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RESEARCH ARTICLE

Conditioned pain modulation and psychological factors in young adults with recurrent or chronic neck pain

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Abstract

Background: Controversy exists with the presence of alterations in descending pain inhibition mechanisms in patients with non-specific neck pain (NSNP). The aim of the present study was to evaluate the status of conditioned pain modulation CPM, remote pressure pain thresholds (PPT), and psychological factors in a specific subgroup of patients with NSNP such as young adult students. In addition, possible associations between CPM, psychological factors, and pain characteristics were analyzed.

Methods: Thirty students with recurrent or chronic NSNP and 30 pain-free students were included in this cross-sectional study. The following measures were assessed: CPM, remote PPT, psychological factors (depression, anxiety, pain catastrophizing, and kinesiophobia), pain characteristics (duration, intensity, severity of chronic pain, interference with daily life), and central sensitization inventory (CSI).

Results: No significant differences were found in the efficacy of CPM between students with chronic or recurrent NSNP and pain-free students (β coefficient = −0.67; 95% CI = −1.54, 0.20). However, students with pain showed a significantly higher remote PPT (mean difference = −1.94; 95% CI = −2.71, −1.18). and a greater presence of anxious (mean difference = 6; 95% CI = 2, 9) and depressive symptoms (mean difference = 8.57; 95% CI = 3.97, 13.16). In addition, significant moderate or strong correlations were found between CPM and pain intensity (partial r = 0.41), pain catastrophizing and mean pain intensity (r = 0.37), grade (r = 0.50), and interference

of pain ($r=0.57$), kinesiophobia and disability ($r=0.38$), and depression and CSI ($r=0.39$).

Conclusions: Young adult students with chronic or recurrent NSNP present remote hyperalgesia and symptoms of depression and anxiety but not dysfunctional CPM.

KEYWORDS
central pain mechanism, central sensitization, conditioned pain modulation, neck pain, psychological factors

INTRODUCTION

Neck pain is a highly prevalent condition that causes considerable pain, disability, and economic costs.[1,2] The prevalence is higher in women and increases with age, peaking between 70 and 74 years of age.[3,4] However, a high prevalence of neck pain has been found in University students despite their young age.[5,6] Regardless of high investments in the study and treatment of neck pain, the age-standardized point prevalence, annual incidence, and years lived with disability due to neck pain have not changed over the last 30 years,[2] and more than one-fifth of acute neck pain patients continue from suffering from recurrent episodes or persistent pain.[7] Most patients with neck pain did not show pathoanatomical causes that could explain their pain[8] or associated trauma, being diagnosed with non-specific neck pain (NSNP). Therefore, knowledge of the pain mechanisms involved in different subgroups of NSNP patients is very relevant to progress toward precision medicine.

Numerous studies have tried to investigate whether there are alterations in endogenous pain modulation mechanisms through quantitative sensory testing (QST) in patients with chronic NSNP. In addition, evidence suggests that these measurements may have predictive value for clinical pain and treatment response.[9] The meta-analysis conducted by Xie et al.[10] showed significantly higher remote pressure pain thresholds (PPT) in NSNP patients compared to pain-free controls. Those results suggested the existence of generalized hyperalgesia in these patients. Conditioned pain modulation (CPM) is a QST that attempts to assess endogenous inhibitory pain modulation capacity in humans. This paradigm assesses the "pain inhibits pain" effect by modulating the perceived pain intensity or by increasing the pain threshold to a noxious test stimulus by another noxious "conditioning" stimulus (COS) applied heterotopically.[11] It is not yet clear the underlying mechanisms that are produced in the CPM paradigm[11,12] and therefore the effect of the complex facilitatory and inhibitory mechanisms of pain processing is being recorded.[13] Several studies have investigated the efficacy of CPM in patients with chronic NSNP compared to a control group of pain-free participants. The results are controversial, with some studies concluding that patients with chronic NSNP have a lower efficacy of CPM.[14,15] Nevertheless, others found no significant differences between groups.[16–20] These differences may be due to heterogeneity between studies in terms of measurement methodologies and analysis of CPM results. In addition, studies differ significantly in the mean age of participants and the percentage of females or males. Significantly higher efficacy of CPM has been reported in healthy young adults compared to healthy older people probably due to age-related hormonal and neural changes.[21] Consequently, the possible involvement of pain inhibitory mechanisms might be different for disparate age groups with NSNP. To our knowledge, there are no studies evaluating CPM in a young adult population with a high prevalence of recurrent or persistent NSNP such as health science students.

