Observational Study

Evaluating Associations and Contributing Factors of Descending Pain Modulation and Autonomic Nervous System Activity in Chronic and Nonchronic Knee Pain

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Background: Central sensitization in individuals with knee pain is associated with altered autonomic nervous system activity and descending pain modulation; however, the exact nature of these relationships remains unclear. We have hypothesized that chronic knee pain (CKP) disrupts the relationship between autonomic nervous system activity and conditioned pain modulation, whereas nonchronic knee pain (nCKP) does not.

Objectives: This study aimed to examine the association between autonomic nervous system activity and descending pain modulation as well as to identify factors contributing to dysfunction in the descending pain modulation system.

Study Design: Observational study.

Setting: An institutional hospital.

Methods: Female patients with knee pain were recruited via advertisements and orthopedic referrals. Patients were categorized as having either CKP or nCKP, based on whether their pain persisted for 3 months or longer. Conditioned pain modulation was assessed using cold-water immersion (8-12°C for 3 minutes) as a measure of descending pain modulation. Autonomic nervous system activity, represented by low- and high-frequency normalized units (LF_{norm} and HF_{norm}), was assessed via heart rate variability. Changes in autonomic nervous system activity were calculated as post-immersion values minus pre-immersion values. Associations between conditioned pain modulation and changes in LF_{norm} and HF_{norm} units were analyzed using linear regression and Cohen's kappa. Path analysis was performed to explore factors affecting autonomic nervous system activity and conditioned pain modulation in patients with CKP.

Results: Of 96 patients, 90 (71 with CKP and 19 with nCKP) were analyzed. Changes in LF_{norm} were significantly associated with conditioned pain modulation only in patients with nCKP (P = 0.012). Among those with CKP, the baseline LF_{norm} was associated with pain catastrophizing and the number of pain sites.

Limitations: The study included only female patients, and the nCKP-pain group was relatively small.

Conclusions: Patients with nCKP exhibited significant relationships between conditioned pain modulation and sympathetic nervous system activity, suggesting that the phenomenon of descending pain modulation was intact. Conversely, in patients with CKP, those associations were absent, and sympathetic activity was rather influenced by pain catastrophizing and the number of pain sites. These findings suggest that chronic pain may impair descending pain modulation through altered autonomic nervous system function.

Key words: Knee pain, chronic pain, nonchronic pain, central sensitization, descending pain modulation, conditioned pain modulation, autonomic nervous system, sympathetic nervous system, parasympathetic nervous system, heart rate variability

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Knee osteoarthritis (KOA) is a common condition that becomes more prevalent with age and is more common in women than in men (1-3). KOA involves degenerative changes in the knee joint components, including the bone, cartilage, and synovium, leading to pain, stiffness, and functional limitations (4). Several recent studies have reported that patients with KOA may have central sensitization, defined as "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" (5). The prevalence of central sensitization in patients with KOA is reportedly high, ranging from approximately 20% to 50% (6-8). Compared to patients with KOA alone, those with both KOA and central sensitization experience more intense pain and worse physical function (7). Furthermore, these doubly affected patients may continue to experience severe and persistent pain after total knee arthroplasty (9). When the conditions appear together, central sensitization may exacerbate knee pain and hinder the effective management of it.

The exaggerated pain perception in central sensitization is thought to be associated with dysfunction of the descending pain modulation system, an intrinsic mechanism that suppresses or amplifies nociception based on biological and behavioral needs (10,11). The rostral ventromedial medulla, a major central neural structure within this system, plays a crucial role in regulating descending pain modulation, and its dysfunction can impair this pain-regulatory mechanism (11). Interestingly, the rostral ventromedial medulla is also involved in regulating autonomic nervous system functions, such as blood pressure (12). As a result, patients with central sensitization often exhibit autonomic nervous system dysfunction (13,14). Furthermore, during conditioned pain modulation—a method used to assess descending pain modulation—the autonomic nervous system and pain modulation appear to be interconnected. Makovac et al (15) demonstrated this association in healthy individuals using functional magnetic resonance imaging (fMRI), revealing a link between conditioned pain modulation and autonomic nervous system activity, as analyzed via heart rate variability. Other studies have also reported similar relationships, demonstrating particularly stronger associations in healthy women (16).

