

The Role of Central Sensitization in Responsiveness to Brain Stimulation for Patients with Nonspecific Chronic Low Back Pain – An Exploratory Study

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Purpose: This exploratory study aimed to examine (1) the effects of a single session of repetitive transcranial magnetic stimulation (rTMS) on pain thresholds in patients with high vs. low central sensitization (CS) levels, and (2) whether individuals with high vs. low CS levels exhibit different cortical excitability responses to rTMS compared with age- and sex-matched asymptomatic controls.

Patients and Methods: Twenty participants who had low back pain (LBP) for longer than 6 months were dichotomized into the high CS group (n = 10) and the low CS group (n = 10) using a Central Sensitization Inventory cutoff score of 33.5. In addition, 16 age- and sex-matched asymptomatic controls (8 for each CS group) were enrolled. Outcome measures, including pressure pain threshold (PPT), thermal pain threshold, and motor evoked potential (MEP) were collected before and after a single session of rTMS (10 Hz, 10-second pulse trains with a 50-second inter-train interval for 20 minutes). Non-parametric statistics were performed for within-group and between-group comparisons with $p < 0.05$ for significance.

Results: Only the high CS group had significantly improved PPTs after rTMS ($p = 0.037$), with a moderate effect size. The low CS group and both matched asymptomatic control groups had an increase of MEPs after rTMS, whereas the high CS group had a decrease of MEPs after rTMS, although none of these MEP changes were statistically significant.

Conclusion: This study identifies a patient population that may benefit from rTMS for reduction of pressure sensitivity. The decreased sensitivity to pressure in participants with high levels of CS corresponded to a decrease of cortical excitability after rTMS, which was in contrast with the rTMS effects observed in participants with low levels of CS and asymptomatic controls.

Plain Language Summary: Central sensitization is a phenomenon that may be an underlying mechanism contributing to chronic pain in some patients. This article explores whether a single session of non-invasive brain stimulation would affect pain sensitivity and brain activity in patients who have different levels of central sensitization. We examined 20 participants who had LBP for longer than 6 months and divided them into two groups, a high CS group and a low CS group, based on their scores on the Central Sensitization Inventory questionnaire. In addition, we enrolled 16 age- and sex-matched asymptomatic controls (8 for each CS group) for the study. We collected pressure pain threshold (PPT), thermal pain threshold and motor evoked potential (MEP) from each participant before and after a single session of non-invasive brain stimulation. The results indicate that non-invasive brain stimulation may reduce sensitivity to pressure in patients with high levels of central sensitization. In addition, patients with high and low levels of central sensitization appeared to respond differently to non-invasive brain stimulation.

Keywords: transcranial magnetic stimulation, pressure pain threshold, thermal pain threshold, hypersensitivity, lumbar spine

Introduction

Central sensitization (CS) is an increased sensitivity of cortical and spinal neurons to sensory stimuli resulting from a maladaptive reorganization of the complex network of the brain.^{1–3} CS has been hypothesized to be an underlying central mechanism for the development of chronic pain, which exists regardless of the presence of peripheral inflammation.^{4,5} Specifically, patients with chronic low back pain (CLBP) have been reported to exhibit more inhibited corticospinal excitability and different primary motor cortex (M1) maps, in which the M1 representation of the back muscles was located more anteriorly compared to those without CLBP.^{6–8} Therefore, non-invasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS), could be an effective neuromodulation intervention to alter cortical excitability, thus reducing chronic pain.^{9,10}

TMS is a non-invasive brain stimulation produced by a brief magnetic field which is generated when electric current goes through a magnetic coil.⁹ When TMS is delivered in a repetitive form, known as rTMS, it can up- or down-regulate corticospinal excitability.¹¹ The M1 is the most frequent stimulation target in chronic pain studies using rTMS.¹² In addition, rTMS to the M1 has shown positive effects in pain reduction.^{12–15} Specifically, high frequency (≥ 5 Hz) rTMS targeting the M1 contralateral to the painful side produces the greatest analgesic effect for chronic neuropathic pain compared to rTMS targeting other locations.^{16,17} Various mechanisms have been proposed to explain the effects of rTMS on the M1 area for pain reduction, including the influence on the cingulate cortex and insula via intracortical projections, increased activity on the opioid system, increased dopamine release in the corticostriatal pathways and other glutamatergic pathways, as well as enhanced activity of the descending pain modulation pathways.^{12,18,19} An increased cortical excitability, as assessed by motor evoked potential (MEPs), suggests an enhanced descending pain modulation activity, leading to pain reduction.¹¹ Furthermore, some investigations on neuropathic pain have revealed that the effects of rTMS to the M1 depend on the degree of cortical excitability present before the stimulation and correlate with the restoration of the defective intracortical inhibition by rTMS.^{20,21} However, such observations have not been reported for chronic non-neuropathic musculoskeletal pain.

