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Mechanistic pain profiling in young adolescents with patellofemoral pain before and after treatment: a prospective cohort study

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Abstract

Patellofemoral pain (PFP) is a common complaint among young sports active adolescents. This study evaluated the longitudinal changes in pronociceptive and antinociceptive mechanisms in young adolescents with PFP, their impact on prognosis, and responsiveness to treatment. Adolescents (N = 151, aged 10-14 years) diagnosed with PFP were compared with age-matched controls (N = 50) and subsequently tracked while participating in an intervention focussed on activity modification. They underwent quantitative sensory testing at baseline (preintervention), 4 weeks (during initial treatment), and 12 weeks (after treatment). Pressure pain thresholds (PPTs) were recorded on the knee, shin, and elbow. Temporal summation of pain (TSP) was assessed by the increase in pain intensity during 10 repeated cuff pressure pain stimulations on the leg. Conditioned pain modulation (CPM) was defined as change in cuff pain thresholds on one leg, during painful cuff conditioning on the contralateral leg. At baseline, adolescents with PFP had decreased PPTs at the knee, shin, and elbow ($P < 0.001$) as well as more facilitated TSP ($P < 0.05$) compared with controls. For CPM at baseline, controls displayed an increase in cuff pain thresholds during conditioning ($P < 0.05$), while those with PFP did not. More facilitated baseline TSP was associated with less improvements in pain intensity during the intervention ($P < 0.01$). Pressure pain thresholds increased at both follow-ups ($P < 0.001$), and the increased PPTs were associated with decreases in pain intensity ($r = 0.316$; $P < 0.001$). Overall, TSP remained facilitated at follow-ups, and there was no change in CPM. This is the first study to demonstrate a pronociceptive mechanism as a prognostic factor in young adolescents with PFP.

Keywords: Paediatric, Quantitative sensory testing, Musculoskeletal pain, Knee pain, Youth

1. Introduction

Musculoskeletal pain is one of the most frequent causes of years lived with disability among 10- to 14-year-old adolescents.[24] One in every 4 children and adolescents experience musculoskeletal pain on a weekly basis,[18] and the knee is the most common site.[32] The underlying cause is often unknown, and most children are diagnosed with an unspecific condition termed patellofemoral pain (PFP). Patellofemoral pain is characterised by diffuse anterior knee pain during everyday activities such as stair walking, running, and other activities that load the knee joint.[17] The localisation of symptoms varies considerably,[6] but it is a persistent and often recurring pain condition, where 4 in every 10 adolescents with PFP continue to suffer from PFP in early adulthood.[30]

In older adults with chronic long-standing knee pain conditions, psychophysical pain assessment has demonstrated altered pronociceptive and antinociceptive pain mechanisms, such as facilitated temporal summation of pain (TSP) and impaired conditioned pain modulation (CPM), respectively.[1] Associations between pain duration and these parameters[2] indicate the potential role of exposure to long-standing pain. In adolescents, those with chronic musculoskeletal pain demonstrate lower pain thresholds compared with pain-free controls, with no differences in CPM.[21] Although there is evidence of maturing somatosensory and pain perception during adolescence (ie, decreased pain sensitivity and increased pain inhibition),[4,39] it is unknown whether long-standing exposure to pain influences these developments.

Young adults in their early twenties with long-standing PFP demonstrate widespread pressure hyperalgesia (ie, increased sensitivity to pressure pain at remote locations) as well as facilitated TSP and impaired CPM.[13,31,33] Furthermore, young adults with a history of long-standing PFP during adolescence demonstrate increased localised knee pressure pain sensitivity and facilitated TSP relative to controls even after pain has resolved.[13] It is unknown whether younger adolescents (ie, <15 years) with PFP display alterations in pronociceptive and antinociceptive mechanisms or if these are associated with prognosis or change during treatment. This indicates a need to further investigate this prospectively in patients with PFP closer to the onset of pain (ie, in younger adolescents).

