OPEN

Pain Sensitization and Descending Pain Inhibition in Fibromyalgia

Ailyn Garcia-Hernandez, PhD, Pablo de la Coba, PhD,† Stephen Bruehl, PhD,‡ Stefan Duschek, PhD,§ and Gustavo A. Reyes del Paso, PhD**

Background: Both facilitation of ascending nociceptive pathways and impaired inhibition of descending ones may contribute to pain sensitization in fibromyalgia (FM). The slowly repeated evoked pain (SREP) protocol is a potential diagnostic marker for assessing this sensitization. Though its mechanisms are unclear, SREP appears linked to ascending facilitation, while the role of descending inhibitory dysfunction in SREP sensitization remains to be clarified.

Objective: To quantify descending pain inhibition in FM compared with healthy individuals and to assess its relationship with pain sensitization via SREP. In addition, associations between descending pain inhibition and clinical symptoms were examined.

Methods: In 55 women with FM and 45 pain-free women, descending pain inhibition was estimated using the conditioned pain modulation (CPM) paradigm, with interdigital web pinching as the conditioning stimulus. The use of the SREP protocol consisted of applying pressure stimuli to the nail of the third finger of the nondominant hand. Clinical symptoms were assessed using self-report questionnaires.

Results: SREP sensitization was stronger and CPM smaller in FM patients than in pain-free women. In individuals with FM , SREP sensitization was inversely associated with CPM, and both were related to clinical symptoms. Individuals with FM who did not show CPM reported greater severity of FM symptoms and higher anxiety and fatigue levels than those who showed CPM.

Conclusions: Impaired endogenous pain inhibition contributes to pain sensitization in FM and may partly explain SREP sensitization. This reduced pain inhibition could also underlie the clinical symptoms commonly seen in FM. Future research may clarify the altered balance between ascending and descending pain processes in FM.

Received for publication May 14, 2025; revised July 23, 2025; accepted September 7, 2025.

From the *Department of Psychology, University of Jaén, Jaén; †Department of Psychology and Anthropology, University of Extremadura, Cáceres, Spain; ‡Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN; and §Institute of Psychology and Medical Sciences, University of Health Sciences, Medical Informatics and Technology, Tirol, Austria.

Supported by the Spanish Ministry of Science and Innovation, co-financed by FEDER funds (grant number PID2022-139731OB-I00), and the FPI predoctoral contract (grant number PRE2019-090833).

The authors declare no conflict of interest.

Reprints: Ailyn Garcia-Hernandez, PhD, Department of Psychology, University of Jaén, Campus Las Lagunillas, 23071 Jaén, Spain (e-mail: aghernan@ujaen.es).

DOI: 10.1097/AJP.0000000000001327

Key Words: central pain sensitization, conditioned pain modulation, fibromyalgia, endogenous pain inhibition, pain assessment

(*Clin J Pain* 2025;41:e1327)

Though the etiology of fibromyalgia (FM) syndrome remains unknown and objective diagnostic markers of the disorder are still lacking,[1,2] it is commonly believed that central nervous system sensitization to pain is crucial to its pathophysiology.[3–5] This is supported, for example, by reduced pain thresholds and tolerance, the presence of hyperalgesia and allodynia, and exaggerated activity in the "pain neuromatrix" during experimental pain stimulation in patients with FM.[6–11] Two different processes leading to pain sensitization must be considered, namely, facilitation of ascending and impaired inhibition of descending, nociceptive pathways.[12] Both may contribute to FM pain.[4,13,14]

Algometry and experimental evoked pain testing procedures have proven effective in assessing pain sensitization in patients with FM,[4,15] particularly dynamic evoked pain measures, such as temporal summation of pain (TSP), noxious flexion reflex threshold and, more recently, slowly repeated evoked pain (SREP).[4] The SREP protocol captures the increase in pain ratings in response to repeated pressure stimuli at frequencies far lower than those used in TSP protocols.[4,16] SREP sensitization has repeatedly been observed in patients with FM, but does not occur in healthy individuals[16–19] or patients with rheumatoid arthritis, a chronic pain condition with primary peripheral pathology.[20] SREP demonstrates high accuracy in terms of diagnosing FM (85% diagnostic accuracy) and was associated with clinical pain severity.[16,17] SREP, therefore, appears to be a valid index of the pain sensitization characterizing FM.

In patients with FM, SREP sensitization correlated positively with TSP, another central sensitization marker.[20] However, given that SREP sensitization, but not TSP, correlated with clinical variables,[20] and the great difference in the frequency of pain stimulation (the TSP effect occurs at 0.33 Hz[21,22] whereas SREP is observed at 0.03 Hz, a frequency that does not generate windup effect), mechanisms other than TSP have been proposed to underlie SREP sensitization.[20,23] One possibility is that SREP sensitization may in part reflect diminished descending inhibition, a hypothesis in line with current concepts of nociplastic pain, in which pain sensitization may be related to some combination of elevated ascending facilitation or impaired descending inhibition.[24,25]

The conditioned pain modulation (CPM) paradigm is a well-established experimental method to estimate descending pain inhibition.[26] It reflects a mechanism known as

"pain inhibits pain."[13,14] The procedure involves the use of 2 concurrent pain stimuli, a conditioning and a test stimulus, applied to contralateral body areas. The magnitude of CPM (ie, the CPM response) is indicated as the difference between pain intensity reported during application of the test stimulus alone and pain intensity reported when the test stimulus is applied during or immediately after the conditioning stimulus. Reduction of pain ratings or increase in pain threshold during the procedure indicate inhibitory CPM.[27] Patients with FM show substantially smaller CPM responses than healthy individuals and patients with other chronic pain conditions.[28,29] Moreover, smaller CPM responses have been associated with sleep disturbance, anxiety, and depression in pain-free populations,[30–32] all characteristics commonly associated with FM.