Evidence on the association between CPM and clinical manifestations is very limited. Previous studies that have included these patients have found no associations with pain duration, cervical disability, or pain severity and conflicting results regarding pain intensity.[17,18,22,23] These findings call into question the possibility that CPM may be a valid biomarker for this population. Therefore, further research aimed at clarifying the value of CPM in chronic NSNP is needed.

In a mechanism-based approach for pain management built on the biopsychosocial model, it is important to understand the pain-relevant psychological factors.[24] Depression symptoms,[6,14,25–27] anxiety symptoms,[6,25,27] and pain catastrophism[14,26–28] have been reported in patients with NSNP. Neuroimaging studies show that psychological factors (expectation, emotion, or attention, among others) affect the neuronal activity of brain regions involved in descending pain inhibition.[29,30] Therefore, it is suspected that pain catastrophizing and depressive and anxious symptoms may contribute to alterations in central pain processing. Previous systematic reviews and meta-analyses have not drawn clear conclusions on the association between CPM and psychological factors.[21,31] In patients with NSNP, associations of disability or pain intensity with catastrophizing[14,27,28,32] and anxiety[27] have been reported but not with CPM. To our knowledge, there are no studies that have evaluated the associations of psychological factors with CPM and pain characteristics in young adult students with NSNP.

For the reasons outlined above, the first aim of this study was to determine the CPM efficacy in students

with chronic or recurrent neck pain compared to pain-free students. The second objective was to estimate differences in remote PPT and psychological parameters and its influence on CPM results. The third aim was to investigate correlations between CPM and pain characteristics. At last, correlations between psychological factors and pain characteristics were explored.

MATERIALS AND METHODS

Study design

A cross-sectional study following the checklist Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[33] was conducted. This is a secondary investigation of a clinical trial with a ClinicalTrials.gov registration ID: NCT05680688. Thirty students with NSNP from the clinical trial were matched by sex and age to a group of pain-free students. Participant assessments were carried out at the health sciences campus of the health sciences campus of the Rey Juan Carlos University in Alcorcón (Madrid, Spain). The study was approved by the Ethics Committee of Rey Juan Carlos University under the protocol number: ENM 35/222803202210022.

Participants

Both neck pain and pain-free students were recruited through student email messages, social media posters, and oral presentations in classrooms.

Participants between 18 and 34 years old, studying or doing an internship in the field of health sciences at one of the Universities belonging to the Community of Madrid (Spain). were included. Inclusion criteria: participants suffering from NSNP (pain in the neck region that is not attributable to a known specific cause such as herniated disc, myelopathy, fractures, spinal stenosis, neoplasm, etc., nor is it associated with traumatic causes such as whiplash) who started more than 3 months ago and has persisted or has experienced two or more episodes with mean pain score ≥2 on the Numerical Rating Scale (NRS)[34] in the last week, and must have pain on the day of the measurement. Exclusion criteria: the presence of signs of radiculopathy or neuropathic pain; neck surgery; inflammatory rheumatic, neurological, cardiorespiratory, oncological, or psychiatric diseases; pregnancy and not being able to read and understand Spanish to fill out the questionnaires.

Controls were pain-free students at the time of recruitment and the assessment session, without having experienced any episodes of chronic pain (pain for more than 3 months) in the last 6 months.

Measures

Central pain processing

Conditioned pain modulation

CPM has shown high test–retest reliability.[35] The CPM has demonstrated high test–retest reliability.[35] As a test stimulus, remote PPT was assessed on the nail bed of the thumb on the symptomatic side in NSNP students and on the right side in pain-free students. A hand-held pressure algometer (Model FDIX, Wagner Instrument Mark), consisting of a 1 cm^2 rubber head attached to a manometer was used to apply perpendicular pressure at a rate of 1 kg/s until the patient reported the onset of pain.[36] A sphygmomanometer was used for the COS. It was placed on the arm of the asymptomatic side in students with NSNP and on the left arm in pain-free students, with its lower edge 3 cm proximal to the ulnar fossa. The cuff was inflated to 260 mmHg and held until the subject perceived pain of 6–7/10 on the Numeric Pain Rating Scale (NPRS).[37] The PPT was measured again, and cuff pressure was released. A final PPT measurement was performed to assess the sustained effect of CPM at 1 min.[38] CPM was considered as the change generated on the baseline PPT by COS. To describe its value, the baseline PPT was subtracted from the PPT during COS.