Conflicting results have been reported regarding the analgesic effect of high frequency M1 rTMS on chronic musculoskeletal pain. Two randomized clinical trials (RCTs) showed significant pain reduction after multiple sessions of 10 Hz rTMS over the left M1 in patients with chronic myofascial pain syndrome,^{11,22,23} but one RCT found no analgesic effect from similar rTMS dosages on patients with fibromyalgia.²⁴ Nevertheless, recent systematic reviews have indicated that rTMS targeting M1 shows a small non-meaningful effect on chronic pain reduction^{14,17,25,26} or CLBP reduction,²⁷ with the limited effectiveness attributed in part to the heterogeneity of study participants with a diagnosis of non-specific chronic pain syndrome. Patients with symptoms related to CS, such as fibromyalgia, have been shown to have greater alteration of M1 excitability than those with localized pain, such as knee osteoarthritis,²⁸ or those with intact endogenous inhibitory control.²⁹ In addition, it has been hypothesized that the presence of abnormal cortical excitability in patients may affect rTMS outcomes.^{18,20} As the rTMS intervention can either inhibit or facilitate cortical excitability, patients with high CS (ie, increased levels of cortical excitability) and low CS may respond to rTMS differently.

As the severity of CS cannot be measured directly in vivo in humans, the Central Sensitization Inventory (CSI) score has been used clinically as an index for the level of CS.^{30–32} In addition, a cut-off score of 40/100 has been established to distinguish two cohorts with and without CS-related syndromes in a general chronic pain population.³³ However, lower cut-off scores of 17/100 and 28/100 also were reported for CLBP and knee OA, respectively.³⁴ Similarly, we also have previously established a cut-off score of 33.5/100 on the CSI for categorizing patients into high and low CS groups, specifically for a patient population with chronic musculoskeletal pain.³⁵ In addition to the CSI, quantitative sensory tests (QSTs), such as mechanical and thermal pain thresholds, have been used to determine the extent of CS.^{4,35} To date, most of the outcome studies and systematic reviews for rTMS examined self-reported pain intensity and did not include objective assessments of CS using either the CSI or QSTs which were linked to the presence or severity of CS. As the degree of CS could mediate the effectiveness of rTMS, QSTs and the CSI may be better tools to objectively determine rTMS responsiveness than previously used self-reported measures such as pain intensity or pain location. Before a large-scale multi-session RCT is conducted, an exploratory study to examine whether different levels of CS could result in different responses to a single session of rTMS is warranted.

Therefore, the first purpose of this exploratory study was to examine the immediate effects of a single session of rTMS on mechanical and thermal pain thresholds in individuals with CLBP. Specifically, the effects of rTMS were examined in two subgroups with CLBP, one with a higher level of CS and one with a lower level of CS. In addition, the changes of pain thresholds before and after rTMS were compared between the two groups. The second purpose of the study was to determine whether individuals with CLBP differing in CS severity exhibit different cortical excitability responses to rTMS as compared to their age- and sex-matched asymptomatic individuals. Two additional cohorts of age- and sex-matched asymptomatic controls were enrolled in the study to serve as a neurophysiological reference standard to examine the effect of rTMS on cortical excitability. We hypothesized that individuals with high CS would demonstrate greater changes in pain thresholds and altered cortical excitability following rTMS compared to those with low CS and asymptomatic controls. Lastly, effect sizes were determined for all within-group and between-group comparisons.

Materials and Methods

Study Design

This prospective, non-randomized, pre- and post-test clinical trial examined the immediate effects of a single session of rTMS intervention on individuals who had CLBP with high and low severities of CS, as well as on their matched asymptomatic controls. All four groups of the participants received the rTMS intervention. The primary outcome measures were QSTs, including pressure pain threshold (PPT), cold pain threshold (CPT), and heat pain threshold (HPT). The secondary outcome measure was the level of cortical excitability as indexed by motor evoked potential (MEP) amplitudes measured using single pulse TMS. All of the outcome measures were collected at two times, before and immediately after a single session of the rTMS intervention.