The present study aimed to compare endogenous pain inhibition, as assessed via the CPM paradigm, between individuals with FM and pain-free participants and to investigate the relationship between SREP sensitization and the CPM response in those with FM. As delineated above, increased SREP sensitization in FM may not be sufficiently explained by facilitation of ascending nociceptive pathways; rather, reduced descending inhibition may play a role in the SREP sensitization effect. Based on this concept, we predict an inverse association between SREP sensitization and the CPM response in the group of individuals with FM. Moreover, the study explored possible associations of CPM with clinical pain and symptoms of fatigue, depression, and anxiety in these patients. Based on previous research, greater symptom severity was expected in individuals with FM who exhibit smaller CPM responses.[33]

METHODS

Participants

Fifty-five women with FM participated in the study. They were recruited through the Jaén Fibromyalgia Association and diagnosed by rheumatologists based on the 2010 criteria of the American College of Rheumatology.[34] Given the higher prevalence of FM in women than men,[35] the study was carried out only in women. In addition, a control group of 45 pain-free women of similar age was recruited. All participants were paid 30 euros to compensate for their time and travel spent conducting the study in the laboratory. Exclusion criteria for both groups comprised a history of metabolic (eg, diabetes), degenerative or cerebrovascular diseases (eg, dementia or cognitive decline), other severe physical or mental disorders (eg, cancer, psychosis, or drug abuse), class II or greater obesity, and pregnancy. Based on these exclusion criteria, 8 potential candidates had to be excluded from the study. Figure 1 shows a flowchart illustrating the processes of participant inclusion, enrollment, exclusion, and assessment. Table 1 presents sociodemographic data, clinical variables, and pain measures of both groups. The mean duration of FM (ie, current age minus the age of the beginning of widespread pain) in the FM sample was 22.15 ± 10.76 years.

Additional data were collected on pain-related conditions reported by individuals with FM who extended beyond symptoms directly attributable to FM. Data revealed that 40% of the sample had comorbid pain conditions, including osteoarthritis, hernias (lumbar, cervical, hiatal), and arthritis—either individually or in combination, in that order of prevalence. Less frequently reported comorbidities included irritable bowel syndrome and migraine, observed in 3 and 2 patients, respectively.

Self-report Questionnaires

Clinical pain was estimated using the Spanish version of the Pain Intensity Scale of the Brief Pain Inventory (BPI).[36] The score range of this scale is 0 to 10, with mild (0 to 4), moderate (5 to 7), and severe (8 to 10) intensity levels, and a Cronbach α of 0.87. Fatigue was measured with the Spanish version of the Fatigue Severity Scale (FSS).[37] This scale quantifies fatigue based on 9 items (score range 9 to 63), with a Cronbach α of 0.88. Anxiety and depression were evaluated using the Spanish version of the Hospital Anxiety and Depression Scale (HADS)[38] (score range: 0 to 21 for the Anxiety and Depression subscales, Cronbach $\alpha = 0.82$ and $\alpha = 0.81$, respectively). State anxiety at the time of laboratory assessment was measured using the State subscale of the State-Trait Anxiety Inventory (STAI; Spanish version with a Cronbach $\alpha = 0.80$).[39] The severity of FM symptoms was evaluated by the Spanish version of the Revised Fibromyalgia Impact Questionnaire (FIQ-R)[40] (score range: 0-100, Cronbach $\alpha = 0.91$). Mean FIQ-R values in our patients with FM were 64.82 ± 17.43.

Experimental Pain Measures

Pressure Pain Threshold and Tolerance

A computer-controlled Tracker Freedom pressure algometer (JTECH Medical) with a stimulation surface of 1 cm^2 was used for the assessment of pain threshold and tolerance. The algometer was specifically designed to fixate the fingernail and to precisely control stimulation pressure. The concept of pain threshold was explained to the participants in terms of "the lowest pressure that causes pain." Pain tolerance was explained as "the highest pressure that you are able to tolerate." Once these concepts were understood, both measures were obtained by applying a pressure of a 1 kg/s increase rate to the third fingernail of the nondominant hand. At first, 2 measurements of pain threshold were taken with a 15-second interval in between. After a 1-minute break, 2 measurements of pain tolerance were taken, again with a 15-second interval in between. The mean values of the 2 measurements of pain threshold and tolerance were used for statistical analysis.

Slowly Repeated Evoked Pain (SREP) Protocol

The SREP protocol was conducted as in previous studies.[16–20] A series of 9 identical painful stimuli (5 s each) was applied to the third fingernail of the nondominant hand at 30-second intervals. Pressure intensity was individually determined using the following formula, based on each participant's pain threshold and tolerance: Intensity = Threshold + 1.25*(Tolerance − Threshold/4). After each stimulus, participants rated their pain perception using a verbal numerical scale (VNS), ranging from 0 "no pain" to 10 "extremely painful." SREP sensitization was calculated as the difference between the last and first pain rating ($T_9 - T_1$). Positive values reflect an increase in pain throughout the 9-stimulus series, suggesting pain sensitization. For details of the protocol, see the study by de la Coba et al.[16,17,20]

Conditioned Pain Modulation (CPM) Paradigm

In the CPM paradigm, interdigital web pinching was used for pain stimulation, which has previously proven effective for inducing the CPM effect.[41,42] Previous research

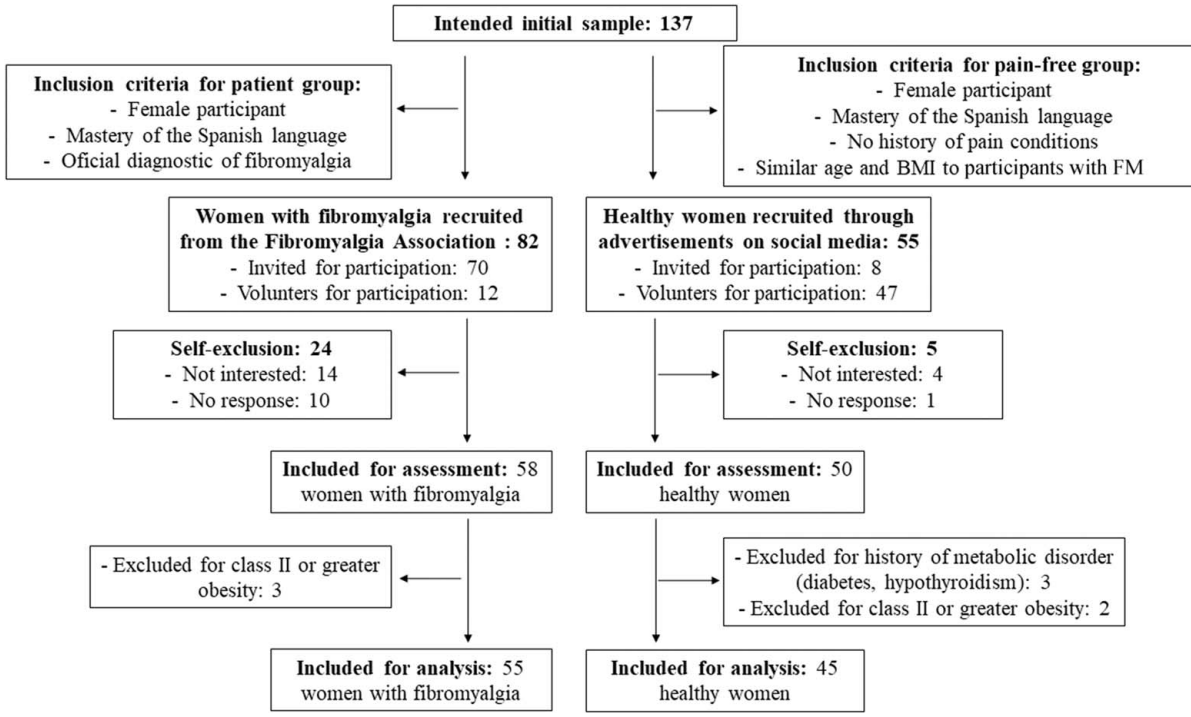

FIGURE 1. Flowchart depicting the processes of participant inclusion, enrollment, exclusion, and assessment. BMI indicates body mass index.

