Journal of Athletic Training 2021;56(8):887–901
doi: 10.4085/1062-6050-0190.20

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Exploring the Pain in Patellofemoral Pain: A Systematic Review and Meta-Analysis Examining Signs of Central Sensitization

Kemery J. Sigmund, MS, ATC*†; Marie K. Hoeger Bement, PhD, PT‡; Jennifer E. Earl-Boehm, PhD, ATC*

*Department of Rehabilitation Sciences, University of Wisconsin-Milwaukee; †Department of Health and Human Performance, Athletic Training Program, Concordia University Wisconsin, Mequon; ‡Department of Physical Therapy, Marquette University, Milwaukee, WI

Background: Patellofemoral pain (PFP) has high recurrence rates and minimal long-term treatment success. *Central sensitization* refers to dysfunctional pain modulation that occurs when nociceptive neurons become hyperresponsive. Researchers in this area of PFP have been increasingly productive in the past decade.

Objective: To determine whether evidence supports manifestations of central sensitization in individuals with PFP.

Data Sources: We searched MeSH terms for quantitative sensory testing (QST) pressure pain thresholds (PPTs), conditioned pain modulation (CPM), temporal summation, sensitization, hyperalgesia, and anterior knee pain or PFP in PubMed, SPORTDiscus, CINAHL, Academic Search Complete, and EBSCOhost.

Study Selection: Peer-reviewed studies that were written in English and published between 2005 and 2020 and investigated QST or pain mapping in a sample with PFP were included in this review.

Data Extraction: The initial search yielded 140 articles. After duplicates were removed, 78 abstracts were reviewed. The full text of 21 studies was examined, and we included 15 studies in our evaluation: 6 in the meta-analysis, 4 in the systematic review, and 5 in both the meta-analysis and systematic review.

Data Synthesis: A random-effects meta-analysis was conducted for 4 QST variables (local PPTs, remote PPTs, CPM, temporal summation). Strong evidence supported lower local and remote PPTs, impaired CPM, and facilitated temporal summation in individuals with PFP compared with pain-free individuals. Evidence for heat and cold pain thresholds was conflicting. Pain mapping demonstrated expanding pain patterns associated with long duration of PFP symptoms.

Conclusions: Signs of central sensitization were present in individuals with PFP, indicating altered pain modulation. The etiologic and treatment models of PFP should reflect the current body of evidence regarding central sensitization. Signs of central sensitization should be monitored clinically, and treatments with central effects should be considered as part of a multimodal plan of care.

Key Words: anterior knee pain, pain sensitization, hyperalgesia

Key Points

- Pain persistence in patients with patellofemoral pain may be the result of central sensitization.
- Individuals with patellofemoral pain demonstrated altered pressure pain thresholds, central pain inhibition, and central pain facilitation compared with pain-free individuals.
- Clinicians should incorporate quantitative sensory tests into the examination process to track improvement over time.

Patellofemoral pain (PFP) is a musculoskeletal pain condition affecting an estimated 25% of the population and is >2 times more prevalent in females.[1–3] A long duration of symptoms is a consistent predictor of poor treatment outcomes for individuals with PFP.[4–6] Currently accepted etiologic theory suggests that pathomechanics of the hip, knee, or foot and ankle lead to elevated patellofemoral joint loading, which drives nociception and pain.[7] Treatment strategies aimed at correcting observed pathomechanics or reducing patellofemoral joint loading have led to short-term pain relief; however, pain persists in >50% of patients at follow ups ranging from 1 to 8 years,[8–12] and PFP is recurrent in 70% to 90% of patients.[13] Whereas pathomechanics are one hypothetical factor in the development of PFP, researchers[14] studying other chronic musculoskeletal conditions have demonstrated the importance of central sensitization in the development of chronic pain.

Central sensitization has been defined by the International Association for the Study of Pain as "increased responsiveness of nociceptive neurons in the central nervous system."[15] Hallmarks of central sensitization include pain in the presence of a non-noxious stimulus (allodynia), pain hypersensitivity at the affected site (primary hyperalgesia), increased receptive fields, and pain hypersensitivity in uninjured tissues beyond the affected

area (secondary hyperalgesia).[16] The presence of central sensitization is especially important when providing health care to patients with chronic musculoskeletal pain, as it may guide treatment selection.[17]

Quantitative sensory testing (QST) is a test battery for assessing the state of endogenous pain facilitation and inhibition.[14,18] It has been used to demonstrate altered somatosensory function in patient populations or subgroups (eg, those with low back pain, knee osteoarthritis),[19,20] predict treatment response,[21–24] and guide treatment selection.[16,17,25] Pressure pain thresholds (PPTs), conditioned pain modulation (CPM), temporal summation of pain, and temperature pain and detection thresholds are all forms of QST.[14,18]

Pain thresholds represent the minimum stimulus (pressure, thermal, or electrical) that is perceived as painful.[14] Pressure pain thresholds are commonly used QST techniques and involve a mechanical stimulus (eg, pressure algometer or cuff algometer),[14] whereas thermal pain thresholds involve heat and cold stimuli.[26] Lower pain thresholds at the affected site (eg, the knee) indicate local pain hypersensitivity and reduced nociceptive thresholds in the peripheral nervous system. Lower pain thresholds remote to the affected site (eg, upper limb for a lower extremity condition) indicate widespread pain hypersensitivity and reduced nociceptive neuron thresholds in the central nervous system.[14,18,27,28]

Conditioned pain modulation is the concept that "pain inhibits pain" and assesses the integrity of central pain inhibition.[14,16,18] During a CPM protocol, pain from a noxious stimulus (test stimulus) is decreased by a second noxious stimulus (conditioning stimulus).[14,29] If there is minimal or no change in the perceived pain of the test stimulus with the conditioning stimulus, CPM is considered impaired. A reduced CPM response indicates less effective descending pain inhibition and is a manifestation of central sensitization.[16]

Temporal summation of pain assesses the efficiency of central pain facilitation.[14] To assess temporal summation, changes in pain perception over time are recorded during a sustained or repeated stimulus at a constant noxious intensity.[18] Increased pain reports over time indicate central sensitization.[14] Temporal summation can be measured using a variety of stimuli, ranging from the application of heat or cold pain to punctate temporal summation, which uses a repetitive pinprick test or monofilament application.[14,18] Facilitated temporal summation indicates enhanced central pain facilitation.[16]

Widespread pain is also indicative of dysfunctional peripheral or central pain modulation.[16] Pain maps allow patients to self-report the pain location and provide objective measures of the pain area. Spreading of a painful area beyond the affected body part (ie, the knee) or an increased number of painful sites may indicate widespread pain.[16,18]

In a systematic review, De Oliveira Silva et al[30] assessed the characteristics of pain sensitization in patients with chronic knee conditions. Moderate evidence supported hyperalgesia at the knee and upper limb in patients with PFP, indicating peripheral or central sensitization, respectively. Researchers in this area have been productive recently, and synthesis of these additional studies may provide further insight into central changes that occur in individuals with PFP, which may guide treatment decisions. Signs of central sensitization are neglected in current etiologic or treatment models of PFP. Treatment plans focusing on strengthening and movement quality alone may not address a key component contributing to pain persistence. Therefore, the question guiding this review was, "Do individuals with PFP exhibit signs of central sensitization compared with healthy, pain-free individuals?"

METHODS

Search Strategy

This systematic review was registered with PROSPERO (Registration No. CRD42019127548) and was prepared according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched MeSH terms for studies using QST methods and pain mapping in individuals with PFP in the PubMed, SPORTDiscus, CINAHL, Academic Search Complete, and EBSCOhost databases (Supplementary Table). The search took place between November 2018 and February 2019 and was repeated in June 2020. Studies were included if they were published in English in the past 15 years, included at least 1 QST or pain mapping measure in human participants, and included a between-subjects (PFP versus pain-free control) comparison for QST (or cross-sectional data for pain mapping).