Participants

This study was approved by the Texas Woman's University's Institutional Review Board (Protocol #: 20394) and registered with ClinicalTrials.gov (NCT03973788). Prior to commencement of data collection, consent was obtained from all study participants. All participants were informed about the purpose of the trial, in accordance with the Declaration of Helsinki. Participants with CLBP were recruited primarily from the physical therapy clinics at which the investigators were employed. It has been suggested that age and sex affect MEPs.³⁶ Therefore, once the enrollment of the target patient participants ($n = 20$) was completed, the enrollment of age- and sex-matched asymptomatic controls began. The asymptomatic controls ($n = 20$) were recruited primarily from employees and students at the investigators' affiliated academic institutions.

Eligible patient participants were adults 18 years of age or older and who had CLBP, defined as having LBP for more than 6 months.³⁷ Asymptomatic controls were those with no existing LBP and no LBP in the past year. Participants for both groups were excluded from the study if they had previous low back surgery, systemic joint disease (eg. rheumatoid arthritis), evidence of red flags (eg. fracture, infection, tumor, cauda equina syndrome), cancer, neurological disorders, neuropathy, Raynaud's disease, pregnancy, or inability to maintain the testing and treatment positions (ie, sitting, supine hook-lying and prone-lying) for 15 minutes at a time. Additional exclusion criteria for the rTMS intervention included: 1) history of significant head trauma, 2) electrical, magnetic, or mechanical implantation (eg, cardiac pacemakers or intracerebral vascular clip), 3) metal implantation in the head and neck areas, 4) history of seizures or unexplained loss of consciousness, 5) immediate family member with epilepsy, 6) use of seizure threshold lowering medicine, 7) current abuse of alcohol or drugs, and 8) history of psychiatric illness requiring medication controls. Once a participant with CLBP was determined to be eligible for the study, the participant completed the CSI to determine the extent of CS and was assigned into either the high or low CS group using the CSI's cut-off score of 33.5.³⁵ The group assignment was performed by the treating investigator (SWP), as all participants received the rTMS intervention. However, the two investigators (KA and YA) who were responsible for QST and cortical excitability assessments were blinded to the group assignment.

Demographics and Questionnaires

Eligible participants were asked to complete an intake form regarding their demographic data, including age, sex, height, weight, occupation, past medical history, and questions related to their low back pain (ie, onset, injury mechanism if any, location, duration, type, and nature). In addition to the CSI, each of the participants completed three questionnaires before the rTMS treatment, including the Numerical Pain Rating scale (NPRS) to determine pain intensity, the Modified Oswestry Low Back Pain Disability Questionnaire (ODI) to determine disability,^{38,39} and the Patient-Reported Outcomes Measurement Information System® - short form (PROMIS-29) to determine quality of life.^{40,41} These questionnaires are commonly used in research studies of CLBP and were used to describe the characteristics of the participants in this study.

Quantitative Sensory Tests

All participants with CLBP underwent a battery of QSTs to determine their neurosensory deficits, including pressure, heat and cold pain thresholds. The pain thresholds were measured from the most tender site of the low back of each participant in both CS groups. The purpose of the pain threshold test was to assess the extent of hypersensitivity, a clinical characteristic of central sensitization.^{35,42} To ensure assessment consistency and because PPT improvements after M1 rTMS are specific to the contralateral tender points of rTMS only, the most tender point of the low back was selected for QSTs.⁴² A hand-held computerized pressure algometer (Medoc Ltd., Ramat Yishai, Israel) was used to measure the PPTs. The algometer consisted of a 1-cm² round tip which was pressed vertically on the target location. To provoke the patient's pain or discomfort, pressure was increased at a rate of 40 kPa/sec until the participant felt pain as indicated by pressing a button on the algometer's patient safety unit.^{43,44} The pressure limit was set at 1000 kPa, meaning that pressure stopped at 1000 kPa to minimize tissue damage. If the participant did not push the button before 1000 kPa, a value of 1000 was used as the threshold value.

