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Pain is Modulated Differently Between Females With and Without Patellofemoral Pain: Factors Related to Sensitization

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Context: Patellofemoral pain (PFP) has poor long-term recovery outcomes. Central sensitization describes central nervous system changes altering pain modulation, which can complicate recovery (poorer prognosis and worse function). Signs of central sensitization include amplified pain facilitation, pain hypersensitivity, and impaired pain inhibition, which can be measured with temporal summation of pain (TSP), pressure pain thresholds (PPTs), and conditioned pain modulation (CPM), respectively. Sex differences exist for these test responses, but female-only PFP investigations of sensitization are uncommon. Understanding pain modulation in females with PFP could improve treatment protocols.

Objective: To determine whether females with PFP exhibit signs of central sensitization (greater TSP, lower PPTs, and reduced CPM) compared with pain-free females.

Design: Cross-sectional study.

Setting: Laboratory.

Patients or Other Participants: Thirty-three females ([20 PFP, 13 pain free]; age: PFP 29.2 ± 7 years, pain free 28 ± 7 years; height: PFP 166.7 ± 5.9 cm, pain free 166 ± 9.5 cm; mass: PFP 66.7 ± 9.6 kg, pain free 69.3 ± 7.5 kg).

Main Outcome Measure(s): Temporal summation of pain was assessed with 10 punctate stimuli applied to the knee and calculated by the difference in pain intensity between beginning and end responses. Pressure pain thresholds were tested at 4 sites (3 for local hypersensitivity [knee] and 1 for widespread hypersensitivity [hand]). Conditioned pain modulation was conducted by comparing PPTs during 2 conditions (baseline and ice immersion). Conditioned pain modulation response was defined as the percent difference between conditions. Between-groups differences in TSP response were analyzed with a Welch test. Separate Welch tests analyzed group comparisons of PPTs and CPM responses at 4 sites.

Results: Females with PFP exhibited greater TSP response ($P = .019$) and lower CPM response at patella center ($P = .010$) and hand sites ($P = .007$) than pain-free females. Pressure pain thresholds group differences were not observed at any site ($P > .0125$).

Conclusions: Females with PFP modulate pain differently than pain-free females. Clinicians should recognize signs of central sensitization and their potential effect on treatment options.

Key Words: anterior knee pain, central sensitization, quantitative sensory testing, conditioned pain modulation, temporal summation, pressure pain thresholds

Key Points

- Females with patellofemoral pain exhibit impaired pain inhibition relative to pain-free females.
- Females with patellofemoral pain exhibit amplified pain facilitation compared with pain-free females.
- Clinicians should assess for clinical signs of central sensitization, as treatment approaches may differ from typical rehabilitation strategies targeting the knee.

Patellofemoral pain (PFP) is a common musculoskeletal condition causing persistent pain around the patella with activity.[1] Females are more likely to experience PFP and symptoms tend to persist longer than males, with no fundamental explanation why.[2,3] Treatment for PFP is based on the concept that nociception is driven by pathomechanics; however, pain becomes recurrent or persistent in over 50% of participants in longitudinal studies lasting 1 to 8 years, regardless of treatment approach.[2,4] It is possible that pathomechanical variables alone may not explain the persistence and recurrence of PFP but that changes in pain modulation may provide additional context for these poor recovery outcomes.

Central sensitization describes structural and functional changes within the central nervous system pathways, altering pain modulation.[5] Motor cortex reorganization and changes in functional sensorimotor connectivity have been observed in individuals with PFP, providing evidence of

central nervous system changes.[6,7] Central sensitization complicates recovery and is associated with poor treatment outcomes including poorer prognosis, worse function, and greater disability.[8] These poor outcomes occur because pain is no longer indicative of tissue damage or nociceptive input but rather reflects a heightened state of the central nervous system.[5] Treatment of central sensitization differs from traditional treatments focused on the extremity itself and would warrant exploration of different centrally driven interventions.[9] If individuals with PFP exhibit signs of central sensitization, it may warrant further exploration of a shift in treatment paradigm.

Central sensitization is characterized by amplified pain facilitation, widespread pain hypersensitivity, ineffective pain inhibition, or any combination of the above.[10] Manifestations of central sensitization can be assessed using quantitative sensory testing.[10] Quantitative sensory testing collectively describes procedures used to measure pain facilitation, pain hypersensitivity, and pain inhibition in a clinical setting.[10] Quantitative sensory testing has helped identify altered pain modulation in patients with chronic musculoskeletal conditions. Quantitative sensory testing has also been useful in differentiating between patients who respond well and respond poorly to common treatment regiments in chronic musculoskeletal conditions.[11] Finally, it has been proposed that quantitative sensory testing could drive pain mechanism-based treatment approach to improve patient outcomes in chronic musculoskeletal pain[9,12] Temporal summation of pain (TSP), pressure pain thresholds (PPTs), and conditioned pain modulation (CPM) are 3 common quantitative sensory testing procedures.

Temporal summation of pain can assess pain facilitation, which is a normally occurring phenomenon in which pain perception increases in response to a repeated stimulus of the same intensity over time due to a summative effect the spinal cord.[10] In populations demonstrating signs of central sensitization, a greater increase in pain intensity occurs more quickly than in pain-free individuals.[10]

Pressure pain thresholds help detect changes in pain sensitivity.[13] A standardized, steadily increasing pressure is applied until the patient indicates the pressure sensation changes to pain. Lower PPTs indicate that it takes less stimulus pressure to achieve a pain response at the affected site, meaning that area is more sensitive to pain.[13] Lower local or widespread (ie, remote) PPTs and can be a sign of peripheral or central sensitization.[13]

