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Repetitive Transcranial Magnetic Stimulation Increases the Corticospinal Inhibition and the Brain-Derived Neurotrophic Factor in Chronic Myofascial Pain Syndrome: An Explanatory Double-Blinded, Randomized, Sham-Controlled Trial

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Abstract: **Chronic myofascial pain syndrome has been related to defective descending inhibitory systems. Twenty-four females aged 19 to 65 years with chronic myofascial pain syndrome were randomized to receive 10 sessions of repetitive transcranial magnetic stimulation (rTMS) (n = 12) at 10 Hz or a sham intervention (n = 12). We tested if pain (quantitative sensory testing), descending inhibitory systems (conditioned pain modulation [quantitative sensory testing + conditioned pain modulation]), cortical excitability (TMS parameters), and the brain-derived neurotrophic factor (BDNF) would be modified. There was a significant interaction (time vs group) regarding the main outcomes of the pain scores as indexed by the visual analog scale on pain (analysis of variance, $P < .01$). Post hoc analysis showed that compared with placebo-sham, the treatment reduced daily pain scores by −30.21% (95% confidence interval = −39.23 to −21.20) and analgesic use by −44.56 (−57.46 to −31.67). Compared to sham, rTMS enhanced the corticospinal inhibitory system (41.74% reduction in quantitative sensory testing + conditioned pain modulation, $P < .05$), reduced the intracortical facilitation in 23.94% ($P = .03$), increased the motor evoked potential in 52.02% ($P = .02$), and presented 12.38 ng/mL higher serum BDNF (95% confidence interval = 2.32–22.38). No adverse events were observed. rTMS analgesic effects in chronic myofascial pain syndrome were mediated by top-down regulation mechanisms, enhancing the corticospinal inhibitory system possibly via BDNF secretion modulation.**

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Perspective: ***High-frequency rTMS analgesic effects were mediated by top-down regulation mechanisms enhancing the corticospinal inhibitory, and this effect involved an increase in BDNF secretion.***

Key words: *Myofascial pain syndrome, transcranial magnetic simulation, clinical trial, brain-derived neurotrophic factor, quantitative sensory testing.*

Myofascial pain syndrome (MPS) is considered a leading cause of musculoskeletal pain.[50] Epidemiologic studies have found that myofascial trigger points might be the source of nociceptive inputs in 30–85% of the patients with chronic pain who seek pain therapy.[49] Although the complete pathophysiology of MPS remains unknown, cumulative evidence suggests that in chronic pain there are defective inhibitory systems as indexed by motor cortex intracortical inhibition.[39,46] The intracortical inhibition is partially reverted by treatment with noninvasive brain stimulation techniques[3,31,32,38] such as repetitive transcranial magnetic stimulation (rTMS).[27]

Previous studies have shown positive therapeutic effects of rTMS in acute pain[41] and in some chronic pain conditions, such as migraine, central pain, fibromyalgia, trigeminal neuralgia, postherpetic neuralgia, and visceral pain.[29,30,33,42] However, results have been mixed. In a recent meta-analysis[43] that included 19 rTMS studies, multiple discrepancies were revealed such as size, sample characteristics, and rTMS parameters, including the site of stimulation and the number of stimulation sessions. In fact, the mechanisms of rTMS underlying its antinociception effects are not completely understood, even though cumulative evidence suggests that the initial effect of rTMS on neuronal depolarization or hyperpolarization[34] induces long-term potentiation or depression, which in turn produces lasting changes on neocortical excitability and synaptic connections[18] that secondarily modulate pain-related neural circuits.

As a neuronal modulator, the brain-derived neurotrophic factor (BDNF) appears to play a role in chronic pain and neuronal plasticity. The BDNF has shown to be an important upstream regulator of long-term potentiation in the hippocampus and neocortex during motor learning.[21] Clinical studies have found higher BDNF levels in blood and in the cerebrospinal fluid in patients with chronic pain conditions such as fibromyalgia and migraine when compared with healthy controls.[20] Additionally, the BDNF effects may be region-specific, as it is downregulated in the hippocampus but upregulated in the spinal dorsal horn in rats exposed to pain.[16] Notably, BDNF can also be regulated using therapeutic interventions. Healthy subjects receiving rTMS increase their plasma BDNF levels almost 3-fold compared to those receiving a sham intervention.[54] Additionally, depressed patients receiving multiple rTMS sessions increase their serum BDNF.[56] Thus, we hypothesize that chronic pain will behave similarly, and that rTMS may change the activity of the BDNF, which plays a role in chronic pain. Although rTMS has shown promising results, few studies have assessed simultaneously its effect on human behavior, neurophysiology, and biochemistry. Thus, besides pain, we assessed TMS-indexed cortical excitability and a neuroplasticity mediator, the BDNF, after either rTMS or a placebo-sham intervention in patients with chronic MPS.

We conducted an explanatory phase II clinical trial to understand the initial efficacy of rTMS in MPS and also the mechanisms underlying the therapeutic effects of rTMS. We tested the hypothesis that 10 sessions of rTMS in MPS as compared with placebo-sham intervention were associated with significant changes in pain score and quantitative sensory testing (QST) during cold water immersion (conditioned pain modulation [CPM]). In addition, we measured 2 biological markers of neuroplasticity: cortical excitability parameters and serum BDNF.

Methods

The methods and results sections are reported according to the CONSORT guidelines. In Fig 1, the flow chart of the study is presented.