has suggested that experimental evoked pain intensity ratings between 4 and 6 on a 10-point scale (0 = no pain, 10 = extremely painful) are required to elicit CPM.[13,26,43,44] Pinch pressure was administered to the interdigital web between the third and fourth fingers of the dominant hand with an algometer similar to that used to determine pain threshold and tolerance. Stimuli were applied increasingly until the participant rated pain intensity as 6 on the VNS (0 to 10). Subsequently, the corresponding pressure was sustained for 30 seconds to induce the pain inhibitory effect, and maintained during test stimulation. Test stimulation involved pain threshold determination at the fingernail of the nondominant hand as described above. The CPM response was assessed by comparing the mean pain threshold recorded without (T_{nc}) and during (T_c) conditioning pain (interdigital web pinching). Positive values (T_c-T_{nc} > 0) indicated an increase in pain threshold during conditioning pain and thus endogenous pain inhibition.

Procedure

The study was conducted in a quiet and comfortable laboratory room. Clinical questionnaires were administered

TABLE 1. Demographic Variables, Experimental Pain Measures, and Questionnaire Scores in Individuals with Fibromyalgia (FM) and Pain-free Woman (M ± SD or Number of Participants and %); Statistics of the Group Comparisons

	Individuals with FM (n = 55)	Pain-free woman (n = 45)	*F*/χ2	*P*	n^2
Age (y)	55.20 ± 6.93	53.96 ± 5.45	0.96	0.330	0.01
BMI (kg/m^2)	27.84 ± 4.01	26.81 ± 3.16	1.96	0.170	0.02
Pain threshold (kg)	2.36 ± 1.24	4.10 ± 1.23	49.20	< 0.001	0.33
Pain tolerance (kg)	4.60 ± 1.83	6.53 ± 1.39	33.88	< 0.001	0.26
SREP sensitization (T_9-T_1)	0.97 ± 1.06	−0.15 ± 1.07	27.37	< 0.001	0.22
CPM response (T_c-T_{nc})	0.07 ± 0.99	0.67 ± 0.98	9.08	0.003	0.09
State Anxiety (STAI)	22.11 ± 10.31	15.09 ± 7.96	34.52	< 0.001	0.26
Anxiety (HADS)	12.96 ± 3.84	7.76 ± 4.15	42.33	< 0.001	0.30
Depression (HADS)	8.29 ± 4.6	3.84 ± 3.65	27.51	< 0.001	0.22
Pain intensity (BPI)	6.1 ± 1.42	2.83 ± 1.41	131.09	< 0.001	0.57
Fatigue (FSS)	49.22 ± 16.27	20.60 ± 10.80	102.28	< 0.001	0.51
Use of analgesics	38 (69.09)	3 (6.67)	39.87	< 0.001	—
Use of anxiolytics	29 (52.73)	8 (17.78)	12.97	< 0.001	—
Use of antidepressants	27 (49.09)	4 (8.89)	18.70	< 0.001	—

BMI indicates body mass index; BPI, Brief Pain Inventory; CPM, conditioned pain modulation; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; SREP, slowly repeated evoked pain; STAI, State-Trait Anxiety Inventory.

before experimental pain testing. An initial familiarization phase ensured the thorough comprehension of the relevant concepts (pain threshold and tolerance) and the correct use of the VNS. The sequence of pain threshold assessments (without vs. with conditioning pain) was counterbalanced across participants. The interval between these 2 assessments was 5 minutes during which the participant maintained a relaxed sitting position. The SREP protocol was conducted 5 minutes after the CPM paradigm. Figure 2 illustrates the entire experimental protocol.

Participants were asked to abstain from using analgesic medication for at least 24 hours before the study and from consuming caffeine for 6 hours. They were informed about the study and completed an informed consent form. The study used the STROBE cross-sectional reporting guidelines,[45] and it was conducted in accordance with the Declaration of Helsinki for experiments involving humans and was approved by the ethics committee of the University of Jaén (Ref: FEB.23/2.PRY).

Statistical Analyses

Previous SREP studies in FM[16,17,20] revealed large effect sizes for analyses of variance (ANOVAs) and multiple regression analyses (F around 0.40, f^2 around 0.35). Based on these effect sizes and an alpha level of 0.05, a sample size of $n \geq 52$ is required to reach a power of 0.80 in ANOVA; a sample size of $n \geq 36$ is sufficient for the same power in regression analyses. According to Shapiro-Wilk tests, none of the variables differed from a normal distribution (all $P > 0.05$).

To analyze the CPM response, an ANOVA was conducted with Group (Individuals with FMF vs, pain-free women) as a between-subjects factor and measurement condition (ie, T_c vs. T_{nc}) as a within-subjects factor. As a complementary analysis, patients showing versus not showing a CPM response (defined according to T_c-$T_{nc} > 0$) were compared regarding clinical variables using (1-tailed) t tests. For testing SREP sensitization, an ANOVA with the between-subjects factor of group (Individuals with FM vs. pain-free women) and the within-group factor of trial (T_1 to T_9) was applied. Parametric correlations were used to quantify the associations of SREP sensitization (T_9-T_1) and the CPM response (T_c-T_{nc}) with the clinical measures. To obtain 95% CIs, bootstrapping with 1000 replications was performed. Finally, a multivariable linear regression analysis was conducted to determine the predictors of SREP sensitization (T_9-T_1). Only the CPM response (T_c-T_{nc}) and those clinical variables that were associated with SREP sensitization in a previously conducted correlation analysis for this study were used as potential predictors; these latter variables were the BPI Pain Intensity scale and the FSS score (no more than 3 predictors, considering the sample size of the study[46]) These predictors were entered simultaneously into the multiple regression model (ie, enter method). Order of CPM evaluation (T_c first vs. T_{nc} first) was not associated with any of the variables studied, so it was not included in the final analyses. Alpha was set at 0.05 in all analyses.