Conditioned pain modulation is used to detect changes in descending pain inhibition networks.[10,14] Conditioned pain modulation is assessed by repeating a noxious test stimulus (eg, PPTs) before and during a secondary noxious conditioning stimulus (eg, ice immersion) and determining the amount of change between conditions.[14] For functional CPM, the addition of the conditioning stimulus would send a pain inhibition signal, increasing the pain threshold, allowing more pressure to be applied (ie, increased PPTs) before pain sensation occurs.[10] If CPM is impaired, little or no change in pain threshold would occur, meaning it would still take less pressure application for pain sensation, even in the presence of a conditioning stimulus. Therefore, PPTs would demonstrate less or no change during the conditioning stimulus compared with baseline PPTs.[14]

Authors of recent meta-analyses have suggested that at least a subgroup of individuals with PFP experience signs of central sensitization, but the strength of these conclusions is debatable.[15,16] First, lower PPTs demonstrated the greatest amount of evidence with the strongest support.[15,16] However, Woolf has suggested that pain hypersensitivity alone is not enough to establish central sensitization as the source because peripheral mechanisms also contribute to lower PPTs.[5] Pressure pain threshold assessment of a remote limb (eg, upper extremity) may contribute additional support for widespread pain sensitivity. Strong evidence of between-groups differences was also reported for CPM and TSP, but this information was based on small group differences in a small number of total studies.[15] Additionally, only PPT data could be analyzed based on the sex of the sample despite the fact that sex differences have been well documented in quantitative sensory testing.[15–17] Therefore, meta-analysis results could be affected by sex differences in the population that were not accounted for in individual study designs. More studies are needed to establish whether females with PFP exhibit different CPM and TSP responses compared with pain-free females.

The purpose of this study was to identify whether females with PFP exhibit signs of central sensitization compared with pain-free females. We hypothesized that females with PFP exhibit higher TSP response, lower PPTs, and lower CPM response than a healthy control (CON) group of females.

METHODS

Study Design and Protocol

This cross-sectional study took place in a laboratory setting in a large midwestern university. This study was approved by the university's institutional review board. Data were collected from the affected (or most painful) side for individuals with PFP. Unequal groups made it difficult to match participants based on age, height, or body mass; however, we did match the distribution of each group relative to test limb (Table). No significant differences between groups existed based on age, height, or body mass. Once screened, participants took part in one 45-minute session consisting of several clinical measures, quantitative sensory testing (order for all participants: TSP, PPTs, and CPM), followed by a series of self-reported inventories. This order was standardized for all participants to limit any cross-over effects of sensory tests and to reduce the need for washout time after CPM.[14]

Participants

Thirty-three female participants volunteered for the study (Figure 1). Twenty females with PFP and 13 pain-free controls (CON) participated. Females aged 18 to 40 were recruited for participation from a large metropolitan area and 3 local college campuses using flyers and social media. The age range was limited due to the potential for differences in quantitative sensory testing results between adolescents and adults with PFP and the increased risk of patellofemoral and knee osteoarthritis after age 40 for females.[16,18] Requirements of the PFP group included nontraumatic onset of retro- or peripatellar knee pain, along with pain during at least 2 of the following: squatting or kneeling, stair ambulation, prolonged sitting, or during or

Table. Demographics and Self-Reported Data by Group

Measure	PFP Group, Mean ± SD or Median (IQR)	CON Group, Mean ± SD or Median (IQR)	*P* Value
Age (y)	29.2 ± 7.0	28 ± 7.0	.634
Height (cm)	166.7 ± 5.9	166.0 ± 9.5	.778
Weight (kg)	66.7 ± 9.6	69.3 ± 7.5	.415
Body mass index	24.0 ± 3.5	25.1 ± 2.6	.674
Symptom duration (mo)	15 (5, 120)	NA	NA
Test limb (R/L)	35% L, 65% R	30% L, 70% R	NA
VAS-current pain (mm)	16.6 ± 16.6	NA	NA
Bilateral vs unilateral PFP (%)	60% bilateral/40% unilateral	NA	NA
Reported taking medications for knee pain (%)	55% yes/45% no	NA	NA
KOOS-overall	71.1 ± 12.0	98.5 ± 2.0	<.001[a]
IPAQ (total metabolic-min)	7802.2 ± 6622.7	8591.5 ± 5970.4	.731
Stress (100 mm VAS)	37.4 ± 25.2	25.4 ± 21.8	.158
Pain Catastrophizing Scale	9.6 ± 7.2	NA	NA
Fear-Avoidance Beliefs Questionnaire-Knee	22.7 ± 9.3	NA	NA
Pain Self-Efficacy Questionnaire	52.5 (50.2, 58.0)	NA	NA
McGill Pain Questionnaire (summed rank)	21.9 ± 10.7	NA	NA
McGill body pain map (pixel area, cm^2)	10 666.0 (8586.75, 15 627.0)	NA	NA

Abbreviations: CON, control; IPAQ, International Physical Activity Questionnaire; IQR, interquartile range; KOOS, Knee Injury and Osteoarthritis Outcome Score; L, left; NA, not assessed; PFP, patellofemoral pain; R, right; VAS, visual analog scale.
[a] PFP group reported significantly lower KOOS scores, indicating greater perceived knee dysfunction than the CON group.

after physical activity or exercise.[19] Additional exclusion criteria were previous knee injury or surgery; lower extremity or back pain or injury in the previous 6 months; pain in the lower extremity, back, or hand at the time of testing; other chronic pain conditions (eg, fibromyalgia, osteoarthritis); neurological conditions; pregnancy at the time of testing; history of adverse reactions to cold or ice; and high blood pressure at the time of testing, which could have affected the biomechanical, quantitative sensory testing, or both or increased participant risk during testing.[1,20,21] Lastly, due to data collection during the COVID-19 pandemic, individuals deemed at high risk for COVID-19 per Centers for Disease Control and Prevention guidelines were not eligible to participate.