Design Overview, Settings and Participants

All patients provided written informed consent before participating in this randomized, double-blinded, 2-group parallel clinical trial, which was approved by the research ethics committee at the Hospital de Clínicas de Porto Alegre (institutional review board 0000921) in accordance with the Declaration of Helsinki (resolution 196/96 of the National Health Council). We recruited 24 right-handed female patients aged 19 to 65 years with a diagnosis of MPS in an upper body segment for at least 3 months prior to enrollment; these patients were experiencing limitations in active and routine activities due to MPS several times a week. The last criterion was evaluated using a questionnaire that included 6 categorical questions (yes/no). These questions were asked by an independent examiner and were aimed at assessing interference with work, personal relationships, pleasure of activities, responsibilities at home, personal goals, and clear thinking (ie, problem solving, concentrating, and/or remembering) during the past 3 months. For enrollment, subjects needed a positive answer to 1 or more of these questions to ensure that chronic pain was lowering the patient's quality of life. Moreover, the diagnosis of MPS was confirmed by a second independent examiner (W.C.) with more than 10 years of clinical experience related to chronic pain. The MPS criteria were defined by regional pain, normal neurologic examination, decreased range of motion, stiffness in the target muscles, presence of trigger

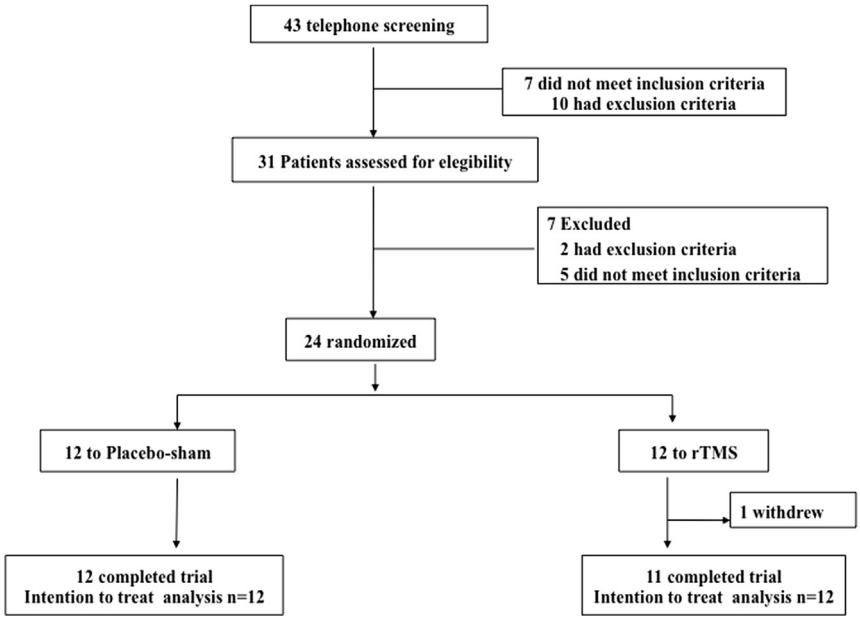

Figure 1. Flow chart showing participants' recruitment and progress through the study.

points, taut bands, tender points, palpable nodules, and pain characterized as dull, hollow, or deep that was exacerbated during stress. To distinguish neuropathic pain from ongoing nociception, the Neuropathic Pain Diagnostic Questionnaire was applied to all patients. Only those with a neuropathic pain component (score ≥ 4) were included[6] to standardize the severity of MPS.

The exclusion criteria included the following: the presence of any other pain disorder, such as rheumatoid arthritis, radiculopathy, and fibromyalgia; previous surgery on the affected areas; and frequent use of anti-inflammatory steroids (because they may interfere with TMS results). Patients with a history of neurologic or oncologic disease, ischemic heart disease, and kidney or hepatic insufficiency were also excluded. Participants were excluded from the trial if they met the following criteria: 1) any metal object or implant in the brain, skull, scalp, or neck; 2) implantable devices, including cardiac pacemakers and defibrillators; 3) any neurologic illnesses; and 4) pregnancy. Information about these criteria was obtained by questionnaires. Additionally, no patients with a history of alcohol or substance abuse in the previous 6 months were included.

Sample Size Justification

The number of patients in each study group was determined using previous clinical trials information.[11] An a priori estimate indicated that a total sample size of 22 patients divided into 2 balanced intervention groups (n = 11) was needed to detect a 1.5-cm reduction (average standard deviation 1.2) in pain intensity on the 10-cm visual analog scale (VAS) after rTMS or placebo-sham, at power and α levels of .8 and .01, respectively; such a reduction would be considered clinically relevant and comparable to other pharmacologic interventions. A sample of 24 patients (12 per group) was determined to account for potential dropouts that would decrease study power.

Randomization

A computer random number generator assigned patients to 1 of 2 groups: rTMS or placebo-sham using a block randomization strategy. Before the recruitment phase, opaque envelopes containing the protocol materials were prepared. Each opaque envelope was sealed and numbered sequentially, containing 1 intervention allocation. After the patient agreed to participate in the trial, the next envelope in the sequence was opened by the coordinator, who was not involved with the patient's intervention.