However, some studies have reported conflicting findings. For instance, patients with musculoskeletal pain, such as those with whiplash-associated disorders, showed no relationship between conditioned pain modulation and autonomic nervous system activity (17,18). Additionally, patients with impaired descending pain modulation, commonly associated with chronic pain, have exhibited altered parasympathetic activity at rest (19). These findings suggest that individuals with chronic musculoskeletal pain may experience a dissociation between autonomic nervous system activity and conditioned pain modulation. Supporting this hypothesis, a study comparing healthy individuals to patients with chronic low back pain reported distinct interactions between autonomic activity and conditioned pain modulation during baroreflex stimulation (20). This difference may stem from prolonged pain's induction of psychological stress, which can disrupt autonomic nervous system function and descending pain modulation, since psychological stress is known to trigger autonomic dysfunction (21,22). These insights highlight the need for further investigation to elucidate the relationship between autonomic nervous system activity and conditioned pain modulation in chronic and nonchronic musculoskeletal pain, particularly knee pain. Additionally, exploring the potential role of psychological factors is essential.

In this study, we sought to examine the association between autonomic nervous system activity and conditioned pain modulation. We also aimed to identify factors that contributed to dysfunction in the descending pain modulation system. We hypothesized that autonomic nervous system activity would be associated with descending pain modulation only in patients with chronic knee pain (CKP) rather than in those with nonchronic knee (nCKP) pain and that psychological dysfunction might contribute to impaired autonomic nervous system function and conditioned pain modulation.

Methods

Study Design, Ethics Approval, and Patients

This observational study was approved by the institutional review board of our facility and complied with the World Medical Association's Declaration of Helsinki, and written informed consent was obtained from all patients.

Patients were recruited from our institutional hospital during February 2023 and August 2024 through advertisements placed at both institutions or referrals from the patients' orthopedists. To meet the inclusion criteria, patients had to be women between the ages of 20 to 80 who were experiencing knee pain. Exclusion

criteria included disorders of the cardiopulmonary or vascular varieties or of the central or autonomic nervous systems; facial, chest, or abdominal pain; cancer-related pain; the inability to communicate effectively or complete questionnaires; and current use of beta-blockers, antidepressants, or anticonvulsants. Due to recruitment challenges, not all patients had received a formal diagnosis of KOA or consulted with an orthopedist. Patients were assigned to either the CKP or nCKP group, based on the duration of their knee pain; chronic pain was defined as pain lasting over 3 months (23).

Sample size was calculated using G*Power version 3.1.9.7, with power set at 0.8, alpha at 0.05, and a large effect size of 0.8 for an independent t-test, which indicated that 64 patients were required for the CKP group and 16 for the nCKP group. For simple linear regression, with power set at 0.8, alpha at 0.05, and a large effect size of 0.35, the total sample size required was 25 patients in each group. Finally, for path analysis, which required 10 patients per outcome (24), the analysis was limited to the CKP group (n = 71).

Procedures and Outcomes

All patients received orientation, eligibility screening, and measurements on the same day. Conditioned pain modulation was assessed following the procedure outlined in previous research (25) (Fig. 1). Patients were seated in a relaxed position for 15 minutes to establish the baseline measurements (REST period). For each patient, the pressure pain threshold was then measured on the left side of the upper trapezius fibers, using the Wagner FPX-25 device (Wagner Instruments) (26). The conditioning stimulus involved a 3-part series of 45-second sessions of immersing the right hand in cold water, each instance of which was separated by 15-second intervals (COLD period) (25). The water temperature was maintained between 8 and 12°C (25). The absolute value of the conditioned pain modulation response was calculated as the difference in pressure pain threshold between the COLD and REST periods (3).

Autonomic nervous system activity was assessed via heart rate variability analysis using electrocardiogram data recorded with the WHS-1 (Union Tool Co. Ltd.). Electrocardiogram data were analyzed using the RRI Analyzer 2 (Union Tool Co. Ltd.), employing frequency-domain indices such as low-frequency (LF) and high-frequency (HF) powers (27). LF_{norm} was calculated as LF/(total power – very low-frequency power) × 100 to reflect sympathetic nervous system activity (28). Parasympathetic nervous system activity was expressed as HF_{norm}, calculated as HF/(total power – very low-frequency power) × 100 (28). LF_{norm} and HF_{norm} were calculated for each REST or COLD period and expressed as LF_{norm} (REST) or HF_{norm} (COLD). In a manner analogous to the conditioned pain modulation effect, variations in autonomic activity from COLD to REST were represented as ΔLF_{norm} and ΔHF_{norm}.