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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The aim of the current investigation was to (1) compare mechanistic pain profiles (pressure pain sensitivity, TSP, and CPM) in adolescents with PFP compared with pain-free controls, (2) evaluate the association between baseline mechanistic pain profiles and improvements in pain intensity after treatment, and (3) examine the temporal mechanistic pain profile during and after treatment in adolescents with PFP. It was hypothesised that (1) young adolescents with PFP will be characterised by widespread pressure pain hyperalgesia, facilitated TSP, and impaired CPM compared with controls, (2) improvements in self-reported pain intensity is associated with normalisation of the mechanistic pain profile, and (3) that increased pronociceptive and decreased antinociceptive mechanisms at baseline would predict less improvement in pain intensity during treatment.

2. Methods

2.1. Study design

This study was designed as a secondary analysis of a prospective cohort study analysing the effect of an activity intervention in young adolescents with PFP. The clinical outcomes of the intervention have been published elsewhere.[29] The prospective trial was registered a priori on clinical trials.gov (NCT02402673). The study was a multicentre (with one centre in Aalborg and one in Copenhagen, both Denmark) single cohort study examining activity modification in young adolescents with PFP. The research ethics committee of the Northern Denmark Region approved (N-20140100) the study, parental informed written consent was obtained before inclusion for all participants, and it was conducted in accordance with the Helsinki Declaration.

2.2. Participants

Adolescents between the ages of 10 to 14 years with PFP were recruited from schools and through social media between March 2015 and February 2016. Adolescents reporting knee pain within the specified age range were offered a clinical examination by 1 of 2 physiotherapists. The diagnosis of PFP was made in line with previously accepted criteria[7] and included (1) insidious onset of anterior knee or retropatellar pain of more than 6-week duration; (2) pain provoked by at least 2 of the following situations: prolonged sitting or kneeling, squatting, running, hopping, or stair climbing; (3) tenderness on palpation of the patella, pain when stepping down or double-leg squatting.

Participants were excluded if they were younger than 10 or older than 14 years, had concomitant injury or pain from the hip, lumbar spine, or other knee structures, previous knee surgery, self-reported patellofemoral instability, current physiotherapy for treating knee pain, or a diagnosis of other knee conditions that may present as anterior knee pain (Mb. Osgood Schlatter disease, iliotibial band syndrome, Sinding-Larsen–Johansson syndrome, patella tendinopathy, or similar).

Control participants were recruited, of a similar age and participation in sports as the PFP participants. No formal sample size was undertaken for this exploratory study.

2.3. Intervention

All participants were exposed to an intervention, consisting of activity modification, education, and graded return to sport. The intervention was delivered by 1 of 2 physiotherapists over 4 sessions during which parents were required to attend. Adolescents were educated on knee pain, alongside activity modification with pain monitoring, a progressive home-based strength exercise program, and a return to sport paradigm. Full details of the intervention are available elsewhere.[29]

2.4. Procedure

At baseline, before initiating treatment, all adolescents and their parents attended a baseline assessment, which included self-report questionnaires and mechanistic pain profiling. Questionnaires included participant demographics, self-reported symptom duration, and frequency. Pain intensity was quantified as self-reported worst pain in the previous week, measured on an 11-point numeric rating scale (NRS) ranging from 0 "no pain" to 10 "worst imaginable pain." Self-reported knee function was assessed using the Knee injury and Osteoarthritis Outcomes Score,[35] which participants completed with the help of their parents.