All interested individuals were screened for inclusion and exclusion criteria. As participants passed the screening, they were offered the opportunity to have their knees evaluated. A certified and state-licensed athletic trainer conducted the evaluation, aimed to rule out knee pain in healthy volunteers and to rule out other causes of knee pain in the PFP group. Once eligibility was determined, participants agreed to a statement of informed consent and were enrolled.

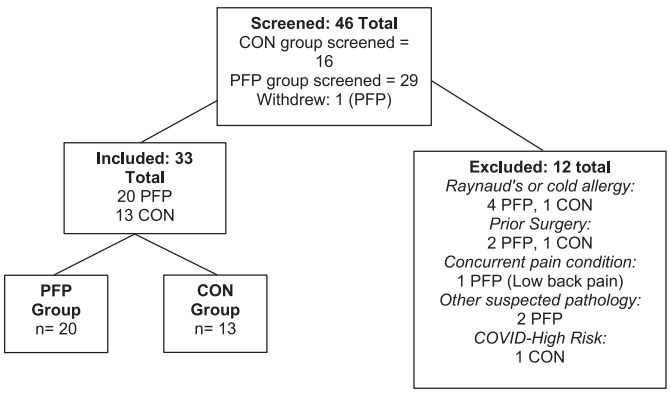

Figure 1. Participant flowchart. Abbreviations: CON, control group; PFP, patellofemoral pain group.

Measurements and Procedures

Participant height (cm) and mass (kg) were measured using a stadiometer and scale, respectively, upon arrival. The PFP group then provided a baseline visual analog scale (VAS) for pain intensity at the time of testing on the 100-mm line and shaded in a body pain map from the McGill Pain Questionnaire to reflect location(s) of pain. All participants then participated in quantitative sensory testing and self-reported inventories. For the PFP group, quantitative sensory tests were conducted on the affected side or the side with worse symptoms. For the CON group, test side was determined by the distribution of (R : L) test limbs in the PFP group.

Temporal summation of pain was assessed using a punctate method with a 300-g nylon monofilament (Baseline).[22] The monofilament was applied perpendicular to the center of the test-side patella until observable bending of the monofilament occurred. The monofilament application was repeated each second for 10 consecutive seconds, and VAS was marked after each application (Figure 2A). Here, TSP-I represented the average VAS of the second through fourth monofilament applications, and TSP-II represented the average VAS for the eighth through tenth monofilament applications. Temporal summation of pain response was defined as the difference between TSP-II and TSP-I (ie, TSP response = TSP II − TSP I) in a manner similar to other studies.[23] Temporal summation of pain response was used for data analysis. Amplified pain facilitation was defined as greater TSP response over time. Intrarater reliability for the TSP measurement for the lead researcher was excellent (intraclass correlation coefficient [ICC][3,2] = 0.955).

Pressure pain thresholds were assessed with a computerized pressure algometer (Algomed) at a pressure rate of 30 kPa/s with a 1-cm^2 round rubber-tipped applicator (Figure 2B).[13] Pressure pain thresholds were assessed at 4 locations: center