Basic patients characteristics were self-reported,

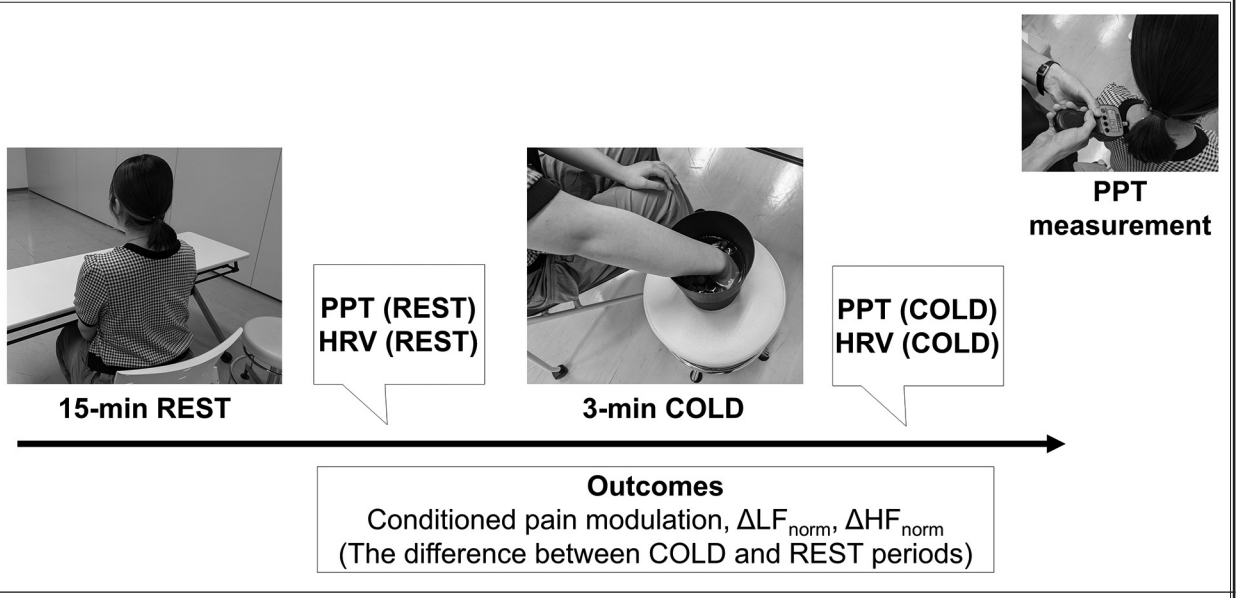

Fig. 1. *Measurement protocol*
HRV: heart rate variability, PPT: pressure pain threshold

including age, height, weight (calculated as body mass index), average knee pain over the past 4 weeks (numeric rating scale), history of orthopedic surgery, and medication use. Several questionnaires were employed to assess various physical and psychological factors, which were also self-reported; those questionnaires included the Western Ontario and McMaster Universities Osteoarthritis Index, which measured symptoms (pain and stiffness) and physical disability in individuals with osteoarthritis (29); the PainDETECT questionnaire, which screened for neuropathic components of pain (30); the Pain Catastrophizing Scale, which assessed pain catastrophizing, defined as "an exaggerated negative mental state resulting from an actual or anticipated painful experience (31)"; the International Physical Activity Questionnaire, which evaluated the amount of physical activity performed in the past 7 days (32); the Hospital Anxiety and Depression Scale, which assessed anxiety and depression as 2 subscales, each comprising 7 questions (33); the Pittsburgh Sleep Quality Index, which assessed sleep quality and disorders (34); and the Checklist for Individual Strength, which evaluated the severity of fatigue and related symptoms (35). Higher scores on all the aforementioned questionnaires indicate more severe symptoms.

Statistical Analysis

Statistical differences between the groups were calculated using an independent samples t-test, Mann–Whitney U test, or chi-squared test, depending on the distribution and type of variables. Simple linear regression analysis was performed to explore the relationships between autonomic nervous system activity and conditioned pain modulation in the overall sample and within each group. Because the result of conditioned pain modulation was interpreted based on whether the score was negative (< 0) or positive (≥ 0), Cohen's kappa was calculated to confirm whether autonomic nervous system activity during cold-water immersion could substitute for the measurement of conditioned pain modulation. All statistical analyses were conducted using IBM® SPSS® Statistics 27.0 for Windows (IBM Corp.). In the CKP group, path analysis was conducted to examine the relationships among pain catastrophizing, number of pain sites, LF_{norm} (REST), conditioned pain modulation, and the Western Ontario and McMaster Universities Osteoarthritis Index, using IBM® SPSS® Amos 27.0 (IBM Corp.). Statistical significance was assessed at an alpha level of 0.05.

