: *
at the p<0.001 level: **

The values in **bold** are significantly different from baseline at the p<0.05 level.

At baseline, the TMS group had significantly higher scores than sham at the p<0.01 level: +
and at the p<0.001 level: ++

Table 3

Mean Ratings (Standard Deviations) for TMS and Sham Groups Before and After 15 Sessions.

Variable	Baseline		After 15 Sessions	
Medical Outcomes Study-Short Form-36 (SF-36)				
Physical Function-Sham	46.82	(21.01)	67.27	(18.22)
Physical Function-TMS	58.33	(24.83)	70.00	(12.65)
Role Physical-Sham	20.45	(35.03)	54.54	(35.03)
Role Physical-TMS	16.67	(25.82)	50.00	(27.39)
Bodily Pain-Sham	36.18	(14.87)	53.91	(17.19)
Bodily Pain-TMS	38.17	(11.62)	51.50	(14.29)
General Health-Sham	46.82	(22.35)	58.36	(19.35)
General Health-TMS	53.83	(16.02)	57.83	(18.55)
Vitality-Sham	29.09	(20.35)	47.73	(25.63)
Vitality-TMS	25.00	(9.49)	36.67	(16.93)
Social Function-Sham	51.27	(20.65)	72.91	(22.14)
Social Function-TMS	58.67	(20.37)	68.83	(27.17)
Role Emotional-Sham	51.55	(45.65)	75.81	(39.68)
Role Emotional-TMS	44.33	(34.54)	55.66	(45.57)
Mental Health-Sham	61.45	(23.88)	70.35	(22.28)
Mental Health-TMS	63.33	(7.34)	69.33	(12.56)
Tender Point Exam				
Number of Tender Points- Sham	16.36	(1.69)	15.82	(2.75)
Number of Tender Points- TMS	16.83	(1.94)	15.00	(5.44)
Mean Severity of Pressure-Sham	4.42	(1.61)	3.01	(1.43)
Mean Severity of Pressure-TMS	4.38	(1.40)	4.37	(2.60)
Dolorimetry				
Ascending-Low-Sham	2.64	(2.88)	1.52	(1.49)
Ascending-Low-TMS	1.45	(2.00)	2.75	(3.14)
Ascending-Medium-Sham	5.95	(2.94)	5.05	(2.92)
Ascending-Medium-TMS	4.15	(3.62)	5.90	(4.28)
Ascending-High-Sham	7.68	(2.80)	7.36	(2.58)
Ascending-High-TMS	6.00	(3.67)	8.00	(3.26)
Random-Low-Sham	1.93	(3.10)	1.73	(2.98)
Random-Low-TMS	0.28	(0.35)	1.98	(2.45)
Random-Medium-Sham	5.66	(3.85)	4.20	(3.17)
Random-Medium-TMS	3.60	(3.72)	4.93	(4.84)
Random-High-Sham	7.31	(3.25)	7.75	(2.36)
Random-High-TMS	5.03	(4.60)	8.00	(3.26)

Table 4

Random Coefficient Analysis Estimates of Predicted Means (SE) During the Open-Label Cross-Over Portion of the Study. V18, three months after the last TMS session; C5, after 5 sessions in the open-label crossover phase; C10, after 10 sessions in the open-label crossover phase; C15, after 15 sessions in the open-label crossover phase; and C16, one week after the 15th session in the open-label crossover phase.