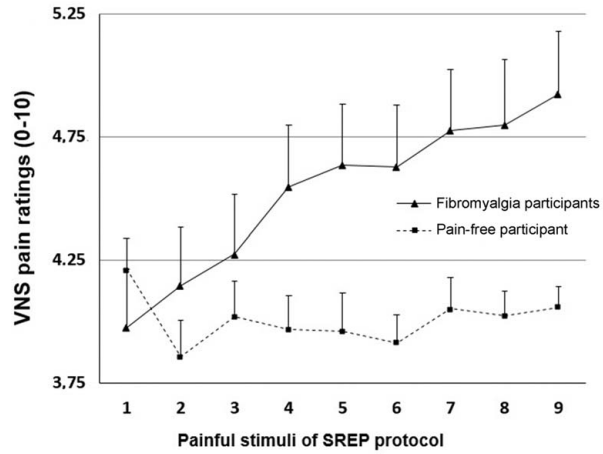

FIGURE 3. Mean values (+SD) of pain ratings (VNS) across the 9 stimuli of the SREP protocol in participants with fibromyalgia and pain-free participants. SREP indicates slowly repeated evoked pain; VNS, verbal numerical scale.

RESULTS

Clinical variables were greater, and pain threshold and tolerance were lower in females with FM compared with pain-freee women (Table 1). SREP sensitization (T_9-T_1) was stronger, and the CPM response (T_c-T_{nc}) was smaller in participants with FM than in pain-free women (Table 1). In the entire sample, pain ratings increased across trials during the SREP protocol, indicating pain sensitization (Trial main effect: $F_{8,784} = 8.78$, $P < 0.001$, $\eta^2 = 0.08$). However, this effect differed between groups (Group × Trial interaction: $F_{8,784} = 10.38$, $P < 0.001$, $\eta^2 = 0.09$). Separate analyses in both groups revealed that pain intensity ratings increased significantly in participants with FM ($F_{8,432} = 18.38$, $P < 0.001$, $\eta^2 = 0.25$) but not in pain-free participants ($F_{8,352} = 1.68$, $P = 0.10$, $\eta^2 = 0.04$) (Fig. 3). A significant CPM effect was also observed in the full sample (Measurement condition main effect: $F_{1,98} = 13.74$, $P < 0.001$, $\eta^2 = 0.09$). However, this effect again differed between groups (group × measurement condition interaction: $F_{1,98} = 9.08$, $P = 0.003$, $\eta^2 = 0.09$). In participants with FM, pain thresholds were similar during presentation of the conditioning stimulus ($T_c = 2.42 \pm 1.51$ kg) and without the conditioning stimulus ($T_{nc} = 2.36 \pm 1.24$ kg) ($F_{1,54} = 0.26$, $P = 0.61$, $\eta^2 = 0.01$). In contrast, pain-free participants showed a lower pain threshold during the conditioning stimulus ($T_c = 4.10 \pm 1.23$ kg) than before the conditioning stimulus ($T_{nc} = 4.77 \pm 1.57$ kg) ($F_{1,44} = 20.88$; $P < 0.001$, $\eta^2 = 0.32$). These latter findings indicate

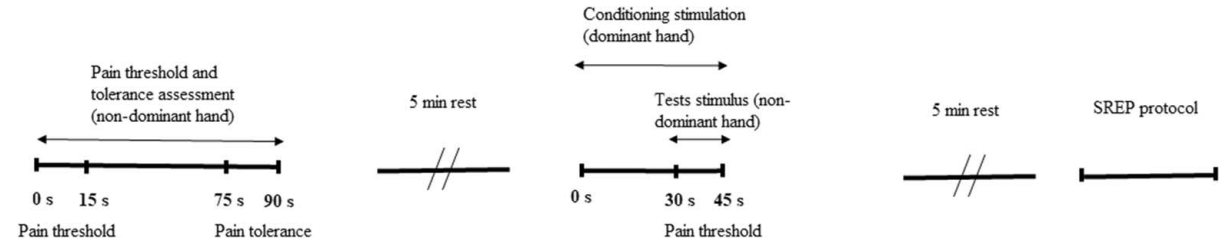

FIGURE 2. Experimental pain assessment procedure. SREP indicates slowly repeated evoked pain.

that a significant CPM effect occurred in pain-free participants that was not observed in the FM participants. Using a categorical definition for a CPM effect being present (T_c-T_{nc} > 0), a CPM response was seen in only 22 patients (40%) but in 36 healthy women (80%) ($\chi^2 = 16.26$; $P < 0.001$).

In the group of FM participants, SREP sensitization (T_9-T_1) correlated positively, and the CPM response (T_c-T_{nc}) correlated negatively, with the fatigue (FSS) score (Table 2). Moreover, SREP sensitization correlated positively with the BPI Pain Intensity scale, and the CPM response correlated negatively with the HADS Anxiety scale and the STAI State Anxiety scale (Table 2). No significant correlations were seen between the experimental pain measures and age, BMI, or disease duration (all Ps ≥ 0.31). In multivariable regression analysis (enter method) with SREP as the dependent variable and the CPM response, the FSS scale and the BPI Pain Intensity scale as predictors, only the CPM response showed a significant and inverse association with SREP sensitization (CPM response: β = −0.37, t = −2.61, $P = 0.02$, 95% CI: −0.70 to −0.09; FSS Scale: β = 0.01, t = 0.53, $P = 0.61$, 95% CI: −0.02 to 0.25; BPI Pain Intensity: β = 0.16, t = 1.37, $P = 0.23$, 95% CI: −0.09 to 0.44; $r^2 = 0.21$). Figure 4 displays the scatterplot of the association between the CPM response and SREP sensitization.

Comparisons between FM participants showing versus not showing a CPM response (defined according to T_c-T_{nc} > 0) revealed higher values on the FIQ-R, FSS, HADS Anxiety and STAI State Anxiety scales, and lower pain tolerance and SREP sensitization, in patients not showing a CPM response compared with those exhibiting a CPM response (Table 3).

Preliminary analyses indicated that patients with additional pain-related conditions beyond FM (n = 33) did not differ significantly from those without such comorbidities (n = 22) in the evoked pain tests (SREP: t = 0.63, $P = 0.534$; CPM: t = 0.76, $P = 0.453$), nor in key symptoms such as pain intensity (BPI: t = −0.61; $P = 0.542$), fatigue (FSS: t = −0.16; $P = 0.870$), severity of FM symptoms (FIQ-R: t = −0.31, $P = 0.755$), anxiety (HADS-A: t = −0.44; $P = 0.661$), and depression (HADS-D: t = −0.55; $P = 0.581$).