The mechanistic pain profiling was conducted by 1 of 2 trained assessors on both PFP at control participants at baseline. Instructions were given in a standardised format based on a script adapted to the understanding needs of the 10 to 14 years. All procedures and instructions were piloted in adolescents of the same age range, to ensure comprehension of instructions, and not elicit fear in the participants with regards to being exposed to painful stimuli. A predetermined testing order was used for all participants, which first included pressure pain thresholds (PPTs) by manual pressure algometry, followed by automated cuff algometry, which assessed pressure detection thresholds (PDTs), pressure tolerance thresholds (PTTs), on the test limb, followed by TSP, PDTs, and PTTs on the contralateral limb, and finally CPM (procedures detailed below). These measures have demonstrated to be reliable.[9,10,15] The test limb was determined as the knee with pain or most painful knee in the case of bilateral pain. The test limb was randomly selected for controls.

All baseline assessments were subsequently repeated during and after treatment, at 4 and 12 weeks, respectively, for those with PFP. Twelve weeks was the endpoint used for analysis of baseline mechanistic pain profiles to predictive post-treatment effect.

2.5. Manual pressure algometry

Pressure pain thresholds were assessed locally, distally, and remotely as follows: at the centre of the patella (knee), on the tibialis anterior muscle (shin), and on the lateral epicondyle (elbow) of the contralateral limb. The PPT was assessed with a handheld pressure algometer with a 1-cm^2 tip (Somedic, Norra Mellby, Sweden) placed perpendicular to the skin, applying an increasing pressure at a rate of 30 kPa/second. Participants were fitted with a handheld switch, which they were instructed to press as soon as the sensation changed from pressure to pressure pain. Two measurements were taken at each site, and the average of the 2 was used for analysis. The average of all PPT across locations was used as surrogate for the overall sensitivity (average PPT).

2.6. Cuff pain sensitivity

Cuff pressure pain sensitivity was assessed using an automated cuff algometer (Nocitech, Aalborg, Denmark). A tourniquet was placed around the head of the gastrocnemius muscle on each limb of the participant. The cuff was automatically inflated at a rate of 1 kPa/second. Participants held a handheld electronic visual analogue scale (VAS, 0-10 cm anchored from "no pain," to "worst pain imaginable"). Participants were instructed to use the VAS

when the sensation first changed from pressure, to pressure pain, and to continue to rate the pain after, until they could no longer tolerate it, at which they should press a button that immediately deflated the cuff. The pain detection threshold was defined as the point at which the VAS reached 1 cm, and PTT was defined as the point at which participants pressed the button and stopped the stimulation.

2.7. Temporal summation of pain

Temporal summation of pain was assessed with the computerised cuff algometer. The TSP paradigm consisted of 10 sequential stimulations (1-second stimulation, 1-second interval without stimulation) inflated rapidly (100 kPa/second) to the level of the PTT. To familiarise participants to the sensation of the rapid inflation, participants were first exposed to 4 stimulations (at 60%, 80%, 90%, and 100% PTT, respectively), with longer intervals in-between (5 seconds). After the fourth, the TSP paradigm of 10 equal pressure stimuli began (at 100% PTT). Using the handheld electronic VAS, participants rated the pain of each stimulus using the electronic VAS, without returning the slider to zero in-between stimuli. Participants were given no indication as to whether stimuli would be more or less painful. Visual analogue scale scores from each stimulus were extracted, and the 4 training stimuli were not used for analysis. The VAS scores for the remaining 10 stimulations (all delivered at 100% PTT) were averaged from the first to the fourth VAS score (VAS-I) and for the final 3 VAS scores (VAS-II). The TSP effect was defined as the difference between VAS-I and VAS-II (ie, VAS-II minus VAS-I) as per previous research[10,13] (ie, greater difference indicating more facilitated TSP).

2.8. Conditioned pain modulation

The PDT was reassessed on the test leg, in the presence of a painful conditioning stimulus on the contralateral leg. At the beginning of the CPM test, the cuff on the contralateral leg was immediately inflated at a rate of 100 kPa/second to a level of 70% of the PTT. This pressure was held constant for the duration of the test. At the same time, the cuff on the test leg began to inflate at a rate of 1 kPa/second. Similar to the baseline PDT assessment, participants were instructed to rate when the sensation on the test leg changed from pressure to pressure pain and to continue to rate the pain from the test leg only. The CPM effect was the change in PDT from the baseline assessment to during the presence of the painful conditioning stimulus (ie, an increase in PDT indicates an efficient CPM).