Psychological factors

The state anxiety inventory (STAI-S)

The Spanish-adapted version of The State Anxiety Inventory (STAI-S) was used.[39] This questionnaire comprises two subsections of 20 items each for the measurement of anxiety as a state, with a 4-point Likert-type response (0: not at all; 3: very much). Scores range from 0 to 60 points, with higher scores indicating greater anxiety. It has demonstrated good reliability and validity.[40,41]

Beck depression Inventory-II

It is the most widely used questionnaire worldwide to assess depression. The Spanish adaptation of the Beck-II depression inventory was used.[42,43] The total score ranges from 0 to 63 points. A change of 5 points corresponds to a minimally important clinical difference.[42] It has excellent internal consistency with an α Cronbach's α of 0.91,[43] is both reliable[44] and valid,[45] and is a standard measurement instrument for depression in medical and psychological research.

Pain catastrophizing scale

The Spanish version of the Pain Catastrophizing Scale (PCS)[46] assesses catastrophizing cognitions and behaviors concerning pain in clinical and non-clinical populations. It has 13 items and each one is rated on a 5-point scale: 0 (not at all) to 4 (all the time). It comprises 3

dimensions: rumination, magnification, and despair. The theoretical range of the instrument is between 0 and 52, with low scores indicating low catastrophism and high values indicating high catastrophism. The Spanish version has consistency with Cronbach's α of 0.79, a test–retest reliability with an intraclass correlation coefficient of 0.84, and a sensitivity to change with an effect size ≤2.[46]

Tampa scale for Kinesiophobia

This is an 11-item scale that assesses the degree of fear of movement and (re)injury. Each item is scored from 1 to 4 according to the degree of agreement with the statement (1: do not agree at all; 4: strongly agree). The validated Spanish version of the 11-item scale has a total score of 11 to 44 items and has two subscales: activity avoidance and harm. It has demonstrated good internal consistency with a Cronbach's α of 0.79.[47,48]

Pain characteristics

Numeric Pain Rating Scale

Pain intensity was evaluated with a Numeric Pain Rating Scale (NPRS). The score is recorded on a Likert scale ranging from 0 (no pain) to 10 (the worst pain ever felt). The NPRS has a moderately reliable ICC of 0.76 and a clinically important difference of 13%.[49]

Graded Chronic Pain Scale

The Chronic Pain Grade Questionnaire is a self-report instrument composed of 7 items in an 11-point Likert format, with a total range of 0 to 70 points.[50] It was found to be valid and reliable ($\alpha = 0.91$) for use in a general population.[51] The Spanish version of the questionnaire was used, which has proven to be a valid and reliable tool for measuring chronic pain.[52]

Neck Disability Index

The validated Spanish version of the Neck Disability Index measures the level of disability perceived by the patient as a consequence of neck pain.[53] It consists of 10 items, related to functional activities of daily living, pain intensity, ability to concentrate, ability to work, and headache. The total score ranges from 0 (good function) to 50 (disability). The reliability (ICC, 0.73–0.98), construct validity, and responsiveness to change have been demonstrated in various populations.[54]

Central Sensitization Inventory

The Central Sensitization Inventory (CSI) is a self-administered questionnaire that assesses the presence of symptoms that may be related to the presence of central sensitization (CS).[55] Part A evaluates a total of 25 symptoms on a 5-point Likert scale with total score ranging from 0 to 100. Its result has been shown to be more associated with the presence of pain-related psychological symptoms than with pain sensitivity.[56] It was found to have high reliability and validity (test–retest reliability = 0.82; Cronbach's alpha = 0.88).[57]

Sample size calculation

The sample size was calculated to detect a difference in CPM between cases and controls like a previous similar study.[15] With a significance level of 0.05, 95% power, two-tailed, and using the means and standard deviations of the reference study (cases: 0.1 [0.46]; controls: 0.66 [0.68]),[15] it was established that a total of 30 students were required in each group. As this study belongs to a larger project with more students with neck pain, 30 of the total sample were selected by individual matching by sex and age (+ − 3 years) with the 30 pain-free controls. Each pain-free student was matched to the student with NSNP closest in age following the order in which they had been evaluated.