DISCUSSION

This study investigated pain sensitization and endogenous pain inhibition in women with FM and pain-free controls based on the SREP protocol and the CPM paradigm,

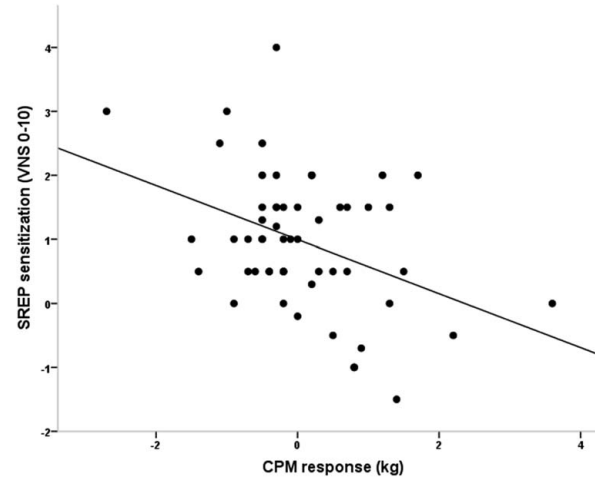

FIGURE 4. Scatterplot and regression line for the association between SREP sensitization and the CPM response fibromyalgia participants. CPM indicates conditioned pain modulation; SREP, slowly repeated evoked pain; VNS, verbal numerical scale.

respectively. Our primary results indicated greater SREP sensitization and a smaller CPM effect in individuals with FM than in pain-free women, suggesting the presence of both pain sensitization and reduced endogenous pain inhibition in the disorder. The magnitude of the CPM response proved predictive of SREP sensitization, which supports the hypothesis that reduced descending pain inhibition is involved in the genesis of pain sensitization in FM. A potential role for reduced endogenous pain inhibition in FM symptomatology is further suggested by our findings that greater CPM was associated with lower FM symptom severity and reduced anxiety and fatigue levels in individuals with FM. Overall, this aligns with the recent conceptualization of nociplastic pain as an additional descriptor or mechanism underlying pain in fibromyalgia syndrome—alongside nociceptive and neuropathic pain, and characterized by a heightened processing and/or reduced inhibition of pain signals at various levels of the nervous system.[24,25]

We further highlight that group comparisons revealed significant differences in all experimentl evoked pain measures. Replicating numerous prior observations,[8,9,15,19]

TABLE 2. Correlations of SREP Sensitization and the CPM Response With Questionnaire Scores in the FMGroup

	CPM	FIQ-R	STAI State	BPI	FSS	HADS anxiety	HADS depression
SREP sensitization							
r	−0.40**	0.12	0.04	0.27*	0.29*	0.21	−0.02
CI 95%							
Lower	−0.58	−0.16	−0.30	0.002	0.03	−0.04	−0.33
Upper	−0.14	0.35	0.33	0.51	0.51	0.41	0.30
CPM response							
r		−0.19	−0.27*	-0.13	−0.35**	-0.33*	−0.11
CI 95%	—						—
Lower	—	−0.42	−0.49	-0.43	-0.52	-0.55	-0.36
Upper	—	0.09	−0.02	0.26	−0.14	-0.11	0.19

**$P < 0.01$.
*$P < 0.05$.
BPI indicates Brief Pain Inventory; CPM, conditioned pain modulation; FIQ, Fibromyalgia Impact Questionnaire—Revised; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; SREP, slowly repeated evoked pain; STAI, State-Trait Anxiety Inventory.

TABLE 3. Comparisons Between FM Participants With and Without CPM Response: Experimental Pain Measures and Questionnaire Scores

	Mean ± SD		CI 95%		
	CPM (n = 22)	No CPM (n = 33)	Lower– upper	t(53)	*P*
Pain threshold (kg)	2.51 ± 1.25	2.26 ± 1.25	−0.93 to 0.44	−0.73	0.235
Pain tolerance (kg)	5.31 ± 1.54	4.12 ± 1.88	−2.16 to −0.23	−2.48	0.008
SREP sensitization	0.56 ± 1.11	1.24 ± 0.94	0.11-0.23	2.41	0.010
FM impact (FIQ-R)	60.03 ± 17.73	68.02 ± 16.73	−1.47 to 17.45	1.69	0.048
State Anxiety (STAI)	22.95 ± 9.55	28.21 ± 10.40	−0.30 to 10.82	1.90	0.032
Anxiety (HADS)	11.50 ± 3.31	13.94 ± 3.91	0.41-4.47	2.41	0.010
Depression (HADS)	8.05 ± 4.82	8.45 ± 4.57	−2.17 to 2.99	0.32	0.375
Pain intensity (BPI)	6.06 ± 1.28	6.12 ± 1.53	−0.74 to 0.85	1.34	0.497
Fatigue (FSS)	40.73 ± 18.61	54.88 ± 11.62	5.05-23.25	3.17	0.002

BPI indicates Brief Pain Inventory; CPM, conditioned pain modulation; FIQ-R, Fibromyalgia Impact Questionnaire—Revised; FM, Fibromyalgia; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; SREP, slowly repeated evoked pain; STAI, State-Trait Anxiety Inventory.

individualss with FM exhibited markedly lower pain threshold and tolerance than pain-free controls. These groups also differed in their responses to the dynamic pain protocols. While pain ratings remained unchanged across the 9 trials of the SREP protocol in pain-free women, they progressively increased over trials in individuals with FM. In accordance with previous studies using the SREP protocol, this confirmed substantial pain sensitization in the disorder.[16,17,19,20] With respect to the CPM paradigm, pain thresholds were higher (ie, pain sensitivity was lower) for trials conducted in the presence of the conditioning stimulus than trials without the conditioning stimulus in pain-free women, which reflects successful induction of descending pain inhibition in controls. In contrast, pain thresholds did not differ based on the presence of the conditioning stimulus in patients. According to categorical analysis, 80% of painb-free women, but only 40% of individuals with FM, exhibited a CPM effect. Although it should be approached with caution, as the observed group differences may be partly attributable to our specific sample characteristics or the particular method used to assess CPM (skinfold pinch), this observation is in accordance with previous findings. Those studies have suggested that, among different chronic pain conditions, FM may be one of the most likely to be associated with impaired CPM.[27,29,47–50] According to literature reviews by Lewis et al[13] and O'Brien et al,[14] alterations in inhibitory pain modulation occur in ~65% of patients with FM, such that the present observation somewhat exceeds this estimation.