Blinding

To control for possible measurement bias and also higher placebo effect in the active treatment, the following steps were taken: all patients were naive to treatment with rTMS; participants were instructed to discuss all aspects related to their rTMS treatment only with the treating physician (rather than the research personnel); we used an inactive rTMS coil (MagPro X100; MagVenture Company, Lucernemarken, Denmark) as a sham method by placing it in the identical area as the active coil. Thus, sham patients underwent similar rTMS experience (including rTMS sound) as those receiving active stimulation. Two independent evaluators who were blinded to the group assignments (W.C. and another) were trained to apply the pain scales and conduct psychophysical and psychological tests. During the entire protocol timeline, 2 investigators who were not involved in the patient evaluations were responsible for the blinding and randomization procedures. Individuals other than those responsible for administering interventions were kept unaware of the allocated intervention.

Interventions

Transcranial Magnetic Stimulation and Study Procedures

Motor cortex excitability was assessed using TMS with a MagPro X100 and a figure-8 coil. The hot spot was marked on the scalp with a soft-tip pen. The subjects were comfortably seated in a reclining chair with armrests for relaxing arms and hand positioning. The coil was placed over the left motor cortex (M1), held tangentially to the scalp with the handle pointing back and away from the midline at 45 degrees. All participants underwent rTMS delivered in trains consisting of 16 series of 10-second pulses with a high frequency of 10 Hz of biphasic magnetic stimulator (MagPro X100) and an interval of 26 seconds between each train, giving a total of 1,600 pulses per session. The stimulation intensity used was 80% of resting motor threshold (RMT). During placebo (sham stimulation), an inactive rTMS coil (MagPro X100) was used as a sham coil and was placed in the identical area as the active coil. The patient recorded identical experiences (including sound effects and somatic sensations caused by contraction of the muscles of the scalp) as during active stimulation.

Supplementary Analgesic Use

All of the patients were permitted to use supplementary analgesic medication (acetaminophen, ibuprofen, codeine, or tramadol) to relieve their pain if necessary. Patients were allowed to take 750 mg of acetaminophen up to 4 times per day and 200 mg of ibuprofen at maximum 4 times per day as a rescue analgesic. If these drugs were ineffective, patients could use Dorflex (Sanofi Aventis, São Paulo, Brazil; 35 mg orphenadrine citrate combined with 300 mg dipyrone and 50 mg caffeine). If their pain persisted, patients were permitted to use 60 mg of codeine up to 4 times per day or tramadol 3 times per day. The patients were asked to record their analgesic intake during the treatment period in their pain diaries, and these diaries were reviewed during each intervention session. The total analgesic dose administered during treatment was considered for the analysis.

Instruments and Assessments

All of the psychological tests used in this study had been validated for the Brazilian population.[8,23,25,47] Two independent medical examiners (W.C. and another) who were blinded to the group assignments were trained to administer the pain scales and to conduct the psychological tests. The patients' baseline depressive symptoms were assessed using the Beck Depression Inventory,[55] and sleep quality was assessed using the Pittsburgh Sleep Quality Index.[7] Anxiety was measured using the refined version of the Rash analysis of the State-Trait Anxiety Inventory.[25] Pain-related catastrophic thinking was assessed using the Brazilian Portuguese Catastrophizing Scale.[47] Demographic data and medical comorbidities were assessed using a standardized questionnaire; patients were asked about any changes that occurred during treatment, such as changes in mood, sleepiness, dizziness, headaches, or allergic reactions.

Outcomes

The primary outcomes were pain as assessed by the pain score diaries (worst pain in the last 24 hours) and the level of serum BDNF. Secondary outcomes were the amount of analgesics used weekly throughout the treatment period, the modulatory effect of a heterotopic stimulus on the numerical pain scale (NPS), the cortical excitability parameters (motor evoked potential [MEP], intracortical facilitation [ICF], cortical silent period [CSP], and short intracortical inhibition [SICI]), sleep quality, and the score on the Brazilian Profile of Chronic Pain: Screen (B-PCP:S). These outcomes are described in more detail below.

1. Pain intensity was measured using a 10-cm VAS. The VAS scores ranged from 0 (no pain) to 10 (worst possible pain). The time of the worst pain during the previous 24 hours was recorded daily in the patients' diaries. They were asked to answer the following question using the pain VAS: "How intense was your worst pain during the last 24 hours?" To improve patient compliance, an evaluator checked their pain records daily.
2. The B-PCP:S[8] was used for quick identification of an individual's multidimensional pain experience. The B-PCP:S comprised a severity scale (4 items; possible score ranging 0–32), an interference scale (6 items; possible score ranging 0–36), and an emotional burden scale (5 items; possible score ranging 0–25). The importance of these 3 dimensions (severity, interference, and emotional burden) has recently been underscored by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).[37] The B-PCP:S was applied at baseline, at the end of the intervention period, and at 2, 4, 6, 8, and 12 weeks after the end of the intervention.
3. Diary entries recording analgesic intake (ie, acetaminophen, nonsteroidal anti-inflammatory drugs, or opioids) were reviewed during each intervention session. The total analgesic dose administered during treatment was considered for analysis.
4. QST was used to assess heat pain thresholds using the method of limits with a computer-controlled Peltier-based thermode (30 × 30 mm)[45] that was attached to the skin on the ventral aspect of the midforearm. The baseline temperature was set at 32°C and was increased at a rate of 1°C/s to a maximum of 52°C. Each patient had reported when a warm sensation was initially felt and when it became painful, with the latter representing the heat pain threshold. Three assessments were performed with an interstimulus interval of 40 seconds.[45] Each subject's heat pain threshold was defined as the mean painful temperature of the 3 assessments. The position of the thermode was altered slightly between trials (although it remained on the left ventral forearm itself) to avoid