Statistical analysis

Normality was checked with the Shapiro–Wilk, Skewness, and kurtosis tests and by visual assessment of the box and the standardized normal probability plots. Normally distributed data were reported as means and standard deviations (SD) and non-normally distributed data as the median, and interquartile range (IQR). To assess between-group differences, and whether the data were normally distributed, the Student's t-test was used for homogeneous variances (if Levene's test $p \geq 0.05$) or for unequal variances (if Levene's test $p < 0.05$). If the data were not normally distributed, the Wiconxon rank-sum test was used. P values of <0.05 were considered significant. Parametric and non-parametric 95% confidence intervals were calculated for mean differences between groups. In the case of CPM, in addition to analyzing differences by the conventional method using the above tests, to account for the influence of baseline PPT on PPT during COS, it was also analyzed using a multiple linear regression model. In this model, the PPT during the COS was included as a dependent variable, the group (neck pain or pain-free) was included as an independent variable, and it was adjusted for the baseline PPT. The results of both methods of CPM analysis will be presented to explore possible differences, however, the adjusted regression model will be the reference method to conclude. In order to assess the possible influence of psychological variables on CPM, the covariates BDI, STAI-S, and PCS were included in the above model. A p-value <0.05 of the psychological variables in the model was considered a significant association with CPM. The variables age and sex were not included in the model because they were controlled by matching cases and controls. The psychological parameter TSK was not included in the model because we considered reverse causality likely.

Correlations between CPM and pain characteristics were assessed in students with chronic or recurrent neck pain. For this purpose, partial correlation coefficients adjusted for baseline PPT were evaluated between PPT during COS and different pain characteristics. To assess correlations between psychological parameters and pain, Pearson's correlation coefficients were calculated when at least one of the two variables was normally distributed. Spearman's correlation coefficient was used when no variables were normally distributed. A significant correlation was considered when the p-value was <0.05. Correlation coefficient values <0.3 were considered low correlation, 0.3–0.5 moderate, and >0.5 strong. Statistical analyses including sample size calculation were conducted in STATA (IC 16.1, StataCorp LLC, Lakeway Drive College Station, USA).

RESULTS

Demographic characteristics are presented in Table 1. There were no statistically significant differences in age, height, weight, BMI, and degree of physical activity between groups. Due to the individual matching, both groups had the same number of females and males.

Conditioned pain modulation and psychological factors

Scores on the BDI and STAI-S were significantly higher in the NSNP group than in pain-free controls. There were no significant differences in PCS and TSK between groups (Table 2).

As for CPM, when a comparison of means of the difference between the PPT during COS minus the baseline PPT was performed, it was significantly higher in pain-free controls than in students with neck pain (mean difference = −0.92; 95% CI = −1.65, −0.19; p = 0.015). Scores on the remote baseline PPT were significantly higher in controls (mean difference = −1.94; 95% CI = −2.71; −1.18; p < 0.001) (Table 2) (Figure 1). However, multiple linear regression analysis adjusting for the baseline PPT showed that there were no significant differences (β coefficient = −0.67; 95% CI = −1.54, 0.20; p = 0.132). When the model was further adjusted for psychological variables, no significant differences were also shown (β coefficient = −0.57; 95% CI = −1.57, 0.42; p = 0.252) (Table 3). None of the psychological variables introduced in the model were significantly associated with the CPM. Due to the limited sample size and the lack of association of psychological variables with CPM in the full model, the results of the initial regression model were considered to analyze differences in CPM between groups.

Correlations between CPM and pain characteristics

Partial correlation analyses adjusted for baseline PPT showed a significant correlation between CPM and mean pain intensity in the last week (partial r = −0.41, p = 0.026) (Table 4).

Correlations between psychological factors and pain characteristics

Pearson correlation identified a moderate positive correlation between PCS and mean pain intensity in the last week (r = 0.37; p = 0.042) and between PCS and GCPS (r = 0.50; p = 0.005). There was also a significantly strong

TABLE 1 Demographic and clinical characteristics of nonspecific neck pain patients and pain-free controls.

	Neck pain (n = 30)	Pain-free controls (n = 30)	Difference (95% CI)	Statistic	Between group p
Sex (f/m)	24/6	24/6			1.000
Age (y)[b]	23 (19, 25)	21 (20, 24)	0 (−1, 2)	z = 0.50	0.618
Height (cm)[b]	163 (160, 173)	167 (162, 171)	–1 (−5, 3)	z = −0.61	0.543
Weight (kg)[b]	59.5 (55, 68)	58.5 (55, 66)	0.5 (−4.5, 5)	z = 0.21	0.836
BMI (kg/m^2)[b]	21.8 (20.3, 24.5)	21.4 (20.6, 23.7)	0.53 (−0.65, 1.80)	z = 0.90	0.367
Pain duration (mo)[b]	36 (24, 62)				
Current Pain intensity (NRS 0–10)[a]	3.67 (1.52)				
Mean Pain intensity in the last week (NPRS 0–10)[a]	4.68 (1.40)				
Graded Chronic Pain Scale (0–70)[a]	28.3 (10.61)				
Central Sensitization Inventory (0–100)[a]	37.7 (11.2)				
Neck Disability Index (0–50)[a]	10 (4.2)				

Abbreviations: BMI, body mass index; CI, confidence interval; f, female; m, male; mo, month; NRS, numerical pain rating scale; y,years.