The inverse relationship between the magnitude of SREP sensitization and the magnitude of CPM effect in indiiduals with FM constitutes a novel finding of this study. While clinical pain severity and fatigue, represented by the BPI and FSS scores, also correlated positively with SREP sensitization, the association was largest with the CPM response. In multivariable regression analysis, the magnitude of the CPM effect was the only significant predictor of SREP sensitization, independent of the clinical variables. This suggests that neural structures[51] and pathways[52,53] known to be involved in the CPM response (Fig. 5) could also partially mediate SREP sensitization. In general, this finding highlights the potentially strong contribution of dysfunction in descending inhibitory mechanisms to pain sensitization in FM. Such dysfunction may facilitate afferent transmission of nociceptive information through sensitized C and A-delta fibers, as well as neurons from more deeply located mechanoreceptors.[2] Though neither activity of C and A-delta fibers, nor activity within the pain neuromatrix was assessed in the study, the results support the notion that impaired inhibitory mechanisms contribute to exaggerated nociceptive processing, in addition to the influence of ascending pain facilitation pathways. As indicated above, TSP-related processes are unlikely to account for SREP sensitization, as its stimulation frequency is 10-fold lower than in the TSP procedure.[20–22] However, SREP sensitization has previously been shown to correlate positively with TSP, underscoring that the SREP measure likely reflects the influences of both increased ascending facilitation and decreased descending inhibition, both of which likely contribute to pain sensitization in FM.[20] Given the cross-sectional design of the study and the heterogeneity of FM, these relationships should be interpreted with caution. Nevertheless, the findings support the need for longitudinal studies to track the evolution of the associations in line with the variability and progression of central pain sensitization. Such an approach would also enable the identification of individual patterns, beyond group-level averages, thereby contributing to the development of more personalized treatment strategies.

On the cellular level, long-term potentiation of synaptic strength in nociceptive spinal pathways is believed to trigger pain amplification and to mediate neurogenic hyperalgesia in chronic pain conditions such as FM.[54,55] Moreover, in pain-free individuals, descending inhibitory control arising from the brain stem prevents spinal LTP during and after physiological noxious stimulation.[56,57] Functional impairments in these mechanisms may relate to exaggerated nociceptive processing in FM. Recent research has also provided evidence that low-level immune and inflammatory activity in FM sensitize nociceptive pathways, suggesting an immunologic contribution to chronic widespread pain, potentially mediated by polymorphonuclear granulocytes.[58,59] Overall, facilitation of ascending nociceptive pathways due to neuroplasticity and immunologic mechanisms, coupled with impaired descending antinociceptive processes, may lead to increased pain sensitivity characterizing FM. Further research is clearly warranted to more precisely define the specific roles of these variables and their interactions in FM pathology.

In addition to pain symptoms, individuals with FM indicated markedly higher levels of fatigue, depression, and anxiety on the FSS, BPI, HADS, and STAI State Anxiety scales than pain-free women. This is in line with numerous

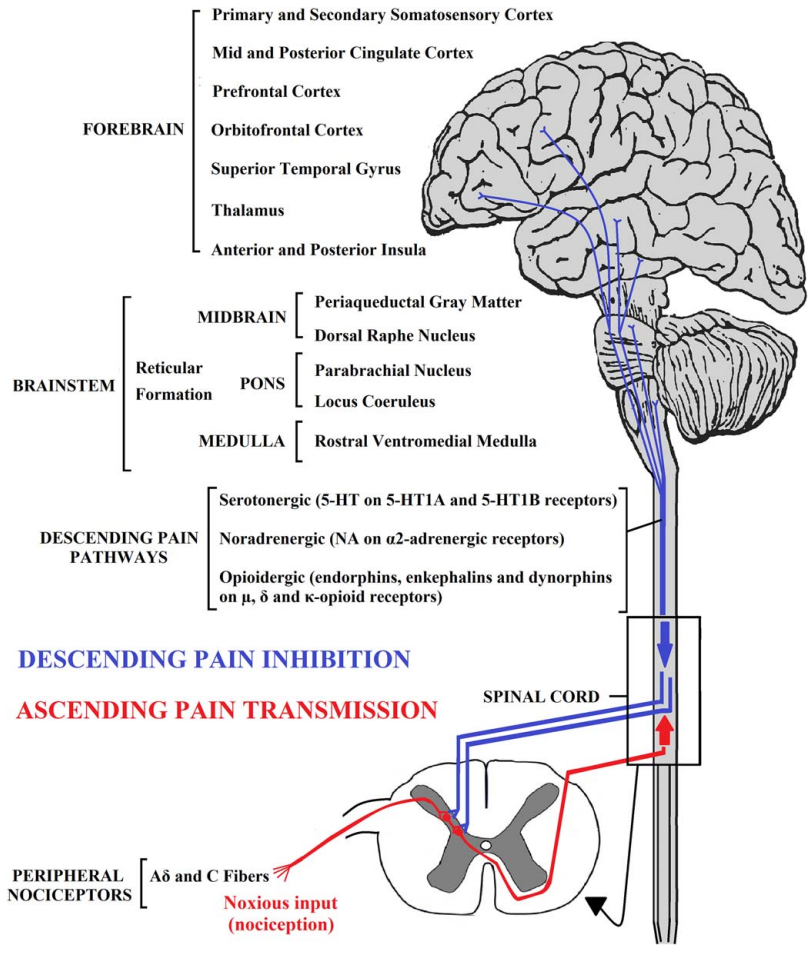

FIGURE 5. Nervous system structures and modulation pathways involved in CPM response, which might also partially mediate SREP sensitization. Descriptive overview of the principal regions and structures of the central nervous system that, according to current scientific evidence, are specifically involved in the conditioned pain modulation response. Also depicted are the noradrenergic, serotonergic, and opioid pathways, along with their respective receptors, which are most directly implicated in this inhibitory pain mechanism.

previous observations and underlines the severe impact of the disorder on physical and mental well-being.[60–62] Analyses within the patient sample indicated that individuals with FMs who did not show a CPM effect, as compared with those who did show a CPM effect, reported greater FM symptom severity on the FIQ-R, as well as greater fatigue and anxiety on the FSS, HADS, and STAI State Anxiety scales. This is consistent with the previously observed inverse association between CPM and the severity of FM symptoms.[33] Given that comorbid pain conditions may exacerbate central sensitization and pain perception in FM,[63] it is relevant to obtain detailed information on their severity, chronicity, and functional impact, particularly in relation to specific combinations of such comorbid conditions. Accordingly, future research should collect more comprehensive information on pain comorbidities and analyze their effect on pain responses and FM impact.

In terms of clinical relevance of our findings, we note a placebo-controlled trial,[64] which observed that one-session application of transcutaneous electrical nerve stimulation (TENS) in patients with FM led to a reduction of pain sensitivity and fatigue, in addition to an increase in the CPM effect. In another controlled trial, daily application of TENS over 4 weeks caused a reduction in both movement-evoked pain and fatigue in patients with FM.[65] TENS reduces central nervous excitability by activation of inhibitory pathways, and as such, these findings support the clinical relevance of deficient pain inhibition in both the pain sensitization and fatigue noted in FM.