A Medoc TSA II Neurosensory Analyzer (Medoc Ltd., Ramat Yishai, Israel) with a 30 mm × 30 mm thermode was used to measure HPT and CPT. All thermal pain threshold tests were performed with ramped stimuli (0.5° C/s), which was terminated when the participant pressed a safety button. Cut-off temperatures were set to 0° C for CPT and 52° C for HPT, and the baseline temperature was set at 32°C.⁴⁵ To ensure that participants were familiar with the three pain threshold tests (PPT, CPT, and HPT), a minimum of one practice trial was administered prior to the formal testing. Three trials were administered at the testing site for each of the three QST tests with a 25-second inter-stimulus interval to minimize the possibility of temporal summation.⁴³ The average of the three trials was used for data analysis. The order of testing was the same before and after the rTMS for all participants. Lastly, the moderate-to-good test-retest reliability of these QST tests has been established.^{46,47} Furthermore, all three QST protocols have been used in our previous studies.^{35,47}

Cortical Excitability Assessment

A TMS machine (Magstim 200, Magstim Co., UK) that generated a series of single pulses was used to determine the cortical excitability of both participants with CLBP and asymptomatic controls. The MEP of the first dorsal interosseous muscle (FDI) was measured using surface electromyography (EMG). First, a pair of surface EMG electrodes was placed on the FDI muscle when the participant was seated on a reclining chair and, if they requested, wearing a pair of earplugs to reduce their awareness of noise from the TMS equipment. EMG activity was measured from the FDI muscle on the same side as the participant's LBP. For those participants who reported no difference in LBP intensity between sides, EMG data was recorded from the FDI muscle of the right hand.

Neuronavigation using MRI or CT scans can provide individualized TMS target locations. However, this approach is cost prohibitive. Therefore, this study followed a previously published protocol to individualize the TMS targeted location for each participant.²² During the cortical excitability assessment, each participant wore a Lycra swimming cap with a pre-marked grid to guide the localization of the hot spot of the FDI muscle. A hot spot is defined as the site at which the largest MEP amplitude is obtained at the lowest TMS stimulation intensity. While the hot spot was being located, the TMS machine's figure-8 coil was targeted to points on the pre-marked grid close to the M1 and the MEP was measured at each point. The intensity of TMS began at 35% of maximum stimulator output and then was increased gradually to yield an MEP from the FDI until a hot spot was observed. Next, the resting motor threshold (RMT) was

determined. RMT is defined as the TMS intensity which yields a peak-to-peak amplitude of MEP larger than 50 μV in 5 out of 10 consecutive trials.²² Once the RMT was determined, the TMS intensity was set at 120% of RMT and 10 stimulations were delivered to the hot spot.⁷ The 10 supra-threshold MEP amplitudes recorded from the FDI were averaged, and the average was used to represent cortical excitability.

rTMS Intervention and Re-Assessments

After the cortical excitability assessment, each participant received 10 Hz rTMS (Magstim Rapid2, Magstim Co., UK) in the form of twenty 10-second pulse trains with a 50-second inter-train interval delivered to the hot spot of the FDI determined during the cortical excitability assessment. Therefore, each participant received a total of 2000 pulses during a 20-minute treatment session. The TMS intensity was set at 90% of RMT.⁴⁸ During the rTMS intervention, each participant was asked to sit and relax in a cushioned recumbent chair. If the participant considered the TMS pulses to be too loud, they were given ear plugs to minimize TMS noise. After the rTMS intervention, each participant's cortical excitability (ie, MEP) was re-assessed without delay to capture immediate neurophysiological effects. Pain threshold assessments also were repeated for participants with CLBP.

Statistical Analysis

As this is an exploratory study, no power analysis was performed to estimate the sample size. Descriptive statistics were calculated for participants' characteristics (ie, demographic and self-reported questionnaire data), PPTs, HPTs, CPTs, and MEPs. IBM SPSS Version 28.0 (IBM Corp., Armonk, NY, USA) was used to perform statistical analysis of the collected data. Due to the small sample size and the nature of an exploratory study, non-parametric statistics, Wilcoxon Signed-Ranked tests were used to compare the differences in pain thresholds before and after rTMS (ie, within-group comparisons) and Mann-Whitney *U*-tests were used to compare changes of between groups. In addition, Mann-Whitney *U*-tests were used to compare participants' characteristics and baseline data between the two CS groups. As this was an exploratory study, the α level was set at 0.05 for all statistical analyses without adjusting for multiple comparisons.