Note: Bold indicates significant (p < 0.05).

[a]Data were normally distributed in both groups and consequently: means and standard deviations are presented.

[b]The data were not normally distributed in any of the groups and consequently: medians and interquartile ranges are presented.

TABLE 2 Comparison of conditioned pain modulation and psychological factors between non-specific neck pain patients and pain-free controls.

	Neck pain ($n=30$)	Pain-free controls ($n=30$)	Difference (95% CI)	Statistic	Between-group p
PPT thumb (kg/cm^2)[a]	3.62 (0.97)	5.56 (1.85)	−1.94 (−2.71, −1.18)	$t=-5.09$	**<0.001**
CPM (difference scores, kg/cm^2)[a]	1.18 (1.14)	2.10 (1.64)	- 0.92 (−1.65, −0.19)	$z=-4.59$	**0.015**
Pain Catastrophizing Scale (0–52)[b]	6 (4–13)	7 (1–15)	1 (−3, 4)	$z=0.45$	0.657
Tampa Scale for Kinesophobia (0–44)[a]	19.3 (4.7)	18.4 (5.7)	0.93 (−1.75, 3.62)	$t=0.70$	0.490
Beck Depression Inventory-II (0–63)[b]	10 (6–13)	3 (0–8)	6 (2, 9)	$z=3.22$	**0.001**
State Anxiety Inventory (0–60)[a]	24.9 (4.3)	16.3 (11.7)	8.57 (3.97, 13.16)	$t=3.78$	**<0.001**

Abbreviations: CI, confidence interval; CPM, conditioned pain modulation; PPT, pressure pain threshold.

Note: Bold indicates significant ($p<0.05$).

[a]Data were normally distributed in both groups and consequently: means and standard deviations are presented.

[b]The data were not normally distributed in any of the groups and consequently: medians and interquartile ranges are presented.

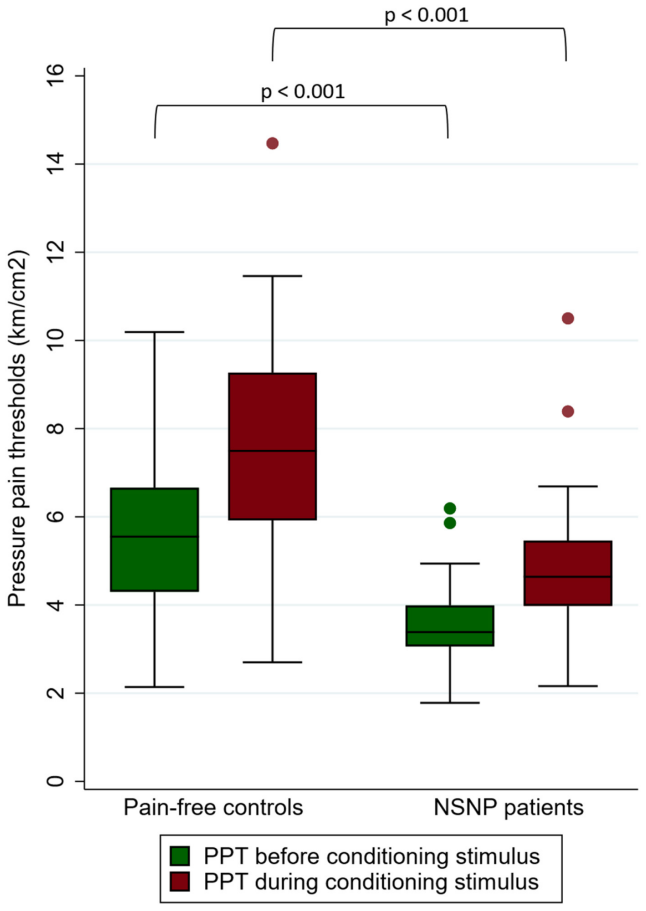

FIGURE 1 Comparison of CPM between NSNP and pain-free students.

correlation between PCS and NDI ($r=0.057$, $p=0.001$). TSK showed a moderate positive correlation with NDI ($r=0.38$, $p=0.038$). There was also a moderate positive correlation between BDI and CSI ($r=0.39$, $p=0.033$). No correlation was identified between STAI-S and pain characteristics (Table 5).

DISCUSSION

The results suggest that students with chronic or recurrent NSNP do not have lower CPM efficacy than pain-free students. However, significant differences were found in thumb PPT suggesting the presence of remote hyperalgesia in these patients. In terms of psychological parameters, the study revealed the presence of depressive and anxiety symptoms in neck pain participants compared to pain-free controls. Furthermore, no differences were found in pain catastrophizing and kinesiophobia.