Review Process

One researcher (K.J.S.) conducted the search across databases and exported all potential studies to EndNote X8 (Clarivate Analytics) for cross-referencing. The process of article screening and review is outlined in Figure 1. Two researchers (K.J.S., J.E.E.B.) independently reviewed titles and abstracts for inclusion. No conflicts needed to be resolved at this stage. Full-text copies of the included articles were screened. Fifteen total studies were included, with 11 studies accepted for the meta-analysis and 9 for the systematic review. Two reviewers (K.J.S., M.K.H.B.) independently conducted a quality review using the modified Downs and Black checklist.[31] The reviewers first discussed any scoring differences, and a plan was in place to have a third reviewer resolve any disputes. No differences required third-party resolution.

Data Extraction

We extracted the following information: publication information (author, year, study design, journal), number of participants, participant characteristics (age, sex, any grouping variables and characteristics), and outcome measures from QST variables (means and SDs or CIs). When CIs were reported instead of SDs, we converted them to SDs. Data not presented in the full text of articles or supplementary data files were requested from 2 primary authors, who provided these values or data files.

Quality Assessment

The modified Downs and Black checklist was selected for quality assessment based on the expectation that most

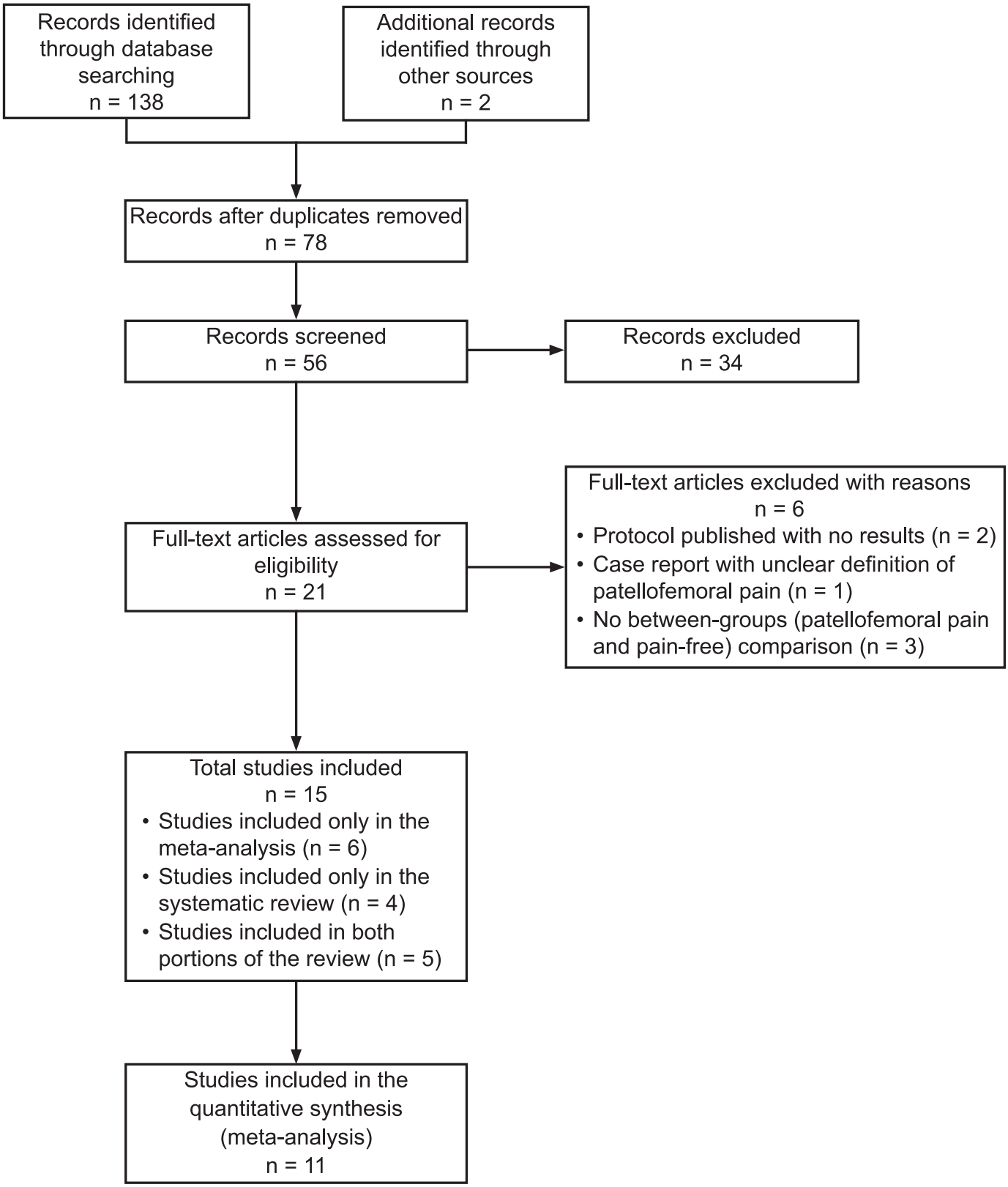

Figure 1. Flowchart of search.

studies would have cross-sectional designs.[32] The modified Downs and Black checklist has a total of 16 scored items across 5 categories (reporting, external validity, internal validity [bias, internal validity], confounding, and power).[32,33] The maximum score is 17, with 15 items scored from 0 to 1 point, and 1 item scored from 0 to 2 points, where 0 indicates lower quality and higher numbers indicate higher quality.

Table 1. Description of Criteria of van Tulder et al[34]

Criterion	Description
Strong	Data pooled from ≥3 studies Minimum of 2 high-quality homogeneous studies Result may be statistically significant or nonsignificant
Moderate	Statistically significant pooled results from multiple heterogeneous studies Includes 1 high-quality study or multiple low-quality homogeneous studies
Limited	Statistically heterogeneous results from 1 high-quality study or multiple low-quality studies
Very limited	Results from 1 low-quality study
Conflicting	Pooled results that are nonsignificant Results derived from multiple statistically heterogeneous studies, regardless of quality

Risk of Bias and Publication Bias

Risk of bias was assessed using the Cochrane risk of bias tool in RevMan 5.0 (Cochrane). Publication bias was assessed using RevMan 5.0 for homogeneous groups of studies.

Data Synthesis and Analysis

A random-effects meta-analysis was conducted for QST variables with ≥3 studies (local PPTs, remote PPTs, and CPM) using RevMan 5.0. For all other variables, too few authors of studies used similar methods to pool data. A moderator analysis was conducted for local and remote PPTs. We report the standardized mean differences (SMDs) with 95% CIs, χ^2 statistics, τ values, I^2 values, and results for the overall effect.

Studies for which meta-analysis was not possible are described qualitatively using means and SDs or medians and interquartile ranges when appropriate. Strength of evidence is described using the criteria of van Tulder et al[34] for the levels of evidence, which categorize studies based on statistical homogeneity (Table 1). Subgroup analyses were conducted after initial review of the evidence and when heterogeneity of pooled results was observed. Moderator analysis was selected because there were too few studies per outcome variable to properly power a meta-regression and allow appropriate interpretation of results.[35]

RESULTS

Study Characteristics

A total of 15 studies were included in this review: 6 in the meta-analysis only,[37–39,41,42,44] 4 in the systematic review only,[45–48] and 5 in both portions of the review.[27,28,36,40,43] Eleven evaluated PPTs at the knee,[27,28.36–44] 10 assessed PPTs at a remote site,[27,28,36–41,43,44] 5 assessed CPM,[27,36,40,43,44] 4 evaluated temporal summation[36,40,43,44] 3 evaluated heat and cold pain thresholds,[43,45,46] and 6 used pain-mapping techniques.[27,28,36,40,47,48] A total of 14 investigations were cross-sectional, and 1 was a cohort study. For the cohort study,[44] only cross-sectional between-groups baseline data were extracted for data analysis, as the aim of our review was not to determine treatment effects. Study and participant characteristics are described in Table 2, and quality scores are provided in Table 3.