Results

Participants

Twenty-five eligible participants with CLBP were enrolled in the study and 20 participants, 10 in the high CS group ($\text{CSI} = 39.9 \pm 4.8$) and 10 in the low CI group ($\text{CSI} = 23.8 \pm 6.3$), completed the study (8 females and 2 males in each group). Two participants chose to withdraw because they did not have transportation to a scheduled visit, two participants withdrew because they declined to stop using an anti-depressant, and one participant was removed from the study for failure to report lumbar surgery during screening. Table 1 shows the characteristics of participants and baseline outcome measures for both the high and low CS groups, indicating that these two groups were distinctly different in several domains at baseline. The high CS group had higher ODI disability scores, lower PROMIS-29 physical function and PROMIS-29 social activity scores, and higher PROMIS-29 pain interference scores than the low CS group. However, there was no difference in pain intensity or pain duration between the two groups. The high CS group also had higher PROMIS-29 fatigue scores than the low CS group, but the difference was not statistically significant ($p = 0.105$). Interestingly, the body mass index (BMI) was higher in the low CS group due to higher body weight. In addition, the high CS group had a higher CPT than the low CS group at baseline ($p = 0.046$), whereas there were no statistically significant differences in PPT, HPT, or MEP ($p > 0.05$) between groups at baseline. Lastly, two participants with CLBP reported mild headaches lasting 24–48 hours. Both participants were in the high CS group, and, after subsiding, their headaches did not return.

Pain Thresholds

Before statistical analyses were performed, the baseline data was examined for the assumption of normality. As planned, we proceeded with non-parametric statistics because the data was not normally distributed. Table 2 lists comparisons performed for pain thresholds. For PPTs, the Wilcoxon Signed-Ranked tests showed that the high CS group had

Table 1 Characteristics of the Participants in the High Central Sensitization (CS) Group and Low CS Group at Baseline

Variable, Mean (SD)	High CS Group (n = 10)	Low CS Group (n = 10)	p value (Between Group)
CSI Score	39.9 (4.8)	23.8 (6.3)	< 0.001*
Age (years)	38.3 (12.6)	39.3 (13.8)	0.796
Height (cm)	167.6 (12.2)	168.9 (9.7)	0.631
Weight (kg)	70.6 (16.5)	89.9 (17.4)	0.035*
Body mass index (kg/m ²)	24.9 (4.1)	31.6 (6.3)	0.035*
NPRS (0–10)			
Now	4.6 (1.8)	3.4 (1.4)	0.165
Worst	5.7 (2.4)	5.4 (1.8)	0.912
Least	3.5 (2.0)	2.9 (1.2)	0.393
Duration of pain (weeks)	117.6 (62.2)	88.8 (67.6)	0.190
ODI	30.6 (10.2)	17.6 (9.9)	0.011*
PROMIS-29 (z score)			
Physical function	40.8 (4.1)	47.0 (6.1)	0.029*
Social activity	53.3 (5.7)	57.4 (5.1)	0.011*
Anxiety	52.8 (8.7)	47.8 (6.0)	0.190
Depression	46.8 (8.2)	42.6 (3.4)	0.353
Fatigue	55.0 (8.3)	49.8 (4.2)	0.105
Sleep disturbance	50.5 (5.5)	48.5 (6.4)	0.315
Pain interference	61.1 (4.1)	53.3 (5.7)	0.003*
Pain thresholds at low back			
Pressure (kPa)	301.0 (165.5)	357.2 (254.5)	0.618
Heat (°)	42.0 (4.4)	44.7 (3.7)	0.094
Cold (°)	19.0 (10.7)	8.5 (11.1)	0.046*
MEP (mV)	2.32 (1.93) ^a	1.29 (1.20) ^a	0.184

Notes: Non-parametric statistics were performed; *p < 0.05 for statistically significant; ^aSample size n = 8.

Abbreviations: CSI, Central Sensitization Inventory; NPRS, Numerical Pain Rating Scale; ODI, Modified Oswestry Low Back Pain Disability questionnaire; PROMIS-29, Patient-Reported Outcomes Measurement Information System[®] - short form.