either sensitization or response suppression of the cutaneous heat nociceptors. The QST during cold water immersion (QST + CPM) was assessed by raising the temperature to the point at which subjects felt 6/10 pain on the NPS ranging from 0 (no pain) to 10 (the worst pain imaginable). By measuring the QST during cold water immersion, we evaluated the degree to which pain perception is modulated following the presentation of an initial heterotopic noxious stimulus (CPM). Subjects immersed their nondominant hands into cold water (0°–1°C) for 1 minute. The QST procedure was administered after 30 seconds of cold water immersion. During this test, subjects were asked to rate the pain of the stimulated hand using the same NPS. The temperature was held constant during the experiment for each subject. Differences (presented in percentage) between the average pain rating before and after cold water immersion was defined as the CPM. To control for individual variation with regard to baseline values, the proportion of difference from baseline was used rather than the difference in raw values. This test was applied after we measured the cortical excitability parameters.

5. Sleep quality during the study period was assessed daily using the 10-cm visual analog sleep quality scale (VASQS). The VASQS scores ranged from the worst possible (0) to the best possible (10 cm) sleep, and using the VASQS, the patients answered the following question in their sleep diaries: "How well did you sleep last night compared with your habitual sleep?"
6. Laboratory outcomes included serum levels of BDNF. Blood samples were collected at 2 time points: at baseline and at the end of the intervention period. The blood samples were centrifuged in plastic tubes for 10 minutes at 4,500 × g at 4°C, and serum was stored at −80°C for hormone assay. Serum BDNF was determined with an enzyme-linked immunosorbent assay using a ChemiKine BDNF Sandwich ELISA Kit, CYT306 (Chemicon/Millipore, Billerica, MA). The lower detection limit of the kit is 7.8 pg/mL for BDNF.
7. Cortical excitability parameters were registered through surface electromyography recordings and were gathered at the contralateral right first dorsal interosseous muscles using Ag/AgCl electrodes. First, the RMT was determined by obtaining 5 MEPs with a peak-to-peak amplitude of 50 μV out of 10 consecutive trials. Next, 10 MEPs were recorded with an intensity of 130% of the individual RMT. Moreover, the CSPs were assessed during muscle activity measured by a dynamometer to be approximately 20% of maximal force. Accordingly, 10 CSPs were recorded using an intensity of 130% of the RMT. The SICI using an interstimulus interval of 2 ms was also assessed. The first conditioning stimulus was set at 80% of the RMT, whereas the second test stimulus was set at 100% of the individual MEP intensity. The ICF was assessed with an interstimulus interval of 12 ms. Paired-pulse TMS was conducted in a randomized order for a total of 30 trials (10 each for SICI, ICF, and control stimuli). The RMT was calculated as the lowest stimulus intensity that was able to evoke an MEP of at least 50 mV in 5 of 10 consecutive trials. Off-line analyses included collection of the amplitudes of all of the MEPs, SICI, and ICF as well as the duration of the CSPs. The corresponding units for these parameters included MEP in millivolts, SICI, and ICF in their ratio to the MEP, and the CSP in milliseconds.[44]

Statistical Analysis

We used t-tests for independent samples and chi-squared or Fisher's exact tests to compare the continuous and categorical variables between intervention groups, respectively. To analyze the effect of the interventions on the outcomes (VAS for pain scores, analgesic consumption, and B-PCP:S scores), we conducted a group analysis by running a mixed analysis of variance model in which the independent variables were time, experimental group (rTMS or placebo-sham), the interaction between time and experimental group, and the subject identification as a within-subject factor. If appropriate, post hoc analyses included Bonferroni's adjustment for multiple comparisons. Differences between the groups at each time point and effects on each experimental group were tested.

We also calculated adjusted mean differences, which were defined as the relative changes in the rTMS group compared to those of the placebo-sham group. This measurement was used to describe the rTMS treatment efficacy and was calculated as the mean difference divided by the mean placebo group outcome, which was further expressed as a percentage. The 95% confidence intervals and associated *P* values were also calculated. The standardized mean difference was computed in terms of the ratio between the mean change and the placebo-sham standard deviation. The standardized mean difference (also known as effect size) was interpreted as follows: small if lower than .20; moderate if between .50 and .60; and large if larger than .80.[8] Intention-to-treat analysis was performed, with the last observation carried forward.

Stepwise multiple linear regression analysis was conducted, with the NPS during the CPM as the dependent variable. The independent variables included in this model were the intervention group and the relative changes in the mean of the ICF and the MEP (ie, relative change from baseline to the end of the intervention). The ICF was excluded after identifying collinearity with the MEP. The data were analyzed using SPSS version 18.0 (SPSS, Chicago, IL).