Strong evidence (n = 983) from 6 high-quality[27,28,36,40,43,44] and 5 moderate-quality[37–39,41,42] studies supported a large SMD (–0.86; 95% CI = –1.13, –0.59; Figure 2) that was different in local (knee) PPTs between individuals with PFP and healthy, pain-free control individuals. A post hoc subgroup analysis was conducted to explore the effect of sex (female-only studies versus mixed-sex studies) on local PPTs. Subgroup analysis demonstrated maintained heterogeneity (I^2 = 73% and 16%, respectively; Figure 2) and differences ($P \leq .001$ for each subgroup).

Strong evidence (n = 946) from 6 high-quality[27,28,36,40,43,44] and 4 moderate-quality[37–39,41] studies was observed for a moderate SMD that was different in remote (upper limb) PPTs between individuals with PFP and the healthy, pain-free control group (SMD = –0.72 [–0.97, –0.47]; Figure 3). We conducted a post hoc subgroup analysis to explore the effect of sex on remote PPTs. This analysis demonstrated maintained heterogeneity in mixed-sex (I^2 = 41%) and female-only (I^2 = 51%) cohorts and differences ($P < .001$ for mixed-sex and female-only studies).

Strong evidence (n = 554) from 5 high-quality studies[27,36,40,43,44] supported a small SMD (–0.42 [–0.61, –0.24]; $P < .001$) that was different for the CPM response between individuals with PFP and healthy, pain-free control individuals (Figure 4). Subgroup analysis (for sex or other variables) was not conducted for CPM, as no heterogeneity was present (I^2 = 0%).

Strong evidence (n = 492) from 4 high-quality studies[27,36,43,44] supported a moderate SMD (0.69 [0.48, 0.90]) that was different for the temporal summation responses between those with PFP and pain-free control individuals (Figure 5). Subgroup analysis was not conducted for CPM, as no heterogeneity existed (I^2 = 0%).

Systematic Review

We conducted a systematic review of the data that could not be pooled because of a low number of total studies or differences in methods that did not allow for pooled results. Nine studies were included in the systematic review: 3 assessed thermal pain thresholds,[43,45,46] and 6 assessed pain mapping.[27,28,36,40,47,48]

Thermal Pain Thresholds. Conflicting evidence has been reported for heat and cold pain thresholds for participants with PFP.[43,45,46] The SMDs could not be calculated because the data were not normally distributed in 1 study.[46] One group[43] reported a large effect size (1.2; 95% CI = 0.8, 1.63), demonstrating lower heat pain thresholds at the knee in the PFP group than in the pain-free group (n = 211), whereas another[45] reported no differences between groups (n = 48).

Pain Mapping. Six high-quality studies[27,28,36,40,47,48] (n = 583) provided evidence that could not be pooled because of variations in methods and reporting. Three studies[27,28,40] used pain-mapping information to characterize and group the location of pain into retropatellar, peripatellar, or both, and total pain-area data were not reported. One group of researchers[36] identified a higher number of painful sites with increased symptom duration in the PFP group relative to a pain-free group. Two studies[47,48] demonstrated increased pain area (pixels) using a digital knee map.

Table 2. Study Characteristics Extended on Next Page

Study	Participants, No. (age, y, mean ± SD or median [IQR])	PFP Symptom Duration, mo, Mean ± SD or Median (IQR)	Patient-Reported Outcome Score, Mean ± SD or Median
Boudreau et al[47] (2017)	35 with PFP (18.8 ± 1.7): 2 males, 33 females	60 ± 33	NR
Boudreau et al[48] (2018)	299 with PFP: 126 males (23.1 ± 8.2), 173 females (19.1 ± 8.2)	24 (12–48)	NR
Holden et al[36] (2018)	65 females: 36 with PFP (22.8 ± 1.1), 29 CON (23.1 ± 1.2)	96 (84–120)	KOOS-Symptoms: 71 ± 16; KOOS-Pain: 67 ± 13; KOOS-ADL: 78 ± 13; KOOS-Sport and Recreation: 48 ± 21; KOOS-Quality of Life: 51 ± 21
Holden et al[44] (2020)	201 total: 151 with PFP (36 males, 115 females; 12 ± 1.2), 50 pain-free (19 males, 31 females; 12.3 ± 1.4)	18 (9–24)	KOOS-Symptoms: 78.2 ± 12.2; KOOS-Pain: 68.5 ± 1.2; KOOS-ADL: 79 ± 14.3; KOOS-Sport and Recreation: 55.3 ± 21.2; KOOS-Quality of Life: 49.3 ± 15.5
Jensen et al[45] (2007)	48 total: 25 with unilateral PFP (9 males, 16 females; 32 [19–44]), 23 healthy (11 males, 12 females; 29 [18–44])	74 (12–260)	NR
Jensen et al[46] (2008)	114 total: 91 with unilateral PFP (56 males, 35 females; 31.2), 23 healthy (11 males, 12 females; 29)	70 (3–240)	Cincinnati Rating Scale: 66
Maclachlan et al[43] (2020)	211 total: 150 with PFP (53 males, 97 females; 32.1), 61 CON (24 males, 37 females; 32.6)	<6: 7.4%; 6–12: 3.3%; 13–60: 37.3%; 60–120: 20.7%; >120: 31.3%	AKPS: 72.5 ± 12; KOOS-Symptoms: 78.4 ± 12.5; KOOS-Pain: 75.8 ± 12.9; KOOS-ADL: 85.7 ± 13.5; KOOS-Sport and Recreation: 65.8 ± 19.7; KOOS-Quality of Life: 51.9 ± 20.5; KOOS-PF: 61.8 ± 17.9
Noehren et al[37] (2016)	40 females: 20 with PFP (23.2 ± 5.6), 20 CON (22.7 ± 5.0)	40.8 ± 52.8	NR
Pazzinatto et al[38] (2016)	71 female runners: 38 with PFP (21.6 ± 2.6), 33 asymptomatic CON (22.4 ± 3.5)	62.3 ± 46.1	NR
Pazzinatto et al[39] (2017)	40 female runners: 20 with PFP (25.62 ± 4.05), 20 asymptomatic CON (27 ± 5.58)	37.7 ± 49.3	AKPS: 80.45
Rathleff et al[28] (2013)	79 female adolescents: 57 with PFP (17.13 ± 1.1), 22 CON (17.1 ± 0.9)	34 (18–51)	KOOS-Symptoms: 97.7 ± 3; KOOS-Pain: 99.7 ± 1.2; KOOS-ADL: 99.9 ± 0.3; KOOS-Sport and Recreation: 99.5 ± 1.5; KOOS-Quality of Life: 99.1 ± 2.1