Table 2 Pain Thresholds of Low Back of the High Central Sensitization (CS) Group and Low CS Group

	High CS Group (n = 10)				Low CS Group (n = 10)				Between Groups ^a p value (ES)
	Pre	Post	Change	Within Group p value (ES)	Pre	Post	Change	Within Group p value (ES)	
PPT (kPa)	301.0 (165.5)	358.3 (221.6)	57.4 (73.3)	0.037* (0.47)	357.2 (254.5)	377.1 (184.5)	19.9 (118.2)	0.445 (0.17)	0.684 (0.10)
HPT (°)	42.0 (4.4)	41.6 (3.2)	-0.5 (3.9)	0.959 (0.01)	44.7 (3.7)	45.4 (3.0)	0.7 (1.6)	0.260 (0.09)	0.968 (0.02)
CPT (°)	19.0 (10.7)	18.6 (10.6)	-0.4 (1.8)	0.401 (0.19)	8.5 (11.1)	8.4 (10.7)	-0.1 (11.2)	0.674 (0.25)	0.631 (0.12)

Notes: Descriptive statistics include mean (SD); non-parametric statistics were performed; *p < 0.05 for statistically significant; ^aChange scores used for between-group comparisons.

Abbreviations: ES, effect size *r*; PPT, pressure pain threshold; HPT, heat pain threshold, CPT, cold pain threshold.

significantly improved PPTs after one session of rTMS ($p = 0.037$, moderate effect size (ES) $r = 0.47$), whereas the low CS group had no significant change in PPTs after rTMS ($p = 0.445$, small ES $r = 0.17$). No significant changes in CPTs or HPTs were observed in either group after the rTMS intervention.

Although there was a statistically significant difference in BMI between groups, BMI was not included as a covariate for statistical analysis because BMI is highly correlated with pain sensitivity.⁴⁹ According to Nimmon and Henson,⁵⁰ when covariates are strongly related to the dependent variable (DV), the DV may no longer accurately measures the intended

Table 3 Participant Characteristics and Cortical Excitability (Mean and SD) of the High Central Sensitization (CS) Group and Low CS Group vs. Their Matched Controls, Respectively

	High CS Group vs. Matched Controls (n = 8 Each)			Low CS Group vs. Matched Controls (n = 8 Each)		
	High CS	Matched	p value (between groups)	Low CS	Matched	p value (between groups)
Age (years)	35.5 (12.2)	33.3 (11.3)	0.574	34.5 (10.5)	31.9 (11.5)	0.234
Height (cm)	168.7 (13.5)	162.6 (5.1)	0.382	167.9 (10.4)	170.4 (6.1)	0.645
Weight (kg)	73.6 (17.0)	66.5 (17.9)	0.505	90.9 (14.6)	66.9 (10.4)	0.015*
BMI (kg/m ²)	25.6 (4.2)	25.1 (4.9)	0.798	32.2 (6.9)	22.9 (2.5)	0.002*
CSI Scores	38.4 (3.1)	14.8 (9.3)	<0.001*	23.8 (6.6)	13.6 (4.3)	0.002*
RMT (%)	51.6 (9.6)	48.8 (12.6)	0.370	45.3 (8.4)	44.0 (7.8)	0.673
MEP (mV)						
Pre	2.32 (1.93)	1.91 (1.09)	1.000	1.24 (1.17)	1.67 (0.99)	0.294
Post	1.62 (1.44)	2.14 (1.06)		1.29 (1.39)	2.39 (1.25)	
Difference	-0.70 (1.24)	+0.23 (0.47)	0.059 (ES = 0.47)	+0.05 (0.40)	+0.72 (1.04)	0.172 (ES = 0.34)
MEP within-group p value (ES)	0.093 (ES = 0.40)	0.263 (ES = 0.59)		0.779 (ES = 0.10)	0.123 (ES = 0.54)	

Notes: Non-parametric statistics were performed; * $p < 0.05$ for statistically significant; a minus sign (–) indicates a decrease; a plus sign (+) indicates an increase.

Abbreviations: BMI, body mass index; CSI, Central Sensitization Inventory; RMT, resting motor threshold; MEP, motor evoked potential, ES, effect size r .

construct. Therefore, Mann–Whitney U -tests were performed to examine pre-post rTMS changes of PPT, HPT, and CPT measurements between the two groups. The results showed no statistical significance between groups ($p > 0.05$).