Results

Of the 96 initially recruited patients, 3 were excluded due to electrocardiogram malfunction or other technical issues, one was excluded due to inability to complete the questionnaire, and 2 were excluded due to being over 80 years old. Ultimately, 90 patients were included in the analysis (Fig. 2).

The numbers of patients in the CKP and nCKP groups were 71 and 19, respectively. Table 1 presents the basic characteristics and questionnaire results for the overall study population, as well as for the CKP and nCKP groups. Significant differences were observed between the groups in pain catastrophizing and depression, while other outcomes did not show significant differences.

A single linear regression analysis across overall samples indicated that ΔLF_{norm} and ΔHF_{norm} were not significantly correlated with conditioned pain modulation (P = 0.08 and 0.135, respectively). After the patients were divided into the 2 groups, a significant association was found between ΔLF_{norm} and conditioned pain modulation in the nCKP group (P = 0.012, R^2 = 0.317, β = -0.563, Fig. 3). Conversely, ΔLF_{norm} in the CKP group was not associated with conditioned pain modulation (P = 0.358). ΔHF_{norm} did not show significant associations with conditioned pain modulation in either group (P = 0.912 and 0.657, respectively).

Cohen's kappa was calculated as -0.12, indicating no significant agreement between autonomic nervous system activities and conditioned pain modulation (Table 2).

Path analysis for the CKP group revealed no significant relationship between LF_{norm} (REST) and conditioned pain modulation (P = 0.077) or between conditioned pain modulation and the Western Ontario and McMaster Universities Osteoarthritis Index (P = 0.785). Similarly, depression showed no significant association with LF_{norm} (REST) (P = 0.586). However, significant associations were found between LF_{norm} (REST) and both pain catastrophizing (P = 0.029) and the number of pain sites (P = 0.003). These relationships are illustrated in Fig. 4.

Discussion

This observational study aimed to examine the association between autonomic nervous system activity and conditioned pain modulation, as well as to identify factors contributing to dysfunction in the descending pain modulation system. Our findings revealed a significant correlation between sympathetic nervous

system activity and conditioned pain modulation in the nCKP group, whereas no significant relationship was observed in the CKP group. Additionally, the number of pain sites and pain catastrophizing were identified as potential factors influencing autonomic nervous system activity in the CKP group.

We found differing results between the 2 groups in the relationship between conditioned pain modulation and sympathetic nervous system activity (Fig. 3). Previous studies have shown that healthy individuals tend to exhibit a significant correlation between con-

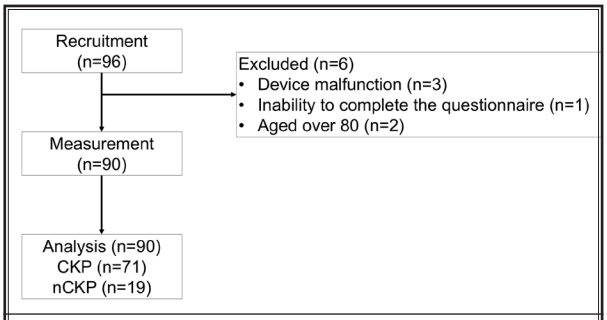

Fig. 2. *Study flow diagram*
CKP: chronic knee pain, nCKP: nonchronic knee pain

Table 1. *Patients' characteristics. The table presents the characteristics and questionnaire results of the overall study population as well as the statistical differences between the CKP and nCKP groups. *P < 0.05*

Variable (Unit)	Overall (n = 90)	Chronic Knee Pain (n = 71)	Nonchronic Knee Pain (n = 19)	*P* value
Age (years)	65.0 ± 10.1	64.5 ± 9.9	67.2 ± 11.0	0.188
Body mass index (kg/m^2)	24.0 ± 4.7	24.0 ± 5.0	23.9 ± 3.6	0.816
Experience of orthopedic surgery (number experienced, %)	28 (31.1)	22 (31.0)	6 (31.6)	0.960
History of diabetes (number, %)	12 (13.3)	9 (12.7)	3 (15.8)	0.711
Average intensity of knee (Numerical Rating Scale)	4.3 ± 2.1	4.4 ± 1.9	3.8 ± 2.7	0.255
PainDETECT	8.4 ± 4.9	8.6 ± 5.1	7.5 ± 4.3	0.381
Pain Catastrophizing Scale	25.2 ± 11.0	27.7 ± 9.7	15.9 ± 10.9	<0.001*
Hospital Anxiety and Depression Scale (Anxiety)	5.1 ± 3.9	5.5 ± 4.1	3.6 ± 2.5	0.068
Hospital Anxiety and Depression Scale (Depression)	6.4 ± 3.4	6.8 ± 3.4	4.7 ± 2.7	0.009*
Western Ontario and McMaster Universities Osteoarthritis Index	28.2 ± 19.0	30.2 ± 19.6	21.1 ± 14.7	0.083
International Physical Activity Questionnaire (Mets)	54.9 ± 79.2	55.7 ± 83.9	52.2 ± 60.1	0.517