On the other hand, the study suggests associations between CPM and pain intensity, between pain catastrophizing and pain severity and disability, between kinesiophobia and disability, and between depressive symptoms and CSI.

Comparison of CPM between NSNP and pain-free students

Experts recommend reporting the CPM as the change in the stimulus test score during or after the COS with respect to the baseline score.[58] Most studies use these change values to account for baseline imbalances between groups. However, analyzing the change does not control for baseline imbalance due to the phenomenon of regression to the mean.[59–61] In this case, it is very likely that baseline PPT is positively correlated with change because participants with higher baseline PPT may have a greater inhibitory response to COS. This relationship between baseline status and intervention effect has a generic name in the statistical literature: "the relation between change and initial value".[62] A better approach is to use a regression model[59] used in the present study, in which PPT during COS is entered as the dependent variable, the group as the independent variable and is adjusted for baseline PPT. This method adjusts the PPT during COS of each patient

TABLE 3 Multiple linear regression analysis for conditioned pain modulation.

Initial adjustment			
Variables	**β coefficient (95% CI)**	**SE**	***p*-value**
Group (Neck Pain-Control)	−0.67 (−1.54, 0.20)	0.44	0.132
Baseline PPT	1.13 (0.88,1.38)	0.13	<0.001
Full adjustment			
Variables	β Coefficient (95% CI)	SE	*p*-value
Group (Neck Pain-Control)	−0.57 (−1,57, 0.42)	0.50	0.252
Baseline PPT	1.12 (0.87, 1.38)	0.13	<0.001
BDI	0.02 (−0.04, 0.07)	0.03	0.521
STAI-S	−0.02 (−0.07, 0.02)	0.02	0.326
PCS	−0.01 (−0.06, 0.04)	0.02	0.731

Abbreviations: BDI, beck depression inventory tampa; CI, confidence interval; PCS, pain catastrophizing scale; PPT, pressure pain threshold; SE, standard error; STAI-S, state anxiety inventory.

Note: Multiple regression analysis with PPT during conditioning stimulus as the dependent variable, the group (with neck pain or without pain) as the independent variable, and adjusted for baseline PPT. For full adjustment, the covariates BDI, STAI-S, and PCS were included in the model.

TABLE 4 Correlations between conditioned pain modulation and pain characteristics.

Variables	***N***	**Partial *r***	**Partial r^2**	***p*-value**
Current Pain intensity	30	−0.36	0.13	0.056
Baseline PPT		0.81	0.64	**<0.001**
Mean pain intensity (last week)	30	−0.41	0.17	**0.026**
Baseline PPT		0.82	0.67	**<0.001**
Pain duration	30	0.05	0.00	0.792
Baseline PPT		0.78	0.61	**<0.001**
GCPS	30	−0.21	0.04	0.277
Baseline PPT		0.79	0.63	**<0.001**
CSI	30	−0.35	0.12	0.062
Baseline PPT		0.81	0.66	**<0.001**
NDI	30	−0.32	0.10	0.091
Baseline PPT		0.81	0.65	**<0.001**

Abbreviations: CSI, central sensitization inventory; GCPS, graded chronic pain scale; NDI, neck disability index; r, correlation coefficient.

Note: Partial correlation analysis between PPT during conditioning stimulus and pain characteristics adjusted by baseline PPT.

with his or her baseline PPT with the advantage of not being affected by baseline differences. In the present study, significant differences were found between groups when analyzed using the change values but not when the proposed regression model was used. The significant differences found in baseline PPTs between groups could explain why the analysis using change showed differences in CPM, since it does not control for baseline imbalance. In other words, these findings suggest that students with chronic or recurrent NSNP present remote mechanical hyperalgesia but not CPM impairment. These findings found in the remote PPT coincide with those reported in a previous meta-analysis.[10] However, comparison with previous studies does not allow clear conclusions on the efficacy of CPM in this population due to the performance of the analyses using change values and the use of different measurement protocols.[14–20]

A possible explanation for not finding impaired CPM in this subgroup of patients with chronic or recurrent NSNP may be the mean age. Greater efficacy of CPM has been reported in healthy young adults compared to healthy older people.[21] Therefore, the NSNP patients in the present study may not have suffered significant changes in the efficacy of CPM, as it is not yet influenced by age-related hormonal and neural changes. In addition, the authors decided to include patients with recurrent NSNP as well, as it is a common condition in the health science student population due to stress and long hours of clinical and/or laboratory practice. These patients have pain-free periods, and they are likely to have less impairment of pain processing mechanisms. Future studies should investigate whether there are differences in the efficacy of CPM between patients with chronic NSNP and recurrent NSNP.