Cortical Excitability

To determine if the presence of LBP or severity of CS mediated the neurophysiological response to rTMS, each participant in each CS cohort was matched with one of eight asymptomatic participants based on their age and sex. Four participants with CLBP, two in the high CS group and two in the low CS group, were not matched. For the two participants in the high CSI group, the RMT could not be obtained, whereas the two participants in the low CSI group were not matched due to a lack of asymptomatic participants who were age 56 or higher. Table 3 lists the characteristics of those age- and sex-matched cohorts, and their cortical excitability data (means and SD), including RMT and MEP values. There were no differences in the RMT or baseline MEPs between each CS group and its controls. Further, the MEP results (Table 3) showed that both the low CS group ($p = 0.779$, $ES\ r = 0.10$) and its matched controls ($p = 0.123$, $ES\ r = 0.54$) had an increase of MEPs after one session of rTMS, but the increases were not significant. In contrast, the high CS group had a decrease of MEPs (–0.70) after rTMS ($p = 0.093$, $ES\ r = 0.40$), whereas its matched controls had an increase of MEPs (+0.23) after rTMS ($p = 0.263$, $ES\ r = 0.59$), although none of the within-group changes of MEP were statistically significant. However, the pre-post rTMS changes of MEP were notably different between the high CS group and its matched controls with a medium effect size ($p = 0.059$, $ES\ r = 0.47$).

Discussion

Pain Sensitivity

Among participants with CLBP, only the high CS group had a significant decrease of sensitivity to pressure (ie, an increase of PPT) with a moderate effect size ($r = 0.47$) immediately after a single session of rTMS (see Table 2). Although the low CS group also had an increase of PPT after rTMS, the change was very small and not significant with an effect size of $r = 0.17$. The significant increase of PPT in the high CS group along with a small change of PPT in the low CS group suggests that CS may influence responses to rTMS for patients with CLBP, specifically hypersensitivity to pressure. Systematic reviews consistently demonstrated a transient analgesic effect of M1 rTMS on patients with neuropathic pain,^{16,51} but the evidence was conflicting for patients with chronic musculoskeletal pain.^{11,22–24} Perhaps individuals with musculoskeletal pain and high CS may have degrees of sensory hypersensitivity similar to those who have neuropathic pain from nervous system pathologies such as stroke, spinal cord injury, or

diabetic neuropathy. However, the between-group comparison did not show statistically significant differences in pre-post rTMS changes of PPT. The lack of between-group differences could be due to small sample size and large variation within the group. Future studies with large sample sizes are warranted to confirm the differing effects of CS in response to rTMS.

Similar to a previous study of a widespread pain population,⁴² the observed improvements of PPT after M1 rTMS were specific to the contralateral side of rTMS and to the tender points only. The immediate increase of PPT in the high CS group indicates that rTMS targeting M1 could modulate other cortical and subcortical pain processing areas (eg, cingulate and periaqueductal gray), and could result in an anti-nociceptive effect through the activation of descending pain inhibitory controls.^{18,42} Interestingly, the M1 is not considered to be a key part of the central pain processing and modulation area, which includes the somatosensory cortex, insular cortex, thalamus, and prefrontal cortex.⁵² However, research consistently has shown that M1 rTMS can produce analgesic effects and often produce greater effects than rTMS targeting other locations, such as the dorsolateral prefrontal cortex.^{16–18,48} As shown in a recent functional MRI study, M1 rTMS significantly changed brain areas associated with pain processing and modulation, including prefrontal cortex, amygdala, and insula.⁵³

In contrast to PPT, we did not observe significant changes in HPT and CPT for either group (see Table 2). These results are in agreement with those of a study in which there were no significant changes in HPT and CPT after M1 rTMS in a cohort of CLBP and insomnia.⁵⁴ As thermal pain thresholds are strongly influenced by genetic and environmental factors,⁵⁵ these uncontrolled factors might explain non-significant findings. However, a study investigating neuropathic pain demonstrated improvements of thermal pain thresholds (HPT and CPT) after rTMS, but no improvement of PPTs.⁵⁶ The different patient populations (neuropathic vs. CLBP of musculoskeletal origin) and the use of different instruments (0.5 mm vs. 1.1 cm tip of pressure algometer) to measure PPTs could have contributed to different results between the two studies. However, the underlying mechanism of the selective sensory changes is not clear, as both thermal and pressure pain threshold tests stimulate A-delta and C-fibers,⁵⁷ but pressure pain provokes deep tissue nociceptors and thermal pain provokes superficial skin nociceptors. Perhaps, rTMS may be more effective at modulating pressure (ie, deep tissue) pain sensitivity than thermal (ie, skin) pain sensitivity for chronic musculoskeletal pain.⁵⁸