Results

Patient Characteristics

The clinical and demographic characteristics of the patients are shown in Table 1. Twelve patients were allocated to the placebo-sham group, and 12 were allocated

Table 1. Characteristics of the Study Sample (N = 24)

	Placebo-sham (n = 12)	*rTMS (n = 12)*	P *Value**
Age (y)	44.83 (14.09)	45.83 (9.63)	.80
Education (y)	13.33 (3.22)	11.25 (5.17)	.44
Smoking, n (%)	1 (5.0)	5 (25.0)	.34
Clinical comorbidity, n (%)	7 (35.0)	6 (30.0)	.16
Hypertension	0 (.0)	3 (15.0)	
Hypothyroidism	2 (10.0)	1 (5.0)	
Asthma	2 (10.0)	0 (.0)	
Other	3 (15.0)	2 (10.0)	
Global pain on VAS	5.89 (2.45)	6.67 (2.06)	.49
Pittsburgh Sleep Questionnaire	15.6 (7.6)	19.0 (5.9)	.15
Beck Depression Inventory	12.05 (8.21)	15.83 (9.15)	
State anxiety on STAI	26.83 (8.47)	30.42 (8.31)	.66
Trait anxiety on STAI	24.77 (6.88)	23.58 (6.88)	.36
Brazilian Portuguese Catastrophizing Scale	26.67 (15.83)	32.83 (10.08)	.20
B-PCP:S	55.08 (15.09)	56.50 (17.0)	.65
Pain intensity reported on B-PCP:S	24.75 (3.05)	24.83 (3.65)	.89
Interference with activities reported on B-PCP:S	18.25 (8.03)	19.17 (10.03)	.63
Emotional burden due pain reported on B-PCP:S	12.08 (7.10)	12.50 (7.20)	.73

Abbreviation: STAI, State-Trait Anxiety Inventory.
NOTE. Values are given as the mean (standard deviation) unless indicated otherwise.

to the rTMS group. Twenty-three patients completed the study; 1 patient in the rTMS group withdrew because of treatment inefficacy. The baseline characteristics were similar across the rTMS and placebo-sham groups (all *P* values >.05) (Table 1). We did not observe serious or moderate side effects from the interventions.

Primary Outcomes: Efficacy With Regard to Pain Scores on the VAS and BDNF

Pain Scores on the VAS

After treatment, the rTMS group had significantly lower pain scores on the VAS ($P < .001$) than the placebo-sham group (Table 2), and the interaction between time and intervention group was significant ($P = .04$) (Fig 2). Compared to the placebo-sham group, the rTMS group demonstrated a relative mean pain reduction of 30.21% (effect size of .69) at 12 weeks after conclusion of the interventions (Table 2).

Biochemical Modulator Changes: Assessment of Serum BDNF Levels

At the end of treatment, the rTMS group had significantly higher serum BDNF ($P < .01$) (Fig 3). One important issue is whether the BDNF level change is secondary to pain improvement or whether it is a primary effect of the intervention. To address this issue, we conducted an additional regression model in which we controlled BDNF changes for cumulative pain scores during the treatment period. The adjusted mean BDNF level for the placebo-sham group was 25.68 ± 10.69 ng/mL versus 38.07 ± 21.39 ng/mL for the rTMS group, with a mean difference of −12.38 (95% confidence interval = −22.38 to −2.32, $P < .01$). This model revealed that a higher pain score on the VAS was correlated negatively with serum BDNF level ($R^2 = .89$, $\beta = -.15$, SE = .008, 95% confidence interval = −.17 to −.13). This finding suggests that the variability in the BDNF level is dependent on the effect of the treatment and the pain level.

Secondary Outcomes

B-PCP:S Score

The rTMS group had significantly higher improvement in the mean B-PCP:S score ($P < .03$; Table 2). The interaction between time and intervention group was not significant ($P = .096$).

Use of Analgesics

The results for the use of analgesics were in agreement with the findings for pain outcomes. There was a significant interaction between time and intervention group ($P < .02$). There was a significant reduction in the number of analgesic doses among patients receiving rTMS ($P < .003$; Table 2). There were 45% less analgesic doses in the group receiving rTMS when comparing to those receiving placebo-sham.

Effects on CPM by Heterotopic Stimulus

The rTMS group exhibited a 41.74% reduction in the pain scores on the NPS during the evoked pain by QST versus QST + CPM (Table 2). These findings suggest that the rTMS intervention also induced an effect on the top-down inhibitory mechanisms.

One important issue is whether the evoked pain by QST versus QST + CPM assessed by the NPS is associated with changes in corticospinal excitability indexed by the MEP changes or the ICF reduction. To address this important issue, we conducted a regression model in which we controlled the change in NPS score for both parameters, MEP and ICF (Table 3). Only the variable MEP was retained in the model because it presented collinearity with the ICF. This analysis showed that the increase of 1% in the mean NPS score was associated with a decrease in MEP of 2.78% or vice versa.

Neurophysiological Changes: Assessment of TMS-Indexed Cortical Excitability Parameters

Compared to the group receiving placebo-sham, the rTMS increased the MEP by 52.02% (Table 2) ($P = .02$) and reduced the ICF by 23.94% ($P = .03$). However, the rTMS did not induce significant changes in SICI and CSP (Table 2).