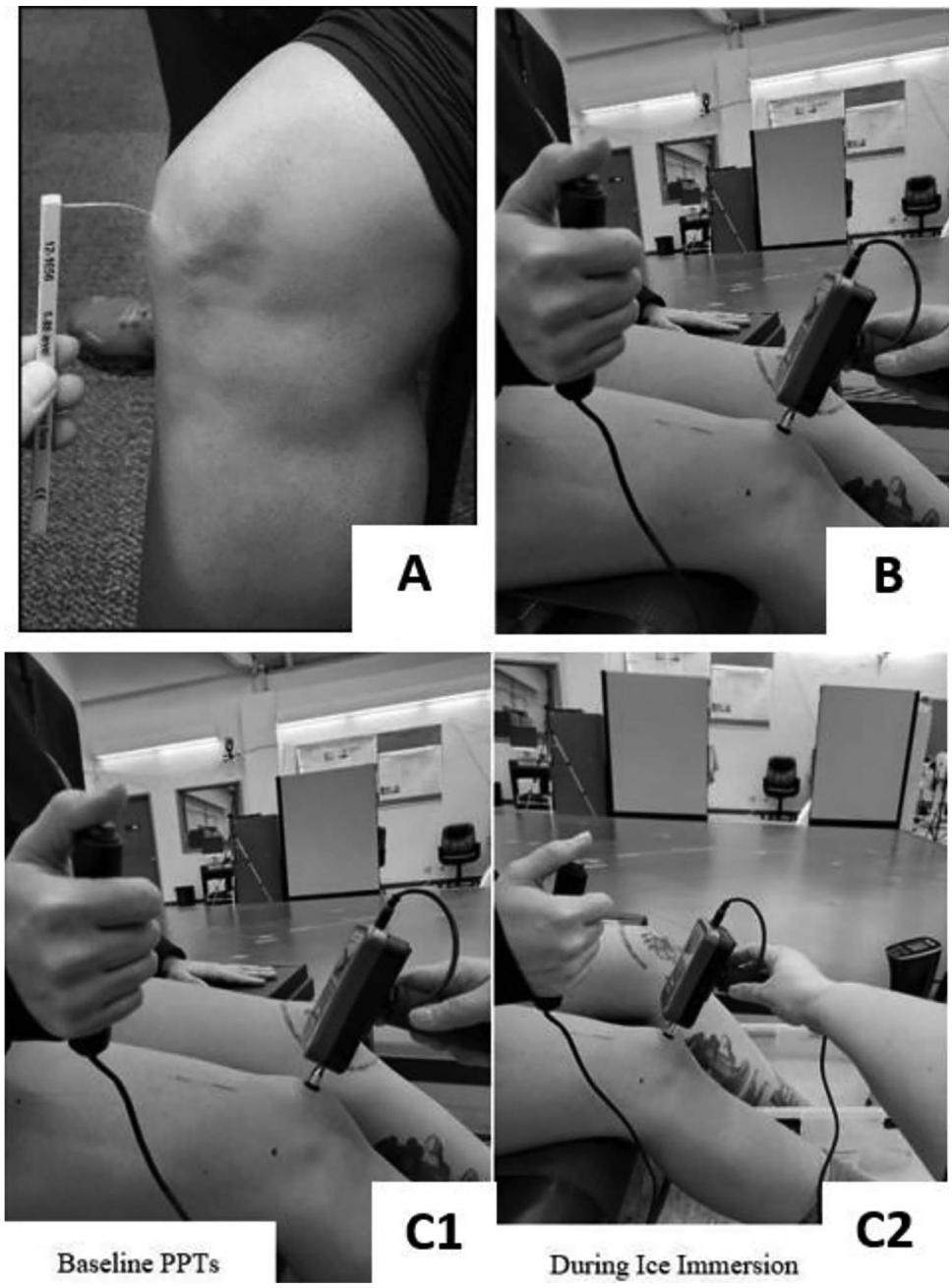

Figure 2. Quantitative sensory testing methods. A, Temporal summation of pain using the monofilament method. B, Knee pressure pain thresholds (PPTs) measured using a computerized pressure algometer. Conditioned pain modulation (CPM) using the cold pressor test, which repeats PPTs in 2 conditions: C1, baseline and, C2, during (7°C) ice immersion. For functional CPM, PPTs increase during ice immersion. If CPM is impaired, PPTs will not change or will be lower during ice immersion compared with baseline PPTs. If CPM is impaired, PPTs will be lower in ice immersion than the control group.

of the patella, 3 cm medial to the medial patellar border on the medial femoral condyle (labeled *medial* throughout text), 3 cm lateral to the lateral patellar border on the lateral femoral condyle (labeled *lateral* throughout text), and on the middle phalanx of the contralateral third finger (labeled *hand* throughout text). These knee sites were selected based on expecting greatest pain for females with PFP over the patella or femoral epicondyles, and the hand site was selected as a remote, upper extremity site with tissue type and superficiality compared with the patella.[13,24] Two repetitions of PPTs were recorded at each site, and the average of each site was used for analysis, consistent with other protocols.[13] Pain hypersensitivity was denoted by lower PPTs, meaning it took less pressure before pain was sensed. Lower PPTs at knee sites would indicate a sign of peripheral sensitization. Lower PPTs at the hand would indicate widespread pain hypersensitivity, 1 sign of central sensitization. Intrarater reliability of the PPT measurement was good to excellent for all test sites for the lead researcher (ICC[3,2] = 0.88–0.92).

Conditioned pain modulation was assessed by repeating PPTs (test stimulus; performed in the aforementioned manner and locations) at baseline and during ice water immersion (conditioning stimulus) of the contralateral foot and

ankle (Figure 2C). Ice water immersion temperature was maintained at 7°C using a water circulation and temperature control device. Pressure pain thresholds measurement began 20 seconds after immersion occurred.[14] Intrarater reliability of the CPM measurement was moderate to excellent for all test sites for the lead researcher (ICC[3,2] = 0.730–0.949). The average PPTs for each of the 2 time points (baseline and during ice water immersion) were calculated for each test site, and the percent difference was used for analysis. Conditioned pain modulation response is defined as the percent difference between conditions.[25] A typical CPM response occurs when the individual can withstand greater pressure before pain is sensed during the ice immersion (ie, higher PPTs). This would also be demonstrated by greater percent difference between baseline and immersion conditions.[14] An impaired CPM response occurs when the participant senses pain with less pressure applied during the immersion condition (ie, lower PPTs) than they experienced during the baseline condition.[14] This would also be demonstrated by a lower percent difference between conditions.

Self-reported inventories were used to characterize the sample. All participants completed a health questionnaire, self-reported knee function inventories, and physical activity levels. The health questionnaire inquired about overall health status, knee injury and treatment history, history of depression and anxiety, and medication use. Participants rated knee function using the Knee Injury and Osteoarthritis Score (KOOS) and associated patellofemoral subscale (KOOS-PF), which asks participants about their experiences over the previous 7 days. Physical activity levels were reported on the International Physical Activity Questionnaire (IPAQ).[26,27] The PFP group also completed the following related to their pain: McGill Pain Questionnaire, Pain Catastrophizing Scale, Fear-Avoidance Beliefs Questionnaire for the Knee (FABQ-Knee), and Pain Self-Efficacy Questionnaire (PSEQ).[28–31]

Statistical Analysis

Statistical analyses were conducted using SPSS 28.0 (IBM Corporation). Due to small, unequal sample sizes between groups, we conducted separate Welch tests for TSP, PPTs, and CPM. Due to the PPT and CPM measurements occurring at 4 test sites, a Bonferroni-corrected, α level was applied a priori ($\alpha = .0125$). Descriptive statistics (mean ± SD for normally distributed variables and median [interquartile range] for nonnormally distributed variables) were used to characterize the sample. Data normality was assessed using Kolmogorov-Smirnoff tests. Demographic and self-reported data were analyzed with Welch tests to illustrate group characteristics. Effect sizes were calculated using Cohen d for all comparisons and interpretations were based on $\leq$0.19 = *trivial*, 0.2–0.59 = *small*, 0.06–1.19 = *moderate*, and $\geq$1.2 = *large*.[32]

RESULTS

Participant Characteristics

Thirty-three females participated in the study (13 in the CON group, 20 in the PFP group). No significant differences were found between groups for age, height, weight, or body mass index. The PFP group reported greater perceived dysfunction (ie, higher KOOS and KOOS-PF scores) but similar physical activity levels compared with the CON group (moderate to high activity levels in >90% of each group sample). Descriptive group statistics for these and for self-reported inventories are reported in the Table.