	Baseline of Crossover		V5		V10		V15		V16	
BIRS	11.38	(1.06)	10.63	(1.14)	*8.88	(1.24)	**6.13	(1.36)	**6.63	(1.39)
BURS	9.00	(0.90)	8.63	(1.07)	7.63	(1.24)	*5.63	(1.41)	*5.88	(1.45)
PL-NRS	4.99	(0.48)	4.63	(0.54)	4.25	(0.60)	*3.25	(0.66)	*3.13	(0.68)
McGill PQ-Total	10.88	(1.08)	9.25	(0.89)	**5.75	(0.70)	**4.38	(0.51)	**4.20	(0.47)
McGill PQ- Sensory	8.73	(0.81)	7.50	(0.71)	*5.25	(0.60)	**3.63	(0.50)	**3.92	(0.48)
McGill PQ-Affective	2.15	(0.41)	1.75	(0.30)	**0.50	(0.19)	*0.75	(0.09)	**0.28	(0.07)
BPI-Severity	4.31	(0.45)	3.94	(0.53)	3.91	(0.63)	*3.06	(0.74)	*2.93	(0.76)
BPI Interference	3.25	(0.90)	3.16	(0.92)	2.73	(0.95)	*2.00	(0.98)	*1.75	(0.99)
Hamilton Depression Rating	10.50	(2.21)	8.75	(2.18)	*7.00	(2.25)	*6.50	(2.43)	6.75	(2.47)
Beck Depression Inventory	8.67	(3.16)	8.88	(3.23)	*5.75	(3.31)	*5.75	(3.38)	6.19	(3.40)
Multidimensional Fatigue Inventory	38.79	(6.34)	40.00	(6.60)	*30.75	(7.06)	31.00	(7.68)	*28.41	(7.82)
VAS-F-Fatigue	43.76	(11.2)	52.81	(10.43)	29.94	(10.39)	28.50	(11.10)	26.21	(11.32)
VAS-F-Sleep	39.34	(8.71)	38.75	(8.35)	37.31	(7.98)	29.06	(7.61)	27.91	(7.53)
VAS-F-Pain	52.36	(7.23)	48.44	(7.27)	*37.13	(7.55)	*30.50	(8.04)	*28.85	(8.16)
VAS-F-Overall Well Being	36.67	(7.89)	38.06	(7.97)	*25.44	(8.09)	25.94	(8.25)	*22.41	(8.28)
Patient Clinical Global Improvement	3.12	(0.23)	3.13	(0.28)	2.50	(0.34)	*2.13	(0.41)	*1.96	(0.42)

Significantly different from baseline at the $p < 0.05$ level *

Significantly different from baseline at the $p < 0.001$ level **

Table 5

Adverse Events Summary in Blind Phase, those receiving Sham in Blind Phase and those receiving TMS in open-label cross-over phase

	TMS (N= 8)		Sham (N= 11)		Subjects in Crossover to real TMS (N= 8)	
	N*	(%)**	N*	(%)**	N*	(%)**
Body System						
Neurologic						
pain at site of stimulation	4	50	3	27	4	50
increased muscle aches	2	25	1	9	0	0
increased fatigue	1	13	1	9	1	13
Headache	5	63	5	45	2	18
insomnia	2	25	1	9	0	0
tingling sensation in scalp during session	0	0	1	9	0	0
dizziness	1	13	1	9	0	0
confusion	0	0	1	9	0	0
tiredness after session	0	0	1	9	0	0
shakiness	1	13	0	0	0	0
anxiety	1	13	0	0	0	0
sensation of pressure on scalp	0	0	0	0	1	13
lightheadedness after session	1	13	0	0	1	13
poor concentration	1	13	0	0	1	13
"fuzzy-headed" after TMS	1	13	0	0	1	13
forgetfulness	0	0	0	0	1	13
migraine	1	13	0	0	0	0
pain in teeth during stimulation	0	0	1	9	0	0
drowsiness	0	0	1	9	0	0
feeling more "distant, detached"	0	0	1	9	0	0
"flat" affect	0	0	1	9	0	0
twitching of R eye	0	0	1	9	0	0

	TMS (N= 8)		Sham (N= 11)		Subjects in Crossover to real TMS (N= 8)		(%)**
	N*	(%)**	N*	(%)**	N*	(%)**	
Body System							
pain in L jaw	0	0	1	9	0	0	0
ENT							
sore throat	1	13	1	9	1	13	13
Coryza	1	13	0	0	0	0	0
cough	1	13	1	9	0	0	0
Sinus Headache	1	13	0	0	0	0	0
flu	2	25	0	0	0	0	0
viral infection	1	13	0	0	0	0	0
tinnitus	1	13	1	9	0	0	0
sinus infection	0	0	1	9	0	0	0
dry mouth	0	0	1	9	1	13	13
sinus congestion	0	0	1	9	1	13	13
sinus drainage	0	0	1	9	0	0	0
ear ache	0	0	0	0	1	13	13
eye pain	0	0	0	0	1	13	13
GI							
nausea	2	25	1	9	0	0	0
abdominal pain	2	25	1	9	0	0	0
diarrhea	1	13	0	0	0	0	0
Other							
sebaceous cyst on thigh	1	13	0	0	0	0	0
abscess of anal fistula	1	13	0	0	0	0	0
TMJ pain	1	13	0	0	0	0	0
heart palpitations	0	0	2	18	0	0	0
dry eyes	0	0	1	9	0	0	0
lacrimation during session	0	0	0	0	1	13	13
pain in R thumb	0	0	1	9	0	0	0
pain in R shoulder	0	0	1	5	0	0	0