Assessment of Sleep Quality

There was no interaction between time and intervention group for the previous night's sleep quality compared with the habitual sleep quality based on the VASQS scores ($P = .54$). However, in exploratory direct

Table 2. Treatment Effect on Pain, Sleep Quality, Cortical Excitability Parameters, and Descendent Modulator System Between Groups (N = 24)

Treatment	Mean (SD) Before (B) Treatment	Mean (SD) After (A) Treatment	Percentage of Mean Change (B to A)*	Mean Difference (95% CI) of Percentage Change (B to A) Placebo-sham vs rTMS	Effect Size	P
Primary outcomes						
Effect of treatment on pain outcomes during 12 wk of follow-up						
Pain reported on VAS†						
Placebo-sham (n = 12)	6.83 (2.45)	5.29 (2.78)	−18.13 (45.40)			
rTMS (n = 12)	6.94 (1.7)	3.57 (2.82)	−48.35 (43.64)	−30.21 (−39.23 to −21.20)	.69	.0001
Secondary outcomes						
B-PCP:S score and analgesic doses (Treatment effect on pain outcomes during 12 wk of follow-up)†						
B-PCP:S						
Placebo-sham (n = 12)	57.47 (14.63)	45.66 (19.64)	−20.30 (29.06)			
rTMS (n = 12)	62.26 (17.51)	40.60 (25.76)	−38.66 (33.75)	−18.37 (−28.39 to −8.35)	.63	.0001
Analgesic doses (daily mean)						
Placebo-sham (n = 12)	.90 (.78)	1.05 (.95)	−31.77 (69.01)			
rTMS (n = 12)	1.38 (1.04)	.40 (.74)	−76.33 (40.18)	−44.56 (−57.46 to −31.67)	1.1	.0001
Effect of treatment on CPM by heterotopic stimulus						
Scores on NPS related to CPM stimulus						
Before treatment (QST vs QST + CPM)‡						
Placebo-sham (n = 12)	5.71 (1.38)	4.13 (1.15)	−18.66 (26.77)			
rTMS (n = 12)	5.48 (1.94)	4.56 (1.53)	−17.05 (33.4)	−1.64 (24.99 to −27.92)	—	.88
After treatment (QST vs QST + CPM)‡						
Placebo-sham (n = 12)	5.51 (2.21)	4.96 (1.96)	−9.98 (32.10)			
rTMS (n = 12)	6.17 (1.64)	4.21 (1.21)	−31.76 (13.68)	−41.74 (−45.89 to −3.78)	.77	.02
Cortical excitability parameters						
MEP‡						
Placebo-sham (n = 12)	1.79 (.46)	1.73 (.51)	−3.13 (48.73)			
rTMS (n = 12)	1.60 (.43)	2.12 (.52)	55.84 (35.97)	52.02 (19.70 to 84.33)	1.07	.004
ICF‡						
Placebo-sham (n = 12)	1.07 (.18)	1.08 (.26)	6.80 (43.34)			
rTMS (n = 12)	1.50 (.67)	.97 (.23)	−30.72 (13.67)	−23.92 (−66.31 to −8.75)	.86	.03
SICI‡						
Placebo-sham (n = 12)	.33 (.13)	.30 (.17)	−3.13 (48.73)			
rTMS (n = 12)	.32 (.18)	.26 (.08)	−11.94 (26.40)	−8.81 (−12.66 to −29.56)	—	.6
CSP‡						
Placebo-sham (n = 12)	70.06 (17.75)	68.69 (13.63)	−1.32 (−1.54)			
rTMS (n = 12)	60.06 (16.27)	65.43 (18.21)	10.52 (23.95)	−8.69 (−29.77 to −12.16)	—	.39
Sleep quality (Treatment effect during 12 wk of follow-up)†						
How well did you sleep last night? (scored on the VASQS)						
Placebo-sham (n = 12)	5.00 (1.68)	5.98 (2.05)	5.44 (49.61)			
rTMS (n = 12)	5.14 (1.46)	7.20 (2.43)	30.33 (42.81)	−24.89 (−38.79 to −7.69)	—	.01

Abbreviations: SD, standard deviation; CI, confidence interval.
NOTE. Effect size (mean difference [rTMS vs placebo-sham] and SD on placebo-sham) 12 weeks after the treatment was concluded.
*Mean difference between treatment groups (rTMS vs placebo-sham) in the change before (B) to after (A).
†Mixed analysis of variance model. Mean difference groups.
‡Compared using Wilcoxon-Mann-Whitney test.

comparisons, we observed that patients in the rTMS group reported a significantly better sleep quality ($P < .01$) (Table 2). rTMS intervention resulted in an improvement of 24% in the VASQS scores for the previous night's sleep quality compared with habitual sleep.

Discussion

This study demonstrated that rTMS was superior to placebo-sham and improved the clinical, neurophysiological, and biochemical outcomes in patients with chronic MPS. The effect size of the pain reduction associated with the rTMS was significant, of probable clinical relevance, and was accompanied by improvements in disability and sleep quality, reductions of ICF, enhancement of the corticospinal inhibitory system, and increments in BDNF secretion. These findings suggest that the rTMS has a top-down effect on pain pathways and that its effect is associated with neuroplastic changes that may enhance inhibitory systems.