TABLE 5 Correlation between psychological factors and pain characteristics.

	PCS		TSK		BDI		STAI-S	
Variables	***r* (CI)**	***p*-value**	***r* (CI)**	***p*-value**	***r* (CI)**	***p*-value**	***r* (CI)**	***p*-value**
Pain duration	0.17[b] (−0.21, 0.50)	0.378	0.08[a] (−0.29, 0.43)	0.683	0.04[a] (−0.33, 0.39)	0.850	−0.13[a] (−0.47, 0.24)	0.488
Mean Pain intensity	0.37[a] (0.02, 0.65)	**0.042**	0.20[a] (−0.17, 0.52)	0.290	0.00[a] (−0.36, 0.36)	0.997	0.00[a] (−0.36, 0.36)	0.987
GCPS	0.50[a] (0.17, 0.73)	**0.005**	0.03[a] (−0.33, 0.39)	0.863	0.06[a] (−0.30, 0.41)	0.736	0.01[a] (−0.35, 0.37)	0.940
CSI	0.31[a] (−0.06, 0.60)	0.099	−0.07[a] (−0.42, 0.29)	0.700	0.39[a] (0.03, 0.66)	**0.033**	−0.00[a] (−0.36, 0.36)	0.980
NDI	0.57[a] (0.27, 0.77)	**0.001**	0.38[a] (0.02, 0.65)	**0.038**	0.14[a] (−0.23, 0.47)	0.471	0.19[a] (−0.18, 0.52)	0.307

Abbreviations: BDI, beck depression inventory; CI, confidence interval; CSI, central sensitization inventory; GCPS,graded chronic pain scale; NDI, neck disability index; PCS,pain catastrophizing scale; r, correlation coefficient; STAI-S, state anxiety inventory; TSK, tampa scale for kinesophobia.

Note: Bold indicates significant ($p<0.05$).

[a]Data for at least one variable were normally distributed and Pearson's correlation coefficient was calculated.

[b]The data for both variables were not normally distributed and Spearman's correlation coefficient was calculated.

Association between CPM and pain characteristics

The findings found in the present study suggest that the efficacy of CPM could be influenced by pain intensity. Consequently, it could cause patients who have experienced pain at the time of measurement or in the last few days, need to be controlled in the CPM analysis. A meta-analysis on the reliability of the CPM reported poor inter-session reliability of the CPM.[63] The authors concluded that CPM may be a dynamic process rather than a stable trait. In patients with recurrent or chronic pain, the severity of pain changes a lot and this, together with the emotional state at the time, could account for the variability in measurement results between sessions. Future studies should clarify whether the CPM is related to the patient's state at the time of measurement or whether the low inter-session reliability is due to methodological limitations and random error.

However, no correlation was found between MPC and other variables such as pain duration, severity or interference, or CSI. These findings are consistent with previous studies that also found no correlation of CPM with these clinical manifestations.[17,18,22,23] Therefore, the evidence to date questions the validity of CPM as a biomarker of neck pain. Much research is still needed to enable CPM to meet the requirements as a diagnostic, prognostic, predictive, and pharmacodynamic measure required for a valid biomarker of chronic pain.[64,65]

Psychological factors and CPM

The findings are in line with other studies which also reported the presence of depression[6,14,25–27] and anxiety[6,25,27] symptoms in patients with NSNP compared to pain-free controls. However, in contrast to previous studies,[26–28] no significant difference in catastrophizing and kinesiophobia was found between participants with neck pain and healthy controls. A study carried out using sonographers with NSNP, analyzed psychological measures comparing different levels of cervical disability.[66] They found that only those with moderate or severe levels of disability showed higher catastrophizing than those without disability. It is possible that in the present study, not having a moderate or high average level of cervical disability may have influenced the lack of significant differences in catastrophizing between groups.