Table 2. Extended From Previous Page

Body Mass Index, Mean	Physical Activity Level	Pain Intensity, Mean ± SD or Median (IQR)[a]	Type of QST	Summary of Findings
NR	NR	VAS current: 4.8 ± 2.7	PM	PM: Most patients reported peripatellar pain, less than half reported combined retropatellar and peripatellar pain, and 1 reported retropatellar pain. Patients with symptoms >5 y demonstrated larger pain area than did those with symptoms of <5 y. Most patients reported symmetric bilateral pain. Longer symptom duration was related to spreading of pain up the thigh and down the leg.
NR	NR	VAS worst: 5.0 (3.3–7.0)	PM	PM: No sex differences in pain clusters or distributions. Longer symptom duration was associated with bilateral PFP. Longer symptom durations were related to larger pain area and specific pain patterns, including pain up the thigh and down the lower leg. Pain intensity was not related to pain area.
PFP group: 24.1; CON group: 22.7	NR	NRS current: 2.0 ± 2.0; NRS worst previous 4 wk: 7.0 ± 2.0; NRS average previous 4 wk: 4.0 ± 1.0	PPTs, TSP, CPM, PM	Local PPTs: PFP group < CON group (center of patella). Remote PPT: PFP group < CON group (elbow). TSP: PFP group > CON group (cuff algometry). CPM: PFP group = CON group (cuff algometry). PM: Most of PFP group reported pain in an area in addition to the knee, and 21% of PFP group met American College of Rheumatology criteria for widespread pain.
NR	NR	NRS worst previous wk: 6.6 ± 2.2	PPTs, CPM, TSP	Local PPTs: PFP group < CON group (center of patella). Remote PPTs: PFP group < CON group (elbow). CPM: PFP group < CON group (cuff algometry). TSP: PFP group > CON group (cuff algometry).
PFP group: 23.8; CON group: 23.4	NR	VAS current: 2.4 (SD NR); VAS worst: 5.5 (SD NR)	HPT, CPT	HPT: PFP group = CON group. CPT: PFP group = CON group.
PFP group: 23.4; CON group: 23.1	NR	NR	HPT, CPT	HPT: PFP group = CON group. CPT: PFP group = CON group. Other: 32% of participants with PFP did not achieve CPT before cold limit (1°C). 15 With PFP reported heat sensation with CPT testing.
PFP group: 25.2; CON group: 24.0	Weekly activity level (IPAQ): PFP group, 4849.2; CON group, 3191.7	VAS worst: 5.4 ± 1.6	PPTs, TSP, CPM, HPT, CPT	Local PPTs: PFP group < CON group (center of patella). Remote PPTs: PFP group < CON group (elbow). TSP: PFP group > CON group (pinprick test). CPM: PFP group = CON group (cold pressor test). HPT: PFP group < CON group. CPT: PFP group < CON group.
NR	NR	NRS current: 5.8 ± 2.0	PPTs	Local PPTs: PFP group < CON group (patellar tendon). Remote PPTs: PFP group < CON group (elbow).
NR	NR	NR	PPTs	Local PPTs: PFP group < CON group (lateral to the patella). Remote PPTs: PFP group < CON group (elbow).
NR	Distance run per week: PFP group, 19.75 km; CON group, 20.75 km	VAS current: 1.2 ± 1.5; VAS worst previous mo: 4.8 ± 1.5	PPTs	Local PPTs: PFP group < CON group (center of patella). Remote PPTs: PFP group < CON group (elbow).
PFP group: 20.5; CON group: 21.4	NR	VAS worst: 5.0 (3.8–6.8); VAS current: 1.3 (0.3–2.7)	PPTs, PM	Local PPTs: PFP group < CON group (center of patella). Remote PPTs: PFP group < CON group (tibialis anterior). PM: Majority of PFP group reported bilateral pain that was peripatellar and diffuse.

Table 2. Continued From Previous Page

Study	Participants, No. (age, y, mean ± SD or median [IQR])	PFP Symptom Duration, mo, Mean ± SD or Median (IQR)	Patient-Reported Outcome Score, Mean ± SD or Median
Rathleff et al[40] (2016)	40 females: 20 with PFP (20 [19–21]), 20 CON (20.5 [20–21])	72 (4.5–7)	KOOS-Symptoms: 96 ± 5; KOOS-Pain: 99 ± 2; KOOS-ADL: 100 ± 1; KOOS-Sport and Recreation: 98 ± 3; KOOS-Quality of Life: 97 ± 7
Rathleff et al[27] (2017)	65 total: 33 with PFP (10 males, 23 females; 28.5 ± 5.3), 32 CON (10 males, 23 females; 27.1 ± 5.2)	24 (14–60)	NR
van der Heijden et al[42] (2015)	38 (12 males, 26 females): 22 with PFP (22 ± 5.8), 16 CON (22.5 ± 6.5)	12 ± 6.5	NR
van der Heijden et al[41] (2018)	134 adults and adolescents (60 males, 74 females): 64 with PFP (35 female, 29 males; 44 adults, 20 adolescents; 23.4 ± 7), 70 CON (41 females, 29 males; 50 adults, 20 adolescents; 23.1 ± 5.9)	Adults: 11 ± 6.4; Adolescents: 14.2 ± 8.1; Females: 13.7 ± 6.8; Males: 9.9 ± 7.1	AKPS: 66.3 ± 11.6

Abbreviations: AKPS, Anterior Knee Pain Scale; CON, control; CPM, conditioned pain modulation; CPT, cold pain threshold; HPT, heat pain threshold; IPAQ, International Physical Activity Questionnaire; IQR, Interquartile range; KOOS, Knee Osteoarthritis Outcome Score; NR, not reported; NRS, numeric rating scale; PF, Patellofemoral subscale; PFP, patellofemoral pain; PM, pain mapping; PPT, pressure pain thresholds; QST, quantitative sensory testing; TSP, temporal summation of pain; VAS, visual analog scale.

[a] Pain intensity was measured on either a 10-cm VAS or an NRS with a maximum score of 10.

Distinct pain patterns associated with spreading of pain up the thigh and down the lower leg were also associated with longer symptom durations. These findings lend support for central sensitization but warrant further examination.

Risk of Bias and Publication Bias. The risk-of-bias assessment indicated that allocation concealment and adequate expression of group differences may be threats to study validity (Table 4). Only 3 investigations[27,36,40] concealed group allocation from the researcher, which could have introduced researcher bias. Unpublished work in this area was not sought. This may have led to an increased risk of publication bias, regardless of our findings. A funnel plot for published studies of CPM (Figure 6) showed some asymmetry, likely due to the low number of studies ($k = 5$)[27,36,40,43,44] and small sample sizes in each study. A funnel plot for temporal summation produced a nearly vertical line with most results on the sensitized portion of the graph, indicating the likelihood that studies with results that were different may be published more frequently (Figure 7). This bias is difficult to confirm with no data from unpublished studies, a low number of studies ($k = 4$),[36,40,43,44] and small sample sizes. We could not assess publication bias for PPTs because of the heterogeneity observed in all meta-analysis results.[35]

DISCUSSION

The purpose of our review was to determine whether the current literature supports central sensitization in individuals with PFP compared with pain-free control individuals. Our findings supplied strong support for signs of central sensitization, including lower local and remote PPTs, impaired CPM, and facilitated temporal summation in those with PFP. The evidence was conflicting regarding altered heat and cold pain thresholds in individuals with PFP. Signs of central sensitization demonstrated ineffective pain modulation in the central nervous system. Although muscle weakness and altered biomechanics may be key components of PFP development, they may not be the only sources of pain persistence. Signs of central sensitization should be monitored clinically, and treatments with central effects should be considered part of a multimodal plan of care.