These findings of this present study are consistent with those of previous randomized clinical trials in which rTMS performed substantially better than placebo in treating fibromyalgia,[48,53] neuropathic pain,[13] and acute postoperative pain.[5] However, according to a recent meta-analysis, there is no agreement among studies on the effect of rTMS on pain, and the issue of potential

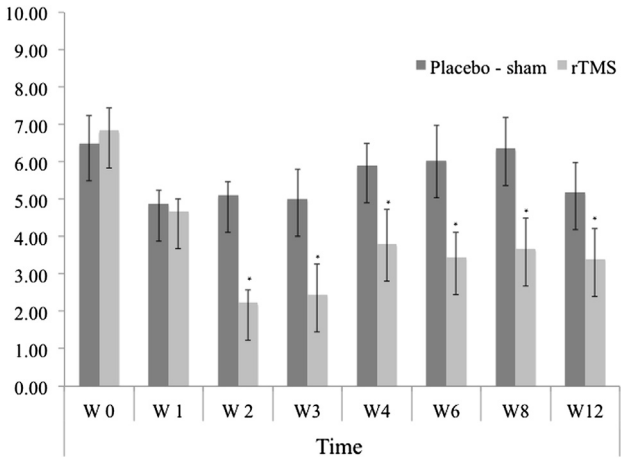

Figure 2. Weekly mean pain levels (as assessed by VAS) from baseline week 0 to week 12 in the 2 experimental groups for the following question: "Considering your chronic pain that motivated the treatment—how intense was your worst pain during the last 24 hours?" Error bars indicate standard error of the mean (SEM). Asterisks positioned above the bars indicate significant differences (*$P < .01$) at those time points between the placebo-sham and the rTMS groups. All comparisons were performed by using a mixed analysis of variance model, followed by Bonferroni's correction for post hoc multiple comparisons.

bias related to blinding also remains unresolved across studies.[43] In fact, our blinding method also may not be considered optimal. Future studies as well need to explore the use of other sham methods, for instance, those used in depression trials[2,15] that mimic the scalp sensation during sham procedures so as to ensure that patients remain blinded. Thus, although this technique has this intrinsic limitation in its assessment, the analgesic effects of rTMS over a long period of time support the notion that it induces an effect with some clinical impact.

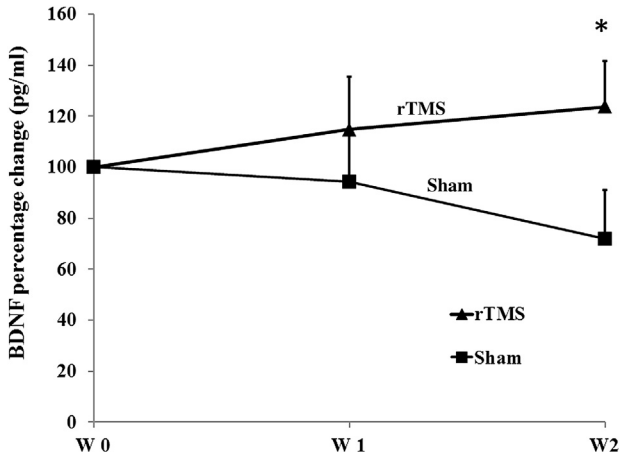

Figure 3. Mean serum BDNF at baseline week 0 and week 2 in the 2 experimental groups. Error bars indicate standard error of the mean (SEM). Asterisks positioned above the symbols indicate significant differences (*$P < .05$) at those time points between the placebo-sham and rTMS groups. All comparisons were performed by using a mixed analysis of variance model, followed by Bonferroni's correction for post hoc multiple comparisons.

Table 3. Multivariate Linear Regression of the Pain Reported on the NPS* Versus MEP† and Group (N = 24)

Parameter	β	T	P Value (95% CI)
Dependent variable: Pain reported on NPS*			
MEP†	−2.78	−2.65	.01 (−12.87 to − .026)
Placebo-sham vs rTMS	−1.40	−2.22	.03 (−2.71 to −.08)
Interaction			
MEP vs rTMS	1.50	1.67	.11 (−.38 to 3.39)
MEP vs placebo-sham	0		

Abbreviation: CI, confidence interval.
NOTE. Linear regression model: adjusted $R^2 = .49$.
*NPS scores are expressed as the percentage of differences in mean before and after cold water immersion.
†MEP values are expressed as percentage of differences in mean MEP before and after treatment.

Our findings also demonstrated that this improvement in pain is related with an increase in serum BDNF. However, we cannot exclude that the changes in BDNF have been an effect secondary to improvement in pain. The increase in serum BDNF in the rTMS group is consistent with the evidence provided by other studies of depressed patients who underwent multiple rTMS treatment sessions and exhibited increased serum BDNF.[56] This finding supports the notion that BDNF levels may constitute a marker of neuroplasticity that underlies the therapeutic effect of rTMS. The finding also suggests that the serum BDNF is a surrogate marker that may be useful to monitor the therapeutic effects of rTMS.

Although the mechanisms underlying motor cortex rTMS-induced analgesia remain unclear, they may be similar to those involved in the analgesia after chronic motor cortex stimulation through surgically implanted epidural electrodes to treat refractory neuropathic pain.[1] Furthermore, neuroimaging studies have demonstrated that the rTMS effect is not confined to the motor area but instead involves the activation of a set of cortical regions that mediate pain processing and modulation, such as the cingulate, insular, orbitofrontal, and prefrontal cortices as well as the thalamus and striatum.[4,52] In addition, the rTMS effect on CPM demonstrated in this study (Table 2) revealed that the rTMS-induced analgesia involves the activation of pain-modulating systems that are organized in the diencephalon and/or descend from the brainstem to the spinal cord. This finding is consistent with recent evidence that the rTMS effects are mediated by opioid,[12] gamma-aminobutyric acid (GABA),[14] and glutamate systems.[10]