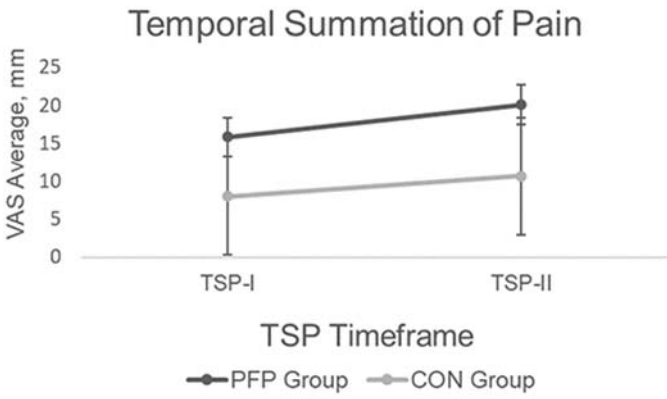

Figure 3. Temporal summation of pain (TSP) by group. TSP-I = mean of applications 2–4, TSP-II = mean of applications 8–10. Note that, in the statistical analysis, the difference score = (TSP response = TSP-II − TSP-I) was compared between groups. Patellofemoral pain (PFP) group (dark line) TSP difference scores were higher than the control (CON) group (light line). This figure illustrates changes in pain intensity (visual analog scale) over time. Error bars represent standard deviations. Significant differences were observed at the *P* = .05 level.

Quantitative Sensory Testing

Females with PFP exhibited higher TSP responses (mean = 6.5 ± 7.7; 95% confidence interval [CI] = 2.9, 10.1) than the CON group (mean = 1.9 ± 2.6; 95% CI = 0.31, 3.45; Welch W [1, 25.1] = 6.23; $P = .019$; Figure 3) with moderate effect sizes (d = 0.76).

No significant between-groups differences in PPTs were observed at any of the 4 test sites: lateral (Welch W [1,30.5] = 2.06; $P = .161$; PFP group 95% CI = 248.4, 364.2; CON group 95% CI = 305.4, 414.4), the center of the patella (Welch W [1, 26.95] = 0.003; $P = .959$; PFP group 95% CI = 312.9, 438.8; CON group 95% CI = 301.9, 454.6), medial (Welch W [1, 22.05] = 0.177; $P = .678$; PFP group 95% CI = 238.2, 332.7; CON group 95% CI = 228.1, 377.4), or the hand (Welch W [1,22.29] = 0.512; $P = .482$; PFP group 95% CI = 251.9, 435.6; CON group 95% CI = 255.2, 435.6; Figure 4).

Females with PFP exhibited lower CPM percent difference (eg, CPM response) than the CON group at the hand (Welch W [1,19.582] = 9.02; $P = .007$; PFP group 95% CI = −19.8, −1.6; CON group 95% CI = −0.9, 32.7) and at the center of the patella (Welch W [1, 25.34] = 7.86; $P = .010$; PFP group 95% CI = −18.4, 5.9; CON group 95% CI = 4.0, 36.2). Moderate effect sizes were observed at the center of patella (d = 1.03) and remote sites (d = 1.19). No differences were observed at sites medial (Welch W [1, 30.39] = 0.083; $P = .775$; PFP group 95% CI = −12.1, 22.3; CON group 95% CI = −4.2, 20.2) or lateral (Welch W [1,25.99] = 0.138; $P = .71$; PFP group 95% CI = −13.9, 6.8; CON group 95% CI = −13.9, 12.6) to the patella (Figure 5).

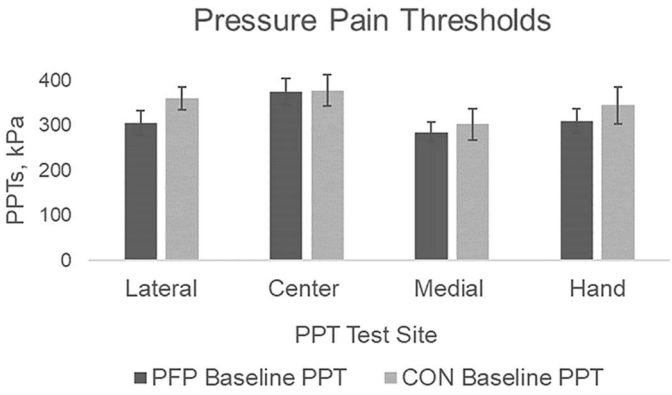

Figure 4. Pressure pain thresholds (PPTs) by test site. PPT group means are displayed as bars (patellofemoral pain [PFP] = dark bar, control [CON] = light bar), with error bars indicating the standard deviation. Lateral = 3 cm lateral to the patella, center = center of patella, medial = 3 cm medial to the patella, hand = third middle phalanx (remote site). No significant differences were observed at the *P* = .0125 level.

DISCUSSION

The purpose of this study was to determine whether females with PFP demonstrate signs of central sensitization compared with pain-free females. We observed differences in TSP and CPM responses but no differences in PPTs at local or remote sites. Our findings add to the mounting evidence that females with PFP demonstrate manifestations of central sensitization, including amplified pain facilitation mechanisms and impaired descending pain inhibition. Clinicians should be aware of these complex pain responses and their implications on treatment approach.[33]

When taken together, amplified pain facilitation and impaired pain inhibition can lead to an greater pain intensity, prolonged pain sensation, or both.[5] It is possible that the pain experienced in PFP is not the result of continual nociceptive input but rather is the net effect of dysfunctional pain modulation.[5] This is an important clinical distinction, though, as central sensitization pain may require different treatment mechanisms than nociceptive pain.[9,33] In our study, two-thirds of the PFP group demonstrated 2 or more of the 3 assessed signs of sensitization, and every PFP participant demonstrated lower CPM at 1 or more test sites.