The main limitation of the study pertains to the restriction of our pain-evoked measurements to behavioral and self-report variables. Accordingly, all participants completed a familiarization phase with pain-related concepts, received training in the use of the VNS, and were given standardized instructions for each test, which helped minimize potential biases and ensure uniform task comprehension Regarding the CPM paradigm, interdigital web pinching was used to induce conditioned pain. This methodology has demonstrated its efficacy in inducing Diffuse Noxious Inhibitory Control, and has been suggested as a conditioning stimulus able to avoid the confounding influences of cardiovascular pain modulation, as occurs with the use of the cold pressor test.[41,42] In the case of SREP, although the mechanisms of SREP sensitization are still under discussion, this protocol provides a dynamic pain indicator recommended for clinical use due to its strong association with

clinical pain[16] and superior reliability and diagnostic accuracy over TSP in identifying patients with FM.[17] Beyond these tests, we highlight for future research the assessment of central nervous pain sensitization using fMRI or evoked EEG potentials, to examine the role of descending inhibition in a potentially more granular way. Direct recording of C and A-Delta fiber activity would also be useful to better estimate functional changes in ascending pathways during CPM. Another limitation pertains to our sample composition. As only women were included in the study, generalization to both genders is limited. The sample size is sufficient to support meaningful preliminary findings. While there is some imbalance between the FM and control groups, addressing this in future studies with more equal distributed participants and a higher total sample size could further strengthen the validity and comparability of the results. Furthermore, the nonconsideration of other confounding factors, such as lifestyles and environmental influences, may be considered another limitation of the study that must be supplied in future research. Finally, the effects of pain medication and psychoactive drugs on the dependent variables could not be controlled.

In conclusion, this study revealed evidence of impaired endogenous pain inhibition as a component of the pain sensitization characterizing FM. Lack of inhibition may also play a role in the occurrence of physical and mental symptoms of the disorder. Continuation of this line of research may involve assessment of central nervous system correlates of pain sensitization and activity in ascending pathways to better characterize disturbances in the interplay between ascending facilitation and descending inhibitory nociceptive processes in FM.

ACKNOWLEDGMENTS

The authors thank all patients and healthy women who participated in the study.

REFERENCES

1. Amsterdam D, Buskila D. Etiology and triggers in the development of fibromyalgia. In: Ablin JN, Shoenfeld Y, eds. *Fibromyalgia Syndrome*. Springer Nature Switzerland AG; 2021:17–32.
2. Tzadok R. Fibromyalgia: classification, criteria, and diagnosis—what is fibromyalgia?. In: Ablin JN, Shoenfeld Y, eds. *Fibromyalgia Syndrome*. Springer Nature Switzerland AG; 2021:83–89.
3. Clauw DJ, Tzadok R. The neuroscience of fibromyalgia and central sensitization. In: Ablin JN, Shoenfeld Y, eds. *Fibromyalgia Syndrome*. Springer Nature Switzerland AG; 2021: 183–192.
4. de la Coba P, Montoro CI, Reyes del Paso GA, et al. Algometry for the assessment of central sensitisation to pain in fibromyalgia patients: a systematic review. *Ann Med*. 2022;54: 1403–1422.
5. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152:S2–S15.
6. Gracely RH, Geisser ME, Giesecke T, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain*. 2004;127:835–843.
7. Gracely RH, Petzke F, Wolf JM, et al. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheumatol*. 2002;46:1333–1343.
8. Duschek S, Mannhart T, Winkelmann A, et al. Cerebral blood flow dynamics during pain processing in patients with fibromyalgia syndrome. *Psychosom Med*. 2012;74:802–809.
9. Montoro CI, Duschek S, Muñoz Ladrón de Guevara C, et al. Patterns of cerebral blood flow modulation during painful stimulation in fibromyalgia: a transcranial Doppler sonography study. *Pain Med*. 2016;17:2256–2267.
10. Reyes del Paso GA, Garrido S, Pulgar A, et al. Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. *J Psychosom Res*. 2011; 70:125–134.
11. Staud R, Bovee CE, Robinson ME, et al. Cutaneous C-fiber pain abnormalities of fibromyalgia patients are specifically related to temporal summation. *Pain*. 2008;139:315–323.
12. Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol*. 2007;26:465–473.
13. Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. *J Pain*. 2012;13:936–944.
14. O'Brien AT, Deitos A, Pego YT, et al. Defective endogenous pain modulation in fibromyalgia: a meta-analysis of temporal summation and conditioned pain modulation paradigms. *J Pain*. 2018;19:819–836.
15. Arendt-Nielsen L, Graven-Nielsen T. Central sensitization in fibromyalgia and other musculoskeletal disorders. *Curr Pain Headache Rep*. 2003;7:355–361.
16. de la Coba P, Bruehl S, Moreno-Padilla M, et al. Responses to slowly repeated evoked pain stimuli in fibromyalgia patients: evidence of enhanced pain sensitization. *Pain Med*. 2017;18: 1778–1786.
17. de la Coba P, Bruehl S, Reyes del Paso GA. Addition of slowly repeated evoked pain responses to clinical symptoms enhances fibromyalgia diagnostic accuracy. *Pain Med*. 2020;21:3479–3487.
18. Garcia-Hernandez A, de la Coba P, Reyes del Paso GA. Blunted sudomotor reactivity in fibromyalgia is associated with levels of depression. *Clin Exp Rheumatol*. 2024;42:1170–1178.
19. Garcia-Hernandez A, de la Coba P, Reyes del Paso GA. Central sensitisation to pain and autonomic deficiencies in fibromyalgia. *Clin Exp Rheumatol*. 2022;40:1202–1209.
20. de la Coba P, Bruehl S, Galvez-Sánchez CM, et al. Slowly repeated evoked pain as a marker of central sensitization in fibromyalgia: diagnostic accuracy and reliability in comparison with temporal summation of pain. *Psychosom Med*. 2018;80:573–580.
21. Price DD. Characteristics of second pain and flexion reflexes indicative of prolonged central summation. *Exp Neurol*. 1971; 37:371–387.
22. Price DD, Hu JW, Dubner R, et al. Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses. *Pain*. 1977;3:57–68.
23. de la Coba P, Bruehl S, Reyes del Paso GA. Slowly repeated evoked pain (SREP) as a central sensitization marker: a study in episodic migraine patients. *Sci Rep*. 2021;11:4582.
24. Fitzcharles MA, Cohen SP, Clauw DJ, et al. Nociplastic pain: towards an understanding of prevalent pain conditions. *The Lancet*. 2021;397:2098–2110.
25. Kaplan CM, Kelleher E, Irani A, et al. Deciphering nociplastic pain: clinical features, risk factors and potential mechanisms. *Nat Rev Neurol*. 2024;20:347–363.
26. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol*. 2010;23:611–615.
27. Schoen CJ, Ablin JN, Ichesco E, et al. A novel paradigm to evaluate conditioned pain modulation in fibromyalgia. *J Pain Res*. 2016;9:711–719.
28. Petersen KKS, O'Neill S, Blichfeldt-Eckhardt MR, et al. Pain profiles and variability in temporal summation of pain and conditioned pain modulation in pain-free individuals and patients with low back pain, osteoarthritis, and fibromyalgia. *Eur J Pain*. 2025;29:e4741.
29. Potvin S, Marchand S. Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. *Pain*. 2016;157:1704–1710.
30. Nahman-Averbuch H, Nir RR, Sprecher E, et al. Psychological factors and conditioned pain modulation. *Clin J Pain*. 2016;32: 541–554.