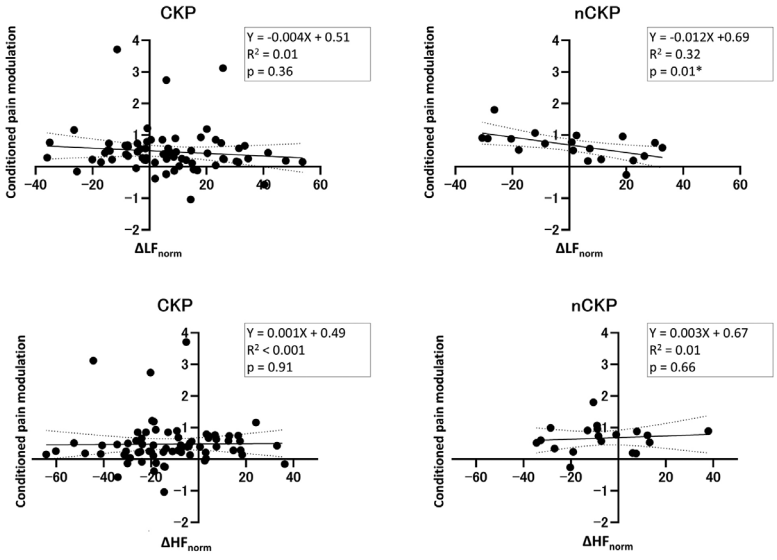

Fig. 3. *The association between autonomic nervous system activity and conditioned pain modulation. Top 2 figures indicate the associations between conditioned pain modulation and* ΔLF_{norm}. *Lower 2 figures indicate the associations between conditioned pain modulation and* ΔHF_{norm}. *Each box shows the statistical results, including the regression equation, coefficient of determination (R²), and P-value (P).*
nCKP: nonchronic knee pain, CKP: chronic knee pain

ditioned pain modulation and sympathetic nervous system activity (15,16); this correlation is often absent in patients with chronic pain (18,19). This phenomenon could be attributable to dysfunction of the rostral ventromedial medulla, which results from prolonged chronic pain (11,12). Conversely, the neuronal function of patients in the nCKP group, who experienced acute or subacute pain and were not subjected to prolonged stress on the autonomic and descending pain modulation systems, was likely preserved (21,22). In fact, the CKP group demonstrated significant correlations between pain catastrophizing and the number of pain sites, as evidenced by the path analysis (Fig. 4). It has been reported that individuals with chronic pain who demonstrate pain catastrophizing tend to exhibit autonomic nervous system dysfunction (36) and impaired conditioned pain modulation (37). In contrast, these relationships were not observed in healthy individuals (38) or in patients with acute pain (39). The presence of a higher number of pain sites has been associated with more severe psychological problems (40) and an increased likelihood of autonomic nervous system dysfunction (41), which aligns with and corroborates our findings.

However, autonomic nervous system activity did not necessarily correlate with conditioned pain modulation, even in patients with acute pain. Our findings showed that in the nCKP group, ΔHF_{norm}, representing parasympathetic nervous system activity during the cold pressor test, did not significantly correlate with these outcomes (Fig. 3). Furthermore, an agreement could not be established between conditioned pain modulation and sympathetic nervous system activity (Table 2), as demonstrated by a Cohen's kappa value of -0.12, indicating low reliability (42). Although we hypothesized that the outcomes related to the autonomic and descending systems would be correlated due to their shared neuronal element, the rostral ventromedial medulla (11,12), that hypothesis was not supported by our findings. A possible explanation is that descending pain modulation involves 3 distinct neuronal pathways: the autonomic nervous system, central nervous system, and opioidergic system (3). The absence of the hypothesized correlation suggests that the autonomic nervous system alone cannot fully explain the mechanisms of the descending pain modulatory system. Our findings do, however, indicate the former can partially contribute to the latter.