Females with PFP exhibited higher TSP than the CON group, suggesting amplified excitatory pain facilitation.[10] Results from the previous 4 studies, in which authors examined TSP in participants with PFP, have not demonstrated a consensus, making comparison difficult.[23,33,34] Methodological differences are most likely to account for differences in study findings. A range of TSP assessment methods have been used in PFP investigations with no gold standard.[10] We used a monofilament method of TSP assessment, which has been used to identify TSP in other chronic musculoskeletal conditions but had not yet been evaluated in patients with PFP.[22] The monofilament method we used was developed as a reliable, cost-effective method, using equipment familiar to clinicians.[22] Comparatively, pinprick assessments, cuff algometry, and thermal heat testing methods have been used previously to assess TSP in individuals with PFP with equivocal results across studies.[23,33,34] Using the monofilament test facilitates clinical interpretation of our TSP findings to patient care. Females with PFP who have higher TSP may experience greater pain intensity than those without amplified pain facilitation.

Authors have widely reported lower PPTs in PFP groups compared with pain-free groups.[13,23,34–36] Females with PFP in our study did not exhibit greater pain sensitivity we expected, and in this study, we are the only researchers to demonstrate a lack of hypersensitivity to pain. The PPT group means in our study appear to be consistent with other PFP studies for the PFP group; however, the CON group means were lower than those in several studies.[23,25,33,34] The same inclusion and exclusion criteria (other than presence of PFP) were applied to both groups, so extraneous pain conditions or comorbidities should not have affected

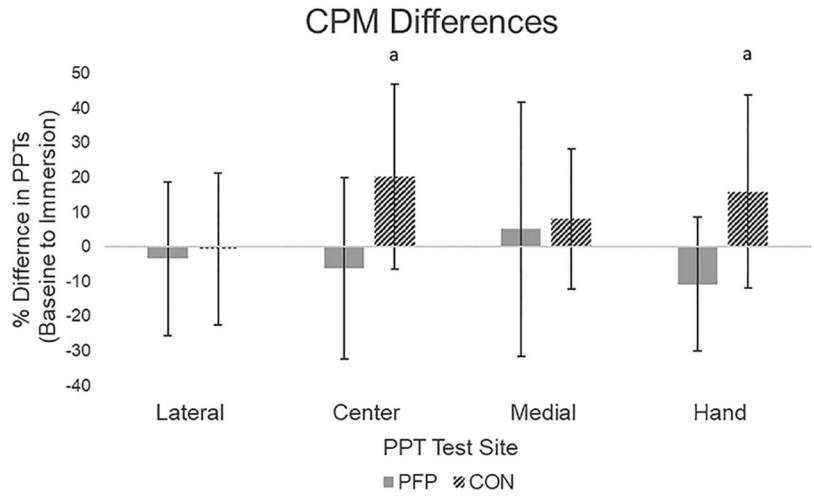

Figure 5. Conditioned pain modulation (CPM) percent difference. Bars indicate the percent difference between the ice immersion and baseline pressure pain threshold (PPT) values during the cold pressor test, with error bars representing the standard deviation. Patellofemoral pain (PFP) group = gray bars, control (CON) group = diagonal-lined bars. Lateral = 3 cm lateral to the patella, center = center of the patella, medial = 3 cm medial to the patella, hand = third middle phalanx (remote site). Positive values indicate that the ice-immersion PPTs were higher than baseline (functional CPM), while negative values represent ice immersion values that did not reach baseline (impaired CPM response). [a] Significance at the *P* = .0125 level.

the CON group PPT results. While we assessed several contextual and psychosocial factors, we did not identify a predominant contextual factor that led to lower CON group PPT means. Depression and low physical activity levels are associated with low PPTs (ie, increased pain sensitivity); however, the PFP and CON groups in our study reported similar self-reported stress, depression, and physical activity levels, and we were unable to identify rationale for the lower CON group values.[37] It is also possible that any number of factors could affect the individual pain experience (ie, social or physical activity changes, nutrition, caffeine use, hormone levels, inflammatory markers, pain-related anxiety, social anxiety) that may not have been identified in this study.[10]

We observed impaired CPM (ie, lower PPTs during ice immersion) at the center of the patella and remote site (hand) in the PFP group, indicating impaired pain inhibition mechanisms. We did not observe between-groups differences at the medial and lateral test sites between groups. We had hypothesized that both the patella and the femoral condyles (eg, medial, lateral sites) would induce an increased central nervous system response. It is possible that compression of the patella into the groove could have occurred during testing due to the position and direction of pressure application. This increased posteriorly directed pressure could mimic the increased patellofemoral joint contact forces females with PFP experience during activity. It is possible that the underlying condyles may not induce the same type of nociceptor response as the patella. These test-site-specific differences could also indicate that the peripheral nociceptor, rather than the central nociceptive neuron, is sensitized; however, the lack of group PPT differences does not support that hypothesis. Because the order of testing was standardized, the delivery of PPTs at the patella may have also led to heightened awareness or pain anticipation for the second set of PPTs delivered during the CPM protocol.

Conditioned pain modulation results in this study may differ from other authors due to our examination of female participants or due to methodological differences testing CPM. Authors who have examined a single group consisting of both males and females with PFP have tended not to report differences relative to a control group.[25,33,34] However, those who have only included females with PFP have observed between-groups CPM differences.[23,35] Sex differences in quantitative sensory testing exist in the population, though they have not been directly compared in PFP studies to our knowledge.[17] Additionally, several CPM assessment methods exist with no current gold standard for assessment. We chose to use the cold pressor test, as it is the most common CPM assessment method.[14] Though the cold pressor test has previously been used to assess CPM in individuals with PFP, minor differences in data collection methods, such as the temperature of ice immersion, can affect results.[14,25,34,35] Ultimately, our data support the notion that CPM is impaired in females with PFP. Females with PFP who have impaired descending pain inhibition may experience prolonged pain or may not achieve as much pain relief as those who have effective pain inhibition networks.