31. Staffe AT, Bech MW, Clemmensen SLK, et al. Total sleep deprivation increases pain sensitivity, impairs conditioned pain modulation and facilitates temporal summation of pain in healthy participants. *PLoS One*. 2019;14:e0225849.
32. Weissman-Fogel I, Sprecher E, Pud D. Effects of catastrophizing on pain perception and pain modulation. *Exp Brain Res*. 2008;186:79–85.
33. Soldatelli MD, Siepmann T, Illigens BMW, et al. Mapping of predictors of the disengagement of the descending inhibitory pain modulation system in fibromyalgia: an exploratory study. *Br J Pain*. 2021;15:221–233.
34. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res*. 2010;62:600–610.
35. Mas AJ, Carmona L, Valverde M, et al. Prevalence and impact of fibromyalgia on function and quality of life in individuals from the general population: results from a nationwide study in Spain. *Clin Exp Rheumatol*. 2008;26:519–526.
36. Badia X, Muriel C, Gracia A, et al. Validation of the Spanish version of the Brief Pain Inventory in patients with oncological pain. *Med Clin (Barc)*. 2003;120:52–9.
37. Bulbena A, Zuñiga A, Martín-Carrasco M, et al. *Gravedad Clínica en Psiquiatría*. Masson; 2000.
38. Caro Y, Ibáñez E. Hospital Anxiety and Depression Scale. Its practical usefulness in Health Psychology. *Bol Psic*. 1992;36:43–69.
39. Spielberger CD, Gonzalez-Reigosa F, Martinez-Urrutia A, et al. Development of the Spanish edition of the State-Trait Anxiety Inventory. *Interam J Psychol*. 1971;5:145–158.
40. Salgueiro M, García-Leiva JM, Ballesteros J, et al. Validation of a Spanish version of the Revised Fibromyalgia Impact Questionnaire (FIQR). *Health Qual Life Outcomes*. 2013;11:1–8.
41. Bossmann T, Brauner T, Lowak H, et al. Reliability of conditioned pain modulation for the assessment of endogenous pain control pathways. *Neurol Psychiatry Brain Res*. 2016;22:155–161.
42. Streff A, Kuehl LK, Michaux G, et al. Differential physiological effects during tonic painful hand immersion tests using hot and ice water. *Eur J Pain*. 2010;14:266–272.
43. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, et al. Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain*. 2010;14:339.
44. Yarnitsky D, Crispel Y, Eisenberg E, et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain*. 2008;138:22–28.
45. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *The Lancet*. 2007;370:1453–1457.
46. Cohen J, Cohen P, West SG, et al. *Applied multiple regression/correlation analysis for the behavioral sciences*. Lawrence Erlbaum Associates; 2003.
47. Jensen KB, Kosek E, Petzke F, et al. Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in rACC during provoked pain. *Pain*. 2009;144:95–100.
48. Julien N, Goffaux P, Arsenault P, et al. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain*. 2005;114:295–302.
49. Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. *Pain*. 1997;70:41–51.
50. Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. *Clin J Pain*. 1997;13:189–196.
51. Nahman-Averbuch H, Timmers I. Neural mechanisms underlying the conditioned pain modulation response: a narrative review of neuroimaging studies. *Pain*. 2023;164:E25–E46.
52. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. *J Clin Invest*. 2010;120:3779–3387.
53. Lubejko ST, Livrizzi G, Buczynski SA, et al. Inputs to the locus coeruleus from the periaqueductal gray and rostroventral medulla shape opioid-mediated descending pain modulation. *Sci Adv*. 2024;10:eadj9581.
54. Rygh LJ, Svendsen F, Fiskå A, et al. Long-term potentiation in spinal nociceptive systems—how acute pain may become chronic. *Psychoneuroendocrinology*. 2005;30:959–964.
55. Sandkühler J. Learning and memory in pain pathways. *Pain*. 2000;88:113–118.
56. Gjerstad J, Tjølsen A, Hole K. Induction of long-term potentiation of single wide dynamic range neurones in the dorsal horn is inhibited by descending pathways. *Pain*. 2001;91:263–268.
57. Svendsen F, Tjølsen A, Gjerstad J, et al. Long term potentiation of single WDR neurons in spinalized rats. *Brain Res*. 1999;816:487–492.
58. Caxaria S, Bharde S, Fuller AM, et al. Neutrophils infiltrate sensory ganglia and mediate chronic widespread pain in fibromyalgia. *Proc Natl Acad Sci*. 2023;120:e2211631120.
59. Dempsey LA. Neutrophils contribute to fibromyalgia. *Nat Immunol*. 2023;24:886.
60. Finan PH, Zautra AJ. Fibromyalgia and fatigue: central processing, widespread dysfunction. *PM&R*. 2010;2:431–437.
61. Galvez-Sánchez CM, Duschek S, Reyes del Paso GA. Psychological impact of fibromyalgia: current perspectives. *Psychol Res Behav Manag*. 2019;12:117–127.
62. Galvez-Sánchez CM, Montoro C, Reyes del Paso GA, et al. Depression and trait-anxiety mediate the influence of clinical pain on health-related quality in fibromyalgia. *J Affect Disord*. 2020;265:486–495.
63. Kindler LL, Bennett RM, Jones KD. Central sensitivity syndromes: mounting pathophysiologic evidence to link fibromyalgia with other common chronic pain disorders. *Pain Manag Nurs*. 2009;12:15–24.
64. Dailey DL, Rakel BA, Vance CG, et al. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. *Pain*. 2013;154:2554–2562.
65. Dailey DL, Vance CG, Rakel BA, et al. Transcutaneous electrical nerve stimulation reduces movement-evoked pain and fatigue: a randomized, controlled trial. *Arthritis Rheumatol*. 2020;72:824–836.