Potential Mechanisms of Central Sensitization in Patients With PFP

The cause of PFP is hypothesized to be pathomechanical. Motor and biomechanical dysfunction of the hip, knee, and foot or ankle have been proposed to lead to increased patellofemoral joint loading.[7] Treatments that align with this theory include movement retraining, hip and thigh

Table 2. Continued From Previous Page

Body Mass Index, Mean	Physical Activity Level	Pain Intensity, Mean ± SD or Median (IQR)[a]	Type of QST	Summary of Findings
NR	Sport participation: PFP group, 80%; CON group, 75%	NR	PPTs, TSP, CPM, PM	Local PPTs: PFP group < CON group (center of patella). Remote PPTs: PFP group < CON group (elbow). TSP: PFP group = CON group (cuff algometry). CPM: PFP group < CON group (cuff algometry). PM: Most participants with PFP reported peripatellar pain that included spreading pain up the thigh.
PFP group: 24.2; CON group: 21.9	NR	NRS worst previous wk: 5.0 (3.0–7.0)	PPTs, CPM, PM	Local PPTs: No difference between PFP and CON groups (center of patella). Remote PPTs: No difference between PFP and CON groups (elbow). CPM: PFP = CON group (cold-pressor test). PM: Most participants with PFP reported retropatellar pain and combined retropatellar and peripatellar pain. One reported only peripatellar pain.
PFP group: 23.9; CON group: 23.3	Sport participation: PFP group, 54.5%; CON group, 81.3%	NRS current: 4.7 ± 2.3	PPTs	Local PPTs: PFP group < CON group (center of patella).
PFP group: 23.6; CON group: 22.3	Sport participation: PFP group, 38%; CON group, 55%	NRS current: 4.7 (SD NR)	PPT	Local PPTs: PFP group < CON group (most painful location). Remote PPTs: PFP group < CON group (forearm). Other: age did not affect PPTs. Lower PPTs for females versus males for bilateral knees and the contralateral arm. Sex modified effect size between PFP and CON groups.

strengthening, and use of corrective orthoses. Despite the efficacy of these treatments, PFP has high rates of recurrence[9,12,49,50] and persistence.[13] With a centrally sensitized nervous system, a pain response to subsequent patellofemoral joint loading may reflect the functional state of central neurons[16] rather than the state of the kinetic chain and patellofemoral joint loading. This means that clinicians may treat the underlying movement factors but still neglect a key mechanism of pain persistence. Treating a patient with signs of central sensitization requires a multimodal treatment plan that affects central pain-modulation mechanisms.[17] Clinicians would best serve patients with PFP by obtaining and tracking signs of sensitization to monitor progress.[17]

Table 3. Quality Review Based on Modified Downs and Black Scores[33]

Study	Score (No./17)	Quality
Boudreau et al[47] (2017)	13	High
Boudreau et al[48] (2018)	14	High
Holden et al[36] (2018)	14	High
Holden et al[44] (2020)	16	High
Jensen et al[45] (2007)	9	Low
Jensen et al[46] (2008)	8	Low
Maclachlan et al[43] (2020)	14	High
Noehren et al[37] (2016)	12	Moderate
Pazzinatto et al[38] (2016)	12	Moderate
Pazzinatto et al[39] (2017)	10	Moderate
Rathleff et al[28] (2013)	13	High
Rathleff et al[40] (2016)	13	High
Rathleff et al[27] (2017)	15	High
van der Heijden et al[42] (2015)	10	Moderate
van der Heijden et al[41] (2018)	12	Moderate

Participant Characteristics

Several interpersonal factors can affect central sensitization and pain perceptions.[43,51] Subjective clinical measures of pain intensity, age, sex, body mass index, physical activity level, perceptions of knee function, and symptom duration may play roles in QST responses. A breakdown of consistently reported participant characteristics is given in Table 2.

Symptom duration had a wide range (3.4 months to >10 years); however, authors of 13 of the 15 studies included in the review noted mean or median symptom durations of 18 months or longer.[27,28,36–40,43–48] Physical activity level was described in different units (mean weekly metabolic minutes of physical activity, kilometers of running per week, and percentage of sport participation) in 5 studies.[39–43] The PFP groups reported more metabolic minutes than did the pain-free groups,[43] PFP and healthy groups reported similar weekly running distances,[39] and comparisons of sport participation varied by study.[40,41,42] In 1 study,[43] 49% of the PFP group (PFP group: n = 150) indicated they stopped normal activity because of their knee pain. Body mass index was provided in 8 studies[27,28,36,41–43,45,46] and was higher in the PFP group in only 1 study.[41] Six investigations assessed females only,[28,36–40] 9 assessed mixed-sex cohorts,[27,41–48] and none assessed males only.

Measures of function and pain intensity were more commonly collected (Table 2). Whereas specific scores on

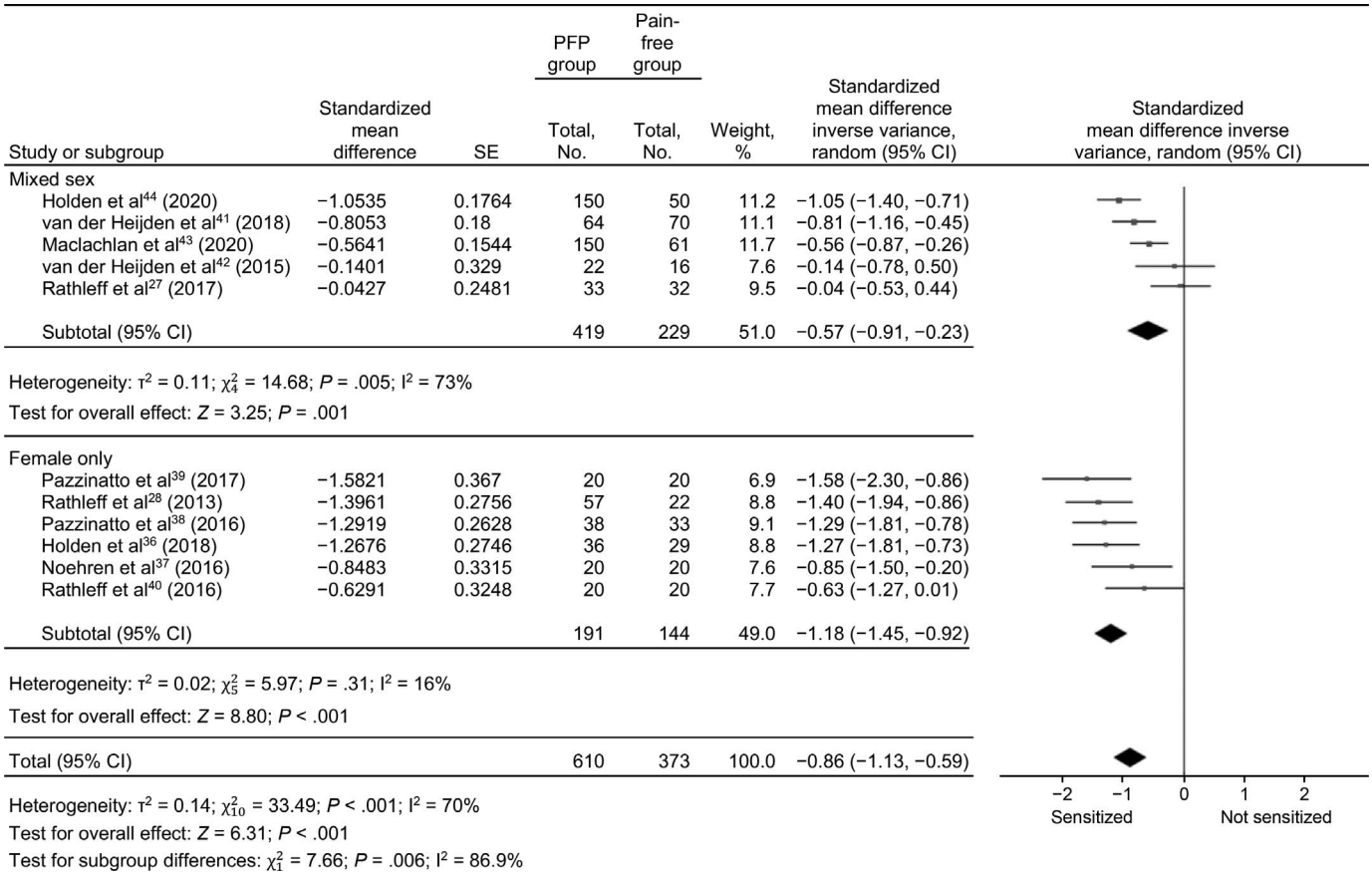

Figure 2. Meta-analysis results of local pressure pain thresholds. [a] Abbreviation: PFP, patellofemoral pain.

the Knee Osteoarthritis Outcome Score and Anterior Knee Pain Scale are not indicative of categorical function or ability, scores closer to 0 represent greater problems, and a score of 100 indicates no problems. The range of scores for the included studies was 63 to 100, which may suggest a moderate to low level of disability. Little evidence to date aligns relationships between central sensitization and perceptions of function. Researchers in 12 studies[27,28,36,37,39,41–45,47,48] reported pain intensity at the time of the study (current), worst pain, or pain in the past week or month using numeric rating scales or visual analog scales.