The biopsychosocial nature of pain produces some limitations in this study. For example, self-reported inventories regarding pain and function were only provided to the PFP group, assuming the CON group would not have data to report (given the long list of exclusion criteria). However, the CON group did report lower PPTs than the PFP group; therefore, the lack of data regarding pain and function in the CON group is a limitation. As previously stated, several methods of quantitative sensory testing are available to assess the efficiency of the central and peripheral nervous systems. No current gold standard exists that is practical in both research and clinical situations.[14] Females also demonstrate higher variability than males in existing assessment methods.[14] Second, within each quantitative sensory testing method, a variety of options exist for analysis. We selected methods that aligned with results of other PFP and knee osteoarthritis studies, but standardization is needed and has been called for by other authors.[14] High interpersonal variability exists with each of these measures, so results are best interpreted for the individual patient with PFP. Additionally, it is far more likely, given what is known about other chronic musculoskeletal pain conditions, that those with centrally sensitized PFP make up a subgroup of the PFP patient population.[15,16] Therefore, we are not advocating that every patient with PFP be treated as if his or her pain is centrally driven but that clinicians should assess signs of central sensitization for each patient as 1 part of the evaluation process and make appropriate patient-centered treatment considerations.

Several treatment approaches exist to restore pain facilitation and inhibition mechanisms for individuals with musculoskeletal pain conditions.[8,9] A PFP-specific approach does not yet exist. The current clinical practice guidelines for management of PFP only direct clinicians toward movement-based interventions such as strengthening and gait retraining.[1] These approaches may not be effective for someone exhibiting signs of central sensitization, as effective pain inhibition and facilitation mechanisms need to be restored. If these mechanisms are not restored, pain persistence or recurrence is likely.[8,9] Researchers should continue to investigate the interaction of central sensitization and pathomechanics, treatment strategies, and psychosocial factors in patients with PFP. Once these factors are better understood, treatment paradigms aligning with pain types should be explored and tested across sex and age groups with PFP.

CONCLUSIONS

Results from this study suggest that the pain experienced in PFP could, in part, be due to changes in pain modulation (specifically, amplified pain facilitation and impaired pain inhibition). Recognition of central sensitization is important in providing effective patient-centered care. Signs of altered pain modulation can be assessed clinically with quantitative sensory testing. When treatments target altered central pain mechanisms, restoration of effective pain modulation can occur.[8,9] Clinicians should consider pain sensitization status as an important factor in the development and persistence of PFP, to align treatments that target central pain modulation.