Psychological measures were entered as covariates in the regression model to assess their possible influence on CPM. In line with the findings of previous studies,[66] there was no relevant change in CPM when psychological variables were introduced into the analysis. No clear conclusions can be reached from this finding, as both studies also found no between-group differences in CPM without adjusting for psychological

variables. The present study is consistent with a previous meta-analysis[31] that found no association between levels of anxiety, depression, and pain catastrophizing with CPM response in patients with pain. However, they did find associations between specific CPM testing paradigms and specific psychological factors in healthy participants which may suggest that each paradigm possibly relates to a different inhibitory mechanism. Neuroimaging studies show that psychological factors (expectation, emotion, attention, etc.) affect the neuronal activity of brain regions involved in the descending inhibition pathways of pain.[29,30] One study showed how expectations blocked the inhibitory response of COS.[67] A review about the association of brain changes with cognitive and emotional factors concluded that pain catastrophizing is related to brain areas involved in pain processing and is associated with reduced engagement of the descending pain modulator system.[68] In contrast, the evidence suggested no association between brain alterations and anxiety/depression symptoms, although some studies reported an association with increased brain activation in cognitive-affective areas. Hence, it is not only necessary to standardize CPM measurement methods, but also to clarify which psychological factors influence CPM and may function as confounders in the analysis of this paradigm. The psychological state of patients at the time of testing should be the focus of future research to understand the mechanisms influencing the CPM paradigm and the clinical relevance of this assessment. Meta-analyses on the status of CPM in pain patients have reported that very few studies controlled the effect of psychological factors which may represent a high risk of bias..[69,70]

Correlations between psychological factors and pain characteristics

The correlations found between pain catastrophizing and mean pain intensity, pain severity, and neck pain-related disability are consistent with findings found in previous studies with chronic neck pain.[32,71] The GCPS contains similar constructs to the NDI related to pain interference in daily life. Therefore, the results suggest that pain catastrophism may be mainly associated with how pain influences activities of daily living. Similarly, kinesiophobia also showed a correlation with disability related to neck pain. This result is controversial, as previous studies in chronic neck pain did not find this association.[32,71]

The correlation found between depressive symptoms and the CSI has been consistently reported in the literature[56,72–75] and may not be surprising, since the CSI explores psychological constructs such as feeling sad or depressed. The association of the CSI with depressive symptoms but not with CPM supports the conclusions obtained in a recent meta-analysis which suggests that this questionnaire is able to identify psychological vulnerability that is associated with pain but not the presence of CS determined with QST.[56]

Clinical implications

The results suggest that students with chronic o recurrent NSNP may have CS due to the presence of hyperalgesia away from the neck. However, the mechanisms related to diffuse noxious inhibitory nociceptive controls do not appear to be impaired. That could lead to treatments that may involve painful stimuli or whose efficacy depends on the activation of descending inhibitory mechanisms such it seems to be manual therapy or exercise. Even so, clinicians should make this decision based on individual responses to CPM assessment and the patient's mean pain intensity over the past week. Furthermore, associating the presence of an impaired CPM with a worse clinical situation of their chronic pain should be avoided. Future studies should focus on investigating the ability of MPC to predict pain manifestations and to predict the success of certain treatments.

The presence of anxiety and depression symptoms in these students with chronic or recurrent NSNP suggests the need to implement specific strategies for the treatment of these disorders. It may also be important to implement treatments such as pain neuroscience education or cognitive behavioral therapy in patients who present with pain catastrophizing, as it seems to be associated with the intensity, severity, and interference of their pain. Finally, if the CSI is used, the results should not be associated with the presence or absence of CS, but rather with psychological vulnerability associated with pain.

Strength and limitations

The main strength is, to our knowledge, that this is the first time that CPM has been assessed in the specific population of young adult students with NSNP. Unlike most previous studies in NSNP, CPM analyses were conducted adjusting for the baseline PPT, which controls the possible influence of COS on the PPT during the COS. In addition, differences in CPM between groups were also analyzed by adjusting for psychological variables that could act as confounders.

The main limitation of this study is that the cross-sectional design meant that causal inferences cannot be drawn from the results obtained. Although neck pain in the age group studied is more prevalent in females,[2] the sample obtained had an under-representation of males.

The sample size was not calculated for a regression model with several covariates, so it might be underestimated for the analysis adjusted for psychological

factors. This precluded the option of introducing other possible confounders such as pain intensity at the time of measurement or in the last few days into the model. Finally, the CPM measurement did not follow some of the latest expert recommendations, such as including a (sham) non-painful conditioning control stimulus.[11]

CONCLUSIONS

The results of the present study suggest the presence of remote hyperalgesia but not dysfunctional CPM in young adult students with chronic o recurrent NSNP. In terms of psychological variables, NSNP students showed a higher presence of depression and anxiety symptoms, but not of catastrophizing and kinesiophobia compared to pain-free controls. Furthermore, it is suggested that CPM correlates with pain intensity; pain catastrophism with pain severity and pain interference in daily life; kinesiophobia with disability related to pain; and depression with CSI.

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The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT CONSENT STATEMENT
"Informed consent was obtained from all subjects involved in the study."

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