Patellofemoral pain is a condition affecting a wide age range, from adolescents to older adults.[52] Only 2 studies[28,44] involved participants with a mean age of <18 years; the mean age of participants was >25 years in 5 studies.[27,39,43,45,46] Some authors[50,52] have contended that PFP may be a different experience for adolescents than adults and that onset in adolescence may result in persistence or recurrence in adulthood. The effect of age on QST results should continue to be explored among individuals with PFP.

Pressure and Thermal Pain Thresholds

Strong evidence supported reduced local and remote PPTs in individuals with PFP. Nine of the included studies assessed pressure algometry,[27,28,36–40,43,44] and 2 studies assessed a handheld dynamometer method.[41,42] We observed group differences in all but 1 investigation,[27] and it may be worth noting that the mean age was older than that reported in most investigations (28.5 years). Based on our subgroup analyses, both female-only and mixed-sex studies maintained statistical heterogeneity. Sex should still be considered during analysis, as females experienced a variety of PFP symptoms and factors differently than did males,[36,40,53,54] but sex alone may not be enough to explain the observed differences in PPTs.

When considered alone, lower local (knee) PPTs are manifestations of peripheral sensitization; however, when considered concurrently with reduced remote PPTs, they indicate central excitability.[16,55] Some authors[55] have proposed a mechanism by which local joint nociceptors may maintain central sensitization. This hypothesis offers potential explanations for findings of local and widespread hyperalgesia in patients with chronic musculoskeletal conditions.[55] The authors postulated that peripheral sensitization spreads to extraterritorial regions by stimulating adjacent neurons in the dorsal horn of the spinal cord. Other researchers[16,18] have supported the idea that if the central nervous system is sensitized, peripheral nociceptors will also demonstrate increased excitability due to dysfunctional descending pain modulation. Without longitudinal evidence, it is impossible to make the distinction. Regardless of the mechanism, clinical manifestations of PFP include local and remote hyperalgesia. Assessing and tracking PPTs using a handheld pressure algometer (a quick, inexpensive, and easy-to-learn option for clinicians) would help clinicians monitor progress by providing an objective measure of pain hypersensitivity.

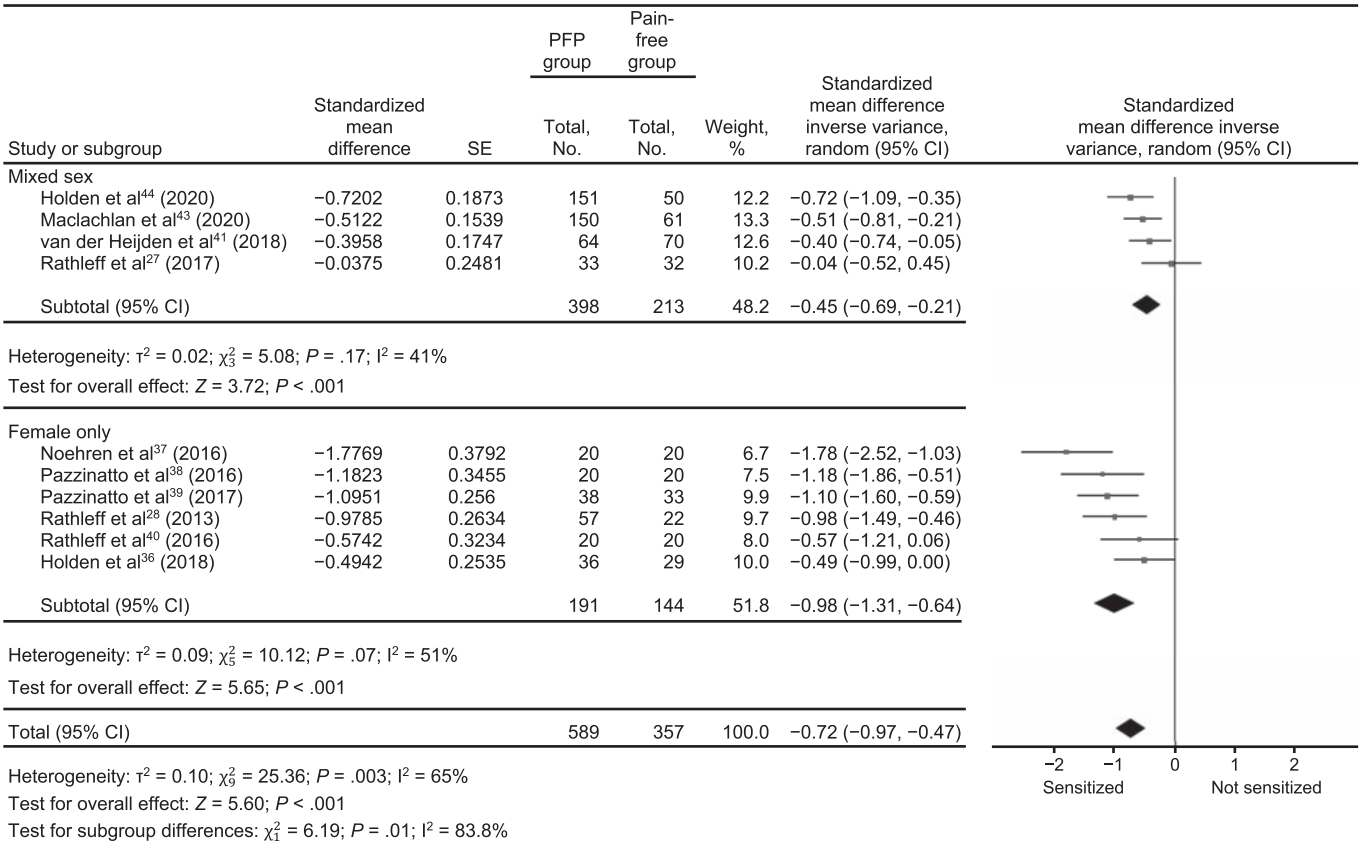

Figure 3. Meta-analysis results of remote pressure pain thresholds. [a] Abbreviation: PFP, patellofemoral pain.

Three studies[43,45,46] assessed thermal pain thresholds, but we could not pool those data. Two groups[45,46] reported no differences between heat and cold pain thresholds between groups, whereas 1 group[43] observed lower thresholds for both modalities in the individuals with PFP. Remote assessment was also conducted at the elbow in 1 investigation[43] and demonstrated lower thresholds for both (heat and cold) modalities in the patients with PFP. Jensen et al[46] noted that 32% of participants with PFP did not achieve cold pain thresholds before reaching the maximum temperature limit. Whereas we could not include these data in the final analysis, increased cold pain thresholds may be inferred due to the lower temperatures that would have been needed to sense pain.[46] This finding may also be a sign of *hypoesthesia*, or loss of sensation, which can manifest because of dysfunctional peripheral or central pain modulation.