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REFERENCES

1. Willy RW, Hoglund LT, Barton CJ, et al. Patellofemoral pain. *J Orthop Sports Phys Ther*. 2019;49(9):CPG1–CPG95. doi:10.2519/jospt.2019.0302
2. Lankhorst NE, van Middelkoop M, Crossley KM, et al. Factors that predict a poor outcome 5–8 years after the diagnosis of patellofemoral pain: a multicentre observational analysis. *Br J Sports Med*. 2016;50(14):881–886. doi:10.1136/bjsports-2015-094664
3. Boling M, Padua D, Marshall S, Guskiewicz K, Pyne S, Beutler A. Gender differences in the incidence and prevalence of patellofemoral pain syndrome: epidemiology of patellofemoral pain. *Scand J Med Sci Sports*. 2010;20(5):725–730. doi:10.1111/j.1600-0838.2009.00996.x
4. Rathleff MS, Graven-Nielsen T, Hölmich P, et al. Activity modification and load management of adolescents with patellofemoral pain: a prospective intervention study including 151 adolescents. *Am J Sports Med*. 2019;47(7):1629–1637. doi:10.1177/0363546519843915
5. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011;152(3 suppl):S2–S15. doi:10.1016/j.pain.2010.09.030
6. Diekfuss JA, Grooms DR, Nissen KS, et al. Does central nervous system dysfunction underlie patellofemoral pain in young females? Examining brain functional connectivity in association with patient-reported outcomes. *J Orthop Res*. 2022;40(5):1083–1096. doi:10.1002/jor.25152
7. Te M, Baptista AF, Chipchase LS, Schabrun SM. Primary motor cortex organization is altered in persistent patellofemoral pain. *Pain Med*. 2017;18(11):2224–2234. doi:10.1093/pm/pnx036
8. Nijs J, Goubert D, Ickmans K. Recognition and treatment of central sensitization in chronic pain patients: not limited to specialized care. *J Orthop Sports Phys Ther*. 2016;46(12):1024–1028. doi:10.2519/jospt.2016.0612
9. Chimenti RL, Frey-Law LA, Sluka KA. A mechanism-based approach to physical therapist management of pain. *Phys Ther*. 2018;98(5):302–314. doi:10.1093/ptj/pzy030
10. Arendt-Nielsen L, Morlion B, Perrot S, et al. Assessment and manifestation of central sensitisation across different chronic pain conditions. *Eur J Pain*. 2018;22(2):216–241. doi:10.1002/ejp.1140
11. Treede RD. The role of quantitative sensory testing in the prediction of chronic pain. *Pain*. 2019;160(suppl 1):S66–S69. doi:10.1097/j.pain.0000000000001544
12. Arendt-Nielsen L, Simonsen O, Laursen MB, et al. Pain and sensitization after total knee replacement or nonsurgical treatment in patients with knee osteoarthritis: identifying potential predictors of outcome at 12 months. *Eur J Pain*. 2018;22(6):1088–1102. doi:10.1002/ejp.1193
13. Rathleff MS, Roos EM, Olesen JL, Rasmussen S, Arendt-Nielsen L. Lower mechanical pressure pain thresholds in female adolescents with patellofemoral pain syndrome. *J Orthop Sports Phys Ther*. 2013;43(6):414–421. doi:10.2519/jospt.2013.4383
14. Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice ASC. Reliability of conditioned pain modulation: a systematic review. *Pain*. 2016;157(11):2410–2419. doi:10.1097/j.pain.0000000000000689
15. Sigmund KJ, Bement MKH, Earl-Boehm JE. Exploring the pain in patellofemoral pain: a systematic review and meta-analysis examining signs of central sensitization. *J Athl Train*. 2021;56(8):887–901. doi:10.4085/1062-6050-0190.20
16. Bartholomew C, Lack S, Neal B. Altered pain processing and sensitisation is evident in adults with patellofemoral pain: a systematic review including meta-analysis and meta-regression. *Scand J Pain*. 2019;20(1):11–27. doi:10.1515/sjpain-2019-0079
17. Greenspan JD, Craft RM, LeResche L, et al. Consensus Working Group of the Sex, Gender, and Pain SIG of the IAS. Studying sex and gender differences in pain and analgesia: a consensus report. *Pain*. 2007;132(suppl 1):S26–S45. doi:10.1016/j.pain.2007.10.014
18. Hinman RS, Lentzos J, Vicenzino B, Crossley KM. Is patellofemoral osteoarthritis common in middle-aged people with chronic patellofemoral pain? *Arthritis Care Res (Hoboken)*. 2014;66(8):1252–1257. doi:10.1002/acr.22274
19. Cook C, Mabry L, Reiman MP, Hegedus EJ. Best tests/clinical findings for screening and diagnosis of patellofemoral pain syndrome: a systematic review. *Physiotherapy*. 2012;98(2):93–100. doi:10.1016/j.physio.2011.09.001
20. Crossley KM, Bennell KL, Cowan SM, Green S. Analysis of outcome measures for persons with patellofemoral pain: which are reliable and valid? *Arch Phys Med Rehabil*. 2004;85(5):815–822. doi:10.1016/S0003-9993(03)00613-0
21. Zhao Q, Bazzano LA, Cao J, et al. Reproducibility of blood pressure response to the cold pressor test: the GenSalt Study. *Am J Epidemiol*. 2012;176(suppl 7):S91–S98. doi:10.1093/aje/kws294
22. Osgood E, Trudeau JJ, Eaton TA, et al. Development of a bedside pain assessment kit for the classification of patients with osteoarthritis. *Rheumatol Int*. 2015;35(6):1005–1013. doi:10.1007/s00296-014-3191-z
23. Holden S, Straszek CL, Rathleff MS, Petersen KK, Roos EM, Graven-Nielsen T. Young females with long-standing patellofemoral pain display impaired conditioned pain modulation, increased temporal summation of pain, and widespread hyperalgesia. *Pain*. 2018;159(12):2530–2537. doi:10.1097/j.pain.0000000000001356
24. Arendt-Nielsen L, Nie H, Laursen MB, et al. Sensitization in patients with painful knee osteoarthritis. *Pain*. 2010;149(3):573–581. doi:10.1016/j.pain.2010.04.003
25. Rathleff MS, Rathleff CR, Stephenson A, et al. Adults with patellofemoral pain do not exhibit manifestations of peripheral and central sensitization when compared to healthy pain-free age and sex matched controls—an assessor blinded cross-sectional study. *PLoS One*. 2017;12(12):e0188930. doi:10.1371/journal.pone.0188930
26. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1:64. doi:10.1186/1477-7525-1-64
27. Craig CL, Marshall AL, Sjöström M, et al. International Physical Activity Questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381–1395. doi:10.1249/01.MSS.0000078924.61453.FB
28. Melzack R. The McGill Pain Questionnaire: from description to measurement. *Anesthesiology*. 2005;103(1):199–202. doi:10.1097/00000542-200507000-00028
29. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. *Psychol Assess*. 1995;7(4):524–532. doi:10.1037/1040-3590.7.4.524
30. Piva SR, Fitzgerald GK, Irrgang JJ, et al. Associates of physical function and pain in patients with patellofemoral pain syndrome. *Arch Phys Med Rehabil*. 2009;90(2):285–295. doi:10.1016/j.apmr.2008.08.214
31. Nicholas MK. The Pain Self-Efficacy Questionnaire: taking pain into account. *Eur J Pain*. 2007;11(2):153–163. doi:10.1016/j.ejpain.2005.12.008
32. Hopkins WG, Batterham AM. Error rates, decisive outcomes and publication bias with several inferential methods. *Sports Med*. 2016;46(10):1563–1573. doi:10.1007/s40279-016-0517-x
33. Rathleff MS, Petersen KK, Arendt-Nielsen L, Thorborg K, Graven-Nielsen T. Impaired conditioned pain modulation in young female adults with long-standing patellofemoral pain: a single blinded cross-sectional study. *Pain Med*. 2016;17(5):980–988. doi:10.1093/pm/pnv017
34. Maclachlan LR, Collins NJ, Hodges PW, Vicenzino B. Psychological and pain profiles in persons with patellofemoral pain as the primary symptom. *Eur J Pain*. 2020;24(6):1182–1196. doi:10.1002/ejp.1563

35. Eckenrode BJ, Kietrys DM, Brown A, Parrott JS, Noehren B. Signs of nervous system sensitization in female runners with chronic patellofemoral pain. *Int J Sports Phys Ther*. 2023;18(1):132–144. doi:10.26603/001c.57603
36. Pazzinatto MF, de Oliveira Silva D, Barton C, Rathleff MS, Briani RV, de Azevedo FM. Female adults with patellofemoral pain are characterized by widespread hyperalgesia, which is not affected immediately by patellofemoral joint loading. *Pain Med*. 2016;17(10):1953–1961. doi:10.1093/pm/pnw068
37. Hennings A, Schwarz MJ, Riemer S, Stapf TM, Selberdinger VB, Rief W. The influence of physical activity on pain thresholds in patients with depression and multiple somatoform symptoms. *Clin J Pain*. 2012;28(9):782–789. doi:10.1097/AJP.0b013e318243e2d1

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