An interesting finding is that the rTMS effect on the corticospinal system is related to increased MEP amplitude and reduced ICF (Table 2). Moreover, the adjusted analysis revealed that the improvement in the descendent modulatory system can be partially explained by the increase in the MEP (Table 3). This result suggests that the rTMS reduced the excitability of the nociceptive pathways (as indexed by the ICF) and enhanced the activity of descending tracts, whose motor portion is assessed by the MEP. Thus, the dynamic state of cortical

hyperexcitability and decreased spinal inhibition found in chronic MPS may be explained by disturbances in both GABAergic and glutamatergic intracortical networks (represented using cortical excitability parameters) that were successfully modulated to favor descending inhibition (possibly GABAergic systems) using rTMS. Although the ICF represents a complex phenomenon that reflects increased activity within glutamatergic circuits, the increases in ICF may also result from a loss of $GABA_A$-mediated modulation.[14,19] The MEP amplitude is an indicator of M1 corticospinal excitability: Larger amplitudes indicate higher excitability of the motor cortex, which may modulate intracortical excitability as well as the transmission efficiency of corticospinal neurons resulting in lower facilitation. Even though the mechanisms underlying these findings are unclear, this is consistent with previous studies in humans[34,44] as well as in animal models.[22] Hence, these findings suggest that the modulatory effects produced by rTMS were not limited to the targeted cortical area but also occur at distant interconnected sites including spinal tracts.

We found that variability in BDNF was correlated negatively with the pain score on the VAS, suggesting that the effect on cortical excitability induced by rTMS might be influenced by the BDNF or vice versa. This is in agreement with previous studies that demonstrated that the increase in inhibitory activity and/or the decrease in excitatory synaptic activity in the cortex is related to BDNF. Additionally, previous studies demonstrated that the susceptibility to rTMS-induced plasticity is significantly influenced by the BDNF.[9] However, it has been shown that BDNF polymorphisms have a substantial influence on neuronal plasticity; for example, subjects with the BDNF [valine (Val)/methionine (Met)] polymorphism exhibit less motor map reorganization and reduced changes in M1 excitability following training on several motor tasks.[26] Neuroimaging techniques also support reduced short-term plasticity in BDNF Val/Met subjects, with a greater reduction in brain activation volume in the Met allele carriers after index finger training.[36] Accordingly, another study comparing monozygotic with dizygotic twins demonstrated that externally induced plasticity is to a large extent (68%) genetically dependent.[40] Thus, further studies could examine the relationship between BDNF polymorphisms and the effect of rTMS on chronic pain.

Therefore, the rTMS not only reduced pain but also improved the restorative effect of sleep (Table 2). According to previous studies, the slow wave activity observed in electroencephalography is linked to the induction of cortical plastic changes.[24,35] Similar changes have been evoked with rTMS, which also enhanced the slow wave activity of non–rapid eye movement sleep during stages 2, 3, and 4. In fact, rTMS cannot directly induce sleep, but it can exploit the underlying disability of sleep, regularly triggering slow oscillations in the background of a seemingly stable electroencephalograph.[35] Overall, these findings suggest that rTMS is a viable, nonpharmacologic means to increase sleep efficiency; however, further studies are needed before definitive conclusions can be drawn. Thus, the effects of rTMS were clearly not limited to the sensory component of pain but reflected instead a more global improvement in the chronic pain state of the patients.

The strengths of the study include the comparison between rTMS treatment and a placebo-sham in a design with blinded evaluators, as well as the use of multiple efficacy and safety measures based on experiences from previous trials. Despite the knowledge of a substantial placebo effect, there remains a scarcity of placebo-controlled studies of rTMS for treatment of MPS with a follow-up according to the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.[17] This study therefore represents an important contribution to evidence-based therapeutics. We conducted this trial according to the CONSORT guidelines, and given that we used the Delphi List (a list of criteria for the quality assessment of randomized controlled trials), our trial can be considered to be of strong quality because our study scores positively on all 8 items in this scale.[51] Although the homogeneity of this study population is methodologically advantageous, the issue of external validity arises. Thus, additional research with a larger number of patients is needed to more widely assess the potential benefits of rTMS in various clinical settings; future studies are required before definitive conclusions regarding rTMS and pain on chronic MPS treatment can be drawn. Some issues concerning the design of our study must be addressed. First, although several strategies were used to protect patients and the team of evaluators from unblinding, formal assessment for awareness of the allocation (either active or placebo) was not performed. Hence, the success of blinding is uncertain. The fact that we could have biased the outcome measures is a limitation in this study. However, we used several strategies to reduce the chances of this possible bias occurring, and our objective surrogates that were less prone to bias (eg, critical excitability parameters, analgesic requirements) were consistent with pain scores. Therefore, hypothetical unblinding from the physician that applied the intervention and from evaluators is unlikely to have influenced our conclusions. Second, although we based our interstimulus interval for SICI and ICF according to the study by Kujirai,[28] it is possible that our other parameters may be better suited. Future studies should vary the interstimulus interval between 1 and 5 ms for SICI and 10 to 15 ms for ICF.

In conclusion, in this 12-week, randomized, blinded, placebo-controlled study, 10 sessions of high-frequency rTMS were associated with significant improvements in chronic MPS and other efficacy measures. rTMS reduced pain scores, lowered analgesic use, and improved sleep quality. Our results also suggested that the rTMS analgesic effects in chronic MPS were mediated by top-down regulation mechanisms enhancing the corticospinal inhibitory and that this effect involved an increase in BDNF secretion.

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