Researchers[37,45,46] have hypothesized that nociception may be prioritized over touch and temperature information in individuals with PFP. Hypoesthesia, or impaired tactile sensation, was seen in 3 studies[37,45,46] and increased vibration thresholds in 1 study,[46] supporting this notion. When assessed concurrently with central sensitization, these data may support inhibition of non-noxious sensory information while nociceptive neurons are activated to subthreshold levels. Further examination is needed to better

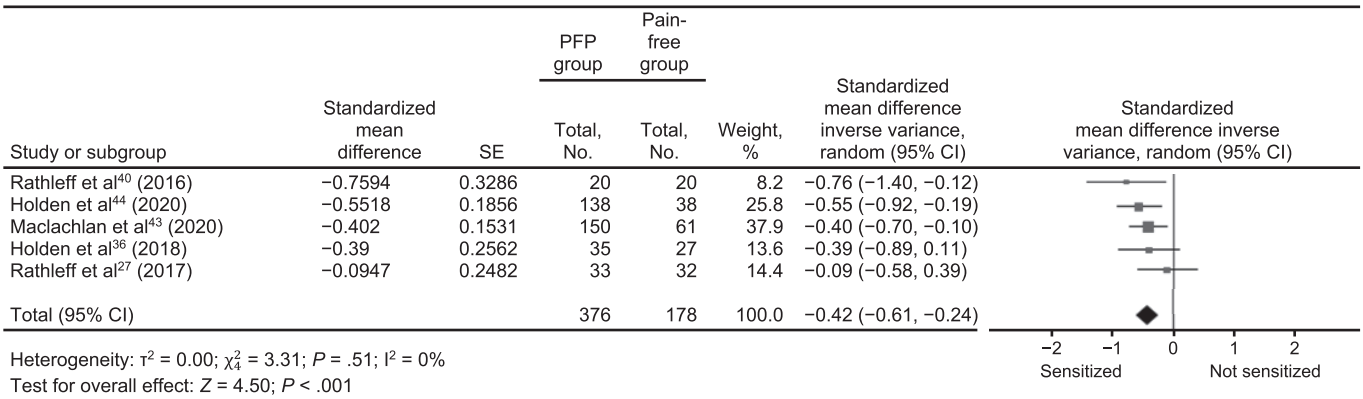

Figure 4. Meta-analysis results of conditioned pain modulation. [a] Abbreviation: PFP, patellofemoral pain.

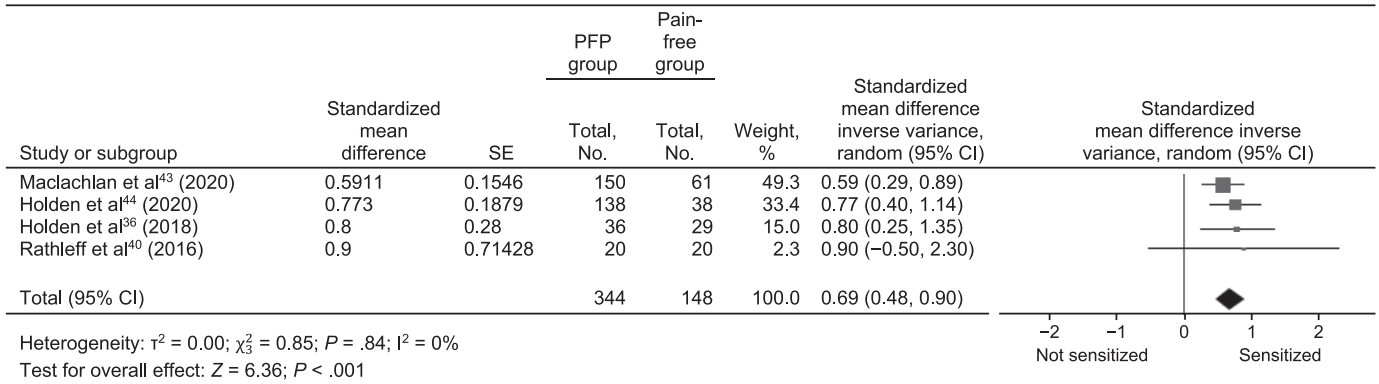

Figure 5. Meta-analysis results of remote temporal summation of pain. [a] Abbreviation: PFP, patellofemoral pain.

understand the role of thermal pain findings in this population.

Conditioned Pain Modulation

A key finding in this review was strong support for impaired CPM in individuals with PFP relative to pain-free individuals.[36,40,43,44] Impaired CPM represents inefficient central pain inhibition.[14] The CPM paradigms can be assessed using a variety of protocols.[29] Three studies included in this review used cuff algometry,[36,40,44] and 2 studies assessed the cold-pressor test.[27,43] Authors of 2[40,44] of the 3 studies that used cuff algometry reported impaired CPM in the PFP group, whereas neither of the 2 studies[27,43] that used the cold-pressor test demonstrated inefficient CPM in the PFP group. This could indicate that the type of conditioning stimulus affects the results even if the measurement unit (pressure in kilopascals) is the same. In addition, the pooled data did not reflect any heterogeneity, and both investigations that used the cold-pressor test involved mixed-sex cohorts, whereas 2[36,40] of the 3 studies assessing cuff algometry involved only females. The SMD was small but different for impaired CPM between groups, and 3[27,43,44] of 5 studies involved mixed-sex samples. We recommend that sex should continue to be considered a subgrouping variable in order to better understand whether sex differences exist.

The CPM responses exist on a continuum and are associated with wide interpersonal differences.[14] For this reason, identifying and tracking within-patient CPM responses can test and ensure restoration of efficient central pain modulation pathways. In other chronic musculoskeletal pain conditions, impaired CPM has been hypothesized to affect a subgroup of the overall patient population, and the same should be expected in PFP.[14,18] Clinical assessment of CPM would be useful for determining individual responses and can be used to monitor descending central pain modulation.

Temporal Summation of Pain

Another key finding from this review was strong evidence[36,40,43,44] for enhanced temporal summation in individuals with PFP. Enhanced temporal summation represents increased central pain facilitation. Three groups of researchers[36,40,44] used cuff algometry, and 1 group[43] used the pinprick test to assess temporal summation. Two sets of authors[36,40] included only females with PFP, and 2 sets of authors[43,44] included both males and females. All studies[36,40,43,44] examined individuals with longstanding PFP symptoms (range = 4.5 months to >10 years).

Table 4. Risk of Bias[a]

Study	Clear Purpose and Aim?	Allocation Concealed?	Unreported or Loss of Participant Data (>2 cases)	Group Differences Reported (Mean ± SD or 95% CI)
Boudreau et al[47] (2017)	+	NS	+	+
Boudreau et al[48] (2018)	+	NS	−	+
Holden et al[36] (2018)	+	+	+	+
Holden et al[44] (2020)	+	NS	+	+
Jensen et al[45] (2007)	+	−	−	+
Jensen et al[46] (2008)	+	−	+	+
Maclachlan et al[43] (2020)	+	NS	+	+
Noehren et al[37] (2016)	+	−	+	+
Pazzinatto et al[38] (2016)	+	−	−	+
Pazzinatto et al[39] (2017)	+	−	−	+
Rathleff et al[28] (2013)	+	−	−	+
Rathleff et al[40] (2016)	+	+	+	+
Rathleff et al[27] (2017)	+	+	−	−
van der Heijden et al[42] (2015)	+	−	+	+
van der Heijden et al[41] (2018)	+	−	+	+

Abbreviation: NS, not specified.

[a] + Indicates no risk of bias and − indicates risk of bias in this category.

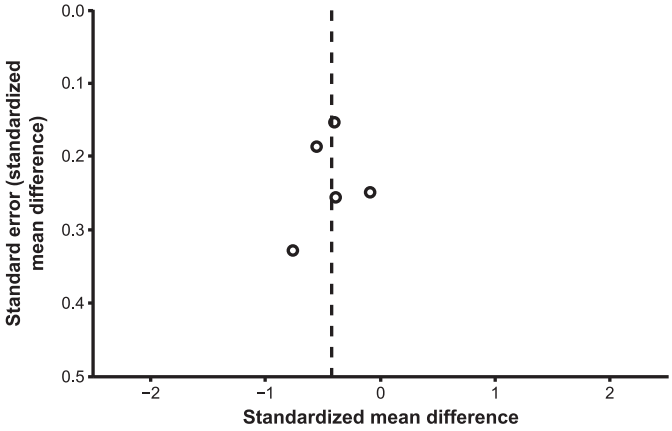

Figure 6. Funnel plot of results from published conditioned pain modulation studies.