Table 2. *Cross-tabulation for LF_{norm} and conditioned pain modulation. The values of conditioned pain modulation and LF_{norm} represent the difference between the COLD and REST periods. The number of patients with positive and negative differences, respectively, was summarized in a cross-tabulation, and Cohen's kappa was calculated. LF_{norm}: low-frequency normalized unit.*

		Conditioned pain modulation		Total
		+ (> 0)	- (< 0)	
ΔLF_{norm}	+ (> 0)	2	33	35
	- (< 0)	9	46	55
Total		11	79	90

Limtations

This observational study had 3 limitations. Firstly, although we aimed to compare path analyses between the nCKP and the CKP groups, conducting a path analysis for the nCKP group was not feasible due to its small sample size, which resulted from challenges in recruitment (43). Secondly, the study focused ex-

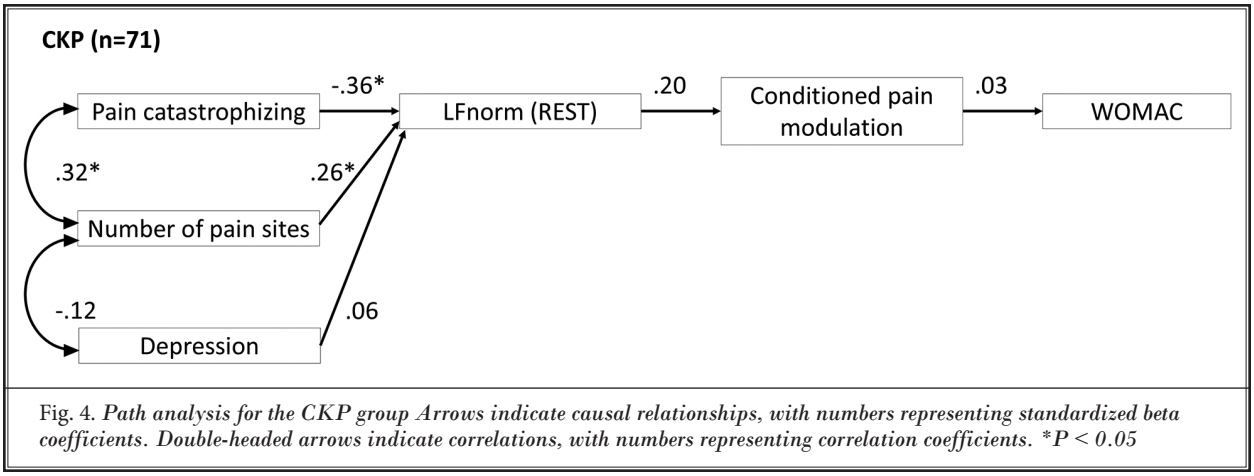

Fig. 4. *Path analysis for the CKP group Arrows indicate causal relationships, with numbers representing standardized beta coefficients. Double-headed arrows indicate correlations, with numbers representing correlation coefficients. *P < 0.05*

clusively on female patients, since descending pain modulation impairments tend to be more prevalent in women (44). However, men may also experience knee pain and central sensitization, so the inclusion of male patients in future studies is warranted. Thirdly, although we inquired whether the patients' pain was chronic, the duration of knee pain was not recorded for either group. We acknowledge that pain duration may have influenced our results (45). Nonetheless, this decision was made to minimize the risk of memory bias associated with self-reported pain duration (46), and we could not access patients' medical records due to privacy concerns. Despite these limitations, our findings provide valuable insights into the relationship between conditioned pain modulation and autonomic nervous system activity, particularly in individuals with nCKP. Future studies could address these limitations by including both women and men to better generalize these findings and exploring the underlying mechanisms of CKP in more detail.

Conclusion

In this study, patients with nCKP demonstrated significant correlations between conditioned pain modulation and sympathetic nervous system activity, suggesting intact descending pain modulation; such relationships were absent in patients with CKP. This difference indicates that chronic pain but not its nonchronic counterpart may impair descending pain modulation through sympathetic nervous system dysfunction. Additionally, the number of pain sites and amount of pain catastrophizing were found to exert a potential influence on resting sympathetic nervous system activity, suggesting their role as further contributing factors.

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Acquisition, administrative, technical, and material support: K.T. and T.O.

Obtaining funding, analysis of data, and drafting the manuscript: H.U.

Critical revision of the manuscript: all authors.

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