Cortical Excitability

Although there were no direct comparisons of cortical excitability between the high and low CS groups, the results of the study showed opposite responses to rTMS at a corticospinal level for the high and low CS groups (see Table 3). Both the low CS group and its controls, as well as the high CS group's controls had a facilitatory response to rTMS as reflected by an increase of MEPs as expected, whereas the high CS group had an inhibitory response to rTMS. Although the decrease of MEPs was not statistically significant, the effect size was moderate ($r = 0.40$). It also was noted that the decrease of MEPs in the high CS group after rTMS corresponded to the decrease of pressure pain sensitivity, further indicating a differential effect of rTMS based on CS. As this study used a high frequency of rTMS (ie, 10 Hz), a facilitatory response was expected.^{11,59} However, research has shown inter-individual variability to the rTMS with the same frequency and duration.^{59,60} It was hypothesized that the rTMS application protocol could activate diffuse cortical networks of different cell types, resulting in the variety of MEP values.⁶¹ In addition, other biological factors, such as age, sex, genetics, and psychical activity levels, could cause inter-individual variability.⁶¹ Nevertheless, the distinctive opposite direction of the change in MEP values after rTMS suggests that this differential response may be used to characterize these two CS groups.

Study Strength and Limitations

A key strength of this study was the use of objective assessments, rather than subjective pain ratings, to differentiate patients with CBP based on their CSI scores and to examine their responses to rTMS with minimal bias. Such a subgrouping approach is consistent with a recent study⁵⁴ in which the QST scores were compared in subgroups: CLBP with and without insomnia. As insomnia is highly related to CS, subgrouping based on the level of CS may guide the triage of heterogeneous CLBP in clinical practice. Another strength of this study is the inclusion of cortical excitability assessment, which allowed us to examine rTMS responses at the central level. Furthermore, although

evidence suggests that patients with positive expectations toward rTMS or prior rTMS experience are more likely to have positive outcomes,^{62,63} the use of objective outcome measures in this study likely minimize the influence of participant's bias on the outcome measures.

One limitation of this study is that only pressure and thermal pain thresholds were examined. Other meaningful quantitative sensory tests such as conditioned pain modulation tests may be more sensitive to detect the differences between the two CS groups.²⁹ In addition, the QSTs were assessed in the low back area rather than in a remote area, such as web space or tibialis anterior, which would demonstrate a widespread CS effect.^{5,57} Similarly, it has been suggested that cortical excitability measures other than MEP may be used for detecting cortical changes related to chronic pain reduction, such as short intracortical inhibition and intracortical facilitation.^{18,64,65} These intracortical excitability measures are believed to be associated with the activation of inhibitory (GABAergic) and excitatory (glutamatergic) pain pathways, but were not assessed in this study. Other complementary brain imaging techniques, such as fMRI, would allow for the examination of other pain-related neural networks (eg. cingulate cortex and insula). These additional measures will further delineate the role of CS in the development and treatment of chronic pain. Furthermore, only immediate effects of a single session of rTMS were examined. It is unclear whether the effects of rTMS for the low CS group or other pain thresholds would emerge after multiple sessions of intervention. Lastly, the results of this study should be interpreted with caution, as this is an exploratory study with a small sample size.

Conclusion

The results of this exploratory study suggest that patients with high levels of CS may experience a reduced sensitivity to pressure to the low back after a single session of rTMS. Furthermore, the decreased sensitivity to pressure in participants with high levels of CS corresponded to a decrease of cortical excitability after rTMS, which was in contrast with the rTMS effects observed in participants with low levels of CS and asymptomatic controls. The results suggest that the extent of CS may play a significant role in mediating both neurophysiological responses to the rTMS intervention. Future studies with large sample sizes are warranted to confirm whether the extent of CS would mediate neurophysiological response to rTMS in patients with CLBP.

Data Sharing Statement

Three years after the manuscript is published, the de-identified datasets used and analyzed for this current study will be available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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