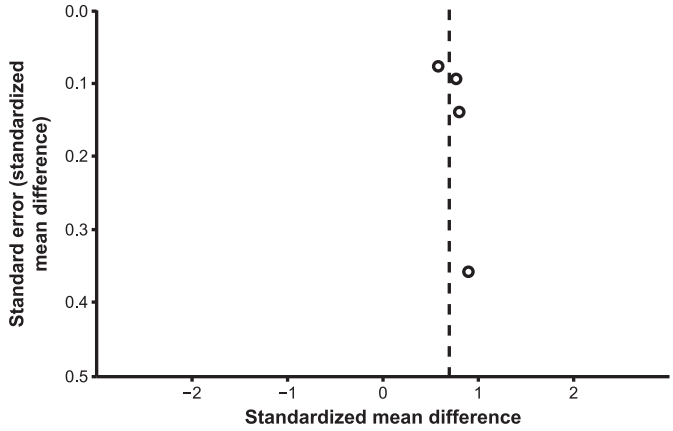

Figure 7. Funnel plot of results from published temporal summation of pain studies.

Analyses of temporal summation responses differed across studies, which may have resulted in different outcomes. Rathleff et al[40] used normalized visual analog scale scores from each of the 10 consecutive test intervals, Holden et al[36] assessed the difference in visual analog scale averages from the last 3 intervals and the second through fourth intervals, and Maclachlan et al[43] measured the maximum possible effect as a percentage between the first and worst numeric rating scale. Interestingly, Holden et al[36] also observed a lower temporal summation response for individuals who had recovered from PFP compared with those who were currently symptomatic. Both PFP groups reported enhanced pain facilitation relative to the pain-free group.[36] Temporal summation responses may be restored among patients with PFP, supporting the clinical relevance of these findings.[17]

Pain Mapping

Pain mapping can provide evidence of widespread pain. Unfortunately, only 2 pain-mapping studies[47,48] involved the same methods or reported outcomes, making an analysis of pooled information difficult. Five[27,28,40,47,48] of the 6 studies[27,28,36,40,47,48] in this area only assessed a knee pain map, which differed among investigations, and 1[36] assessed pain maps for a number of painful sites. Other painful locations were the hip, pelvis, back, and neck.[36,47,48] However, we were able to determine from the existing evidence that individuals with PFP may have an increased pain area or number of painful sites as symptoms persist over time.[27,28,36,47,48] In fact, Boudreau et al[47,48] suggested that specific pain patterns may extend beyond the knee with increased symptom duration. The observed patterns represented a broader pain area around the knee in addition to pain spreading up the thigh and down the lower leg.[47,48] These results are supported by Rathleff et al,[28] who noted that diffuse pain was experienced by 54% of the sample, regional pain by 30%, and local pain by only 16%. Bilateral PFP[28,47,48] was more common than unilateral PFP. Bilateral PFP was also associated with longer symptom durations (median = 24 months; interquartile range = 12–60 months), and patients with bilateral pain described mirror-image pain in 56% of cases.[48] Both neural and immune factors have been hypothesized to cause mirror-image pain patterns, and this finding is commonly attributed to central sensitization, especially if the original pain was unilateral.[56] In the data presented, whether the original onset of pain was bilateral, mirror image, or unilateral was not indicated, but this aspect would be an interesting addition to the pain-mapping research in patients with PFP.

Although pain maps limited to the knee can provide useful information on localized pain, widespread pain may be better portrayed on bilateral lower extremity or whole-body maps. To improve our understanding of the effect that expanding pain areas have on individuals with PFP, consistency in analyzing and reporting these data is important. Pain spreading beyond the knee and mirror-image bilateral pain offer support for central sensitization.

Risk of Bias and Publication Bias

Our assessment of the risk of bias suggested that more studies in which group allocation is concealed from the researcher are needed. We could not properly evaluate publication bias because of the lack of homogeneity in results and a lack of data regarding unpublished or prepublication studies. This information may be useful in drawing meaningful conclusions and extrapolating the results of this review to the population with PFP.

Clinical Relevance

Although exploration of treatment effects was beyond the scope of our review, central pain modulation has been effectively restored using interventions with known central effects. These treatment options include transcutaneous electrical nerve stimulation, manual therapy, pain education, and exercise therapy. Thus far, few researchers have explored the effectiveness of these interventions in patients with PFP. Given the hypothesized pathomechanical cause of the condition, it is necessary to determine whether central sensitization has any effect on or relation to observed movement or motor dysfunction. Without that information, a multimodal patient-centered treatment approach may offer the best opportunity for long-term symptom relief. If restoration of central pain modulation, pain control, or coping can occur, then movement retraining and exercise therapy may be more effective than using any of the aforementioned interventions alone.

Central sensitization mechanisms may reflect a subgroup of patients with PFP. In this case, it would be important to screen patients individually in order to select a treatment program that accounts for central changes. In addition, QST can be tracked over time to determine whether selected treatment approaches effectively restore normal central pain modulation.

A variety of QST protocols and methods can be applied clinically. One example is handheld algometers, which are an affordable clinical alternative to computerized algometers, although they cannot standardize the pressure delivered over time. Similarly, PPTs can be used to determine the magnitude of CPM. In this test, the CPM response is calculated by comparing PPTs before and during the application of another noxious stimulus (ie, ice immersion of an extremity). Temporal summation can be assessed via the change in reported pain intensity with repetitive application of a monofilament.

As our understanding of PFP evolves, the use of QST in the clinical environment becomes more imperative. In knee osteoarthritis (among other conditions), QST has helped to identify dysfunctional pain processing resulting from and contributing to pain perceptions.[57] The QST responses also predicted analgesic responses, operative and nonoperative treatment responses in individuals with knee osteoarthritis,[57] and chronic pain development.[14,16,18] The outcomes of QST can guide treatment selection among options with known peripheral or central effects.[17] Similar findings have not yet been reported for PFP; however, our review provides support for these endeavors.

Limitations

The main limitations of this review were the small number of studies for each QST variable and population differences among them. As discussed, personal factors (ie, age, sex, activity level) may play a role in pain perceptions during QST assessment. We were unable to identify the role of potential subgroups because of limited consistency in reported participant characteristics and inclusion of a wide variety of characteristics (ie, participants from adolescent through adulthood, both sexes). For example, we identified statistical heterogeneity for PPTs, but sex alone was not a factor that explained this finding.

Authors should continue to explore how these biopsychosocial factors influence QST to better interpret and apply these findings. The main risk of bias across studies was the lack of allocation concealment. Future investigators should blind researchers to group allocation whenever possible. Exploring treatment types that restore effective pain modulation in patients with PFP, as well as factors influencing QST in this population, will also be helpful.

CONCLUSIONS

Our findings support signs of central sensitization in patients with PFP compared with pain-free control individuals. For individuals with PFP who demonstrate signs of central sensitization, clinicians should structure a multimodal care plan that addresses both movement and pain, as these factors may contribute to pain persistence. Tracking these outcomes during rehabilitation can demonstrate restoration of effective central pain modulation, which may be critical for long-term treatment success.

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Address correspondence to Kemery J. Sigmund, MS, ATC, Department of Kinesiology, Integrative Health Care and Promotion Unit, University of Wisconsin-Milwaukee, 3409 North Down Avenue, Milwaukee, WI 532111. Address email to ksigmund@uwm.edu.