2.9. Statistics

Data are presented as mean and SD for descriptive purposes, and mean 95% confidence interval (95% CI) for inferential statistics, with median (interquartile range) used in cases of non-normal distribution.

Differences between groups were assessed by a mixed-model analysis of variance (ANOVA) with a between-group factor, *Group* (PFP, Controls) on baseline measures of PPTs, and *Site* (knee, leg, and elbow) as a within-subject factor. Similarly, a mixed-model ANOVA was used to evaluate differences between *Groups* (PFP, Controls), on PDT and PTTs, with *Limb* (test-leg, contralateral leg) as the within-subject factor. A one-way ANOVA with Groups as a factor was run to determine whether TSP was different between groups, with TSP effect as the dependant variable. To evaluate the CPM paradigm, we used a mixed-model ANOVA with *Group* (PFP, Control) as the between-subject factor, and *Condition* (before vs during conditioning) as the within subjects repeated factor. Post hoc simple main effects with Bonferroni adjustment for multiple comparison was used in case of significant interaction.

General linear mixed models, with fixed and random effects were used to evaluate changes in parameters over time. *Time* (baseline, 4 and 12 weeks) was a fixed repeated-measures factor, with participants as a random effect and restricted maximum likelihood estimation. The best-fitting covariance structure for the residuals was evaluated by Akaikes Information Criterion. This procedure was repeated for PPTs, TSP effects and CPM effects as dependent variables. Furthermore, Pearsons correlation was used to determine whether changes in parameters (specifically average PPT, TSP, or CPM) were associated with improvements in pain NRS scores (as per Kosek et al.[20]). Linear regression was used to determine whether the baseline parameters were prognostic of improvements in pain NRS scores during the 12-week intervention. The outcome was change in pain intensity NRS scores from baseline to 12 weeks. The potential prognostic factors were average PPT, TSP effects, and CPM effects. These were evaluated in univariable analyses, and potential prognostic factors were then included in a multivariable model adjusted for sex and pain duration ($P < 0.05$ accepted). *P*-values below 0.05 were considered to reflect a significant difference or association.

3. Results

3.1. Participants

One hundred and fifty-one adolescents diagnosed with PFP were recruited and included at baseline (Flowchart; Figure S1, http://links.lww.com/PAIN/A938), as well as 50 pain-free control adolescents aged 10 to 14 years (**Table 1**). Data on cuff pain sensitivity, TSP, and CPM were available at baseline for 138 PFP participants and 48 controls. Data from 18 PFP participants were lost at 12-week follow-up (88% response rate). Worst pain in the past week was 6.6 ± 2.1 NRS points at baseline, which decreased to 3.1 ± 2.6 at 12-week follow-up (mean difference 3.5 95% CI 3.0-4.1; $P < 0.001$).

Table 1

Demographics of patellofemoral pain (PFP) and control participants.

	PFP	Control
Age (y)	12.6 (1.2)	12.3 (1.4)
Sex (% female)	76	62
Height (m)	1.62 (0.1)	1.60 (0.1)
Weight (kg)	50.4 (9.4)	48 (10.4)
Bilateral pain (%)	73.5	—
Pain duration (mo)*	18 (9-24)	—
KOOS symptoms (0-100)	78.2 (12.2)	97.7 (5.2)
KOOS pain (0-100)	68.5 (1.2)	99.7 (1.2)
KOOS function in daily living (0-100)	79.0 (14.3)	100 (0)
KOOS function in sport and recreation (0-100)	55.3 (21.2)	99.8 (1)
KOOS quality of life (0-100)	49.3 (15.5)	99.7 (1.3)
Worst pain in the last week (NRS 0-10)	6.6 (2.2)	—

Values presented as mean (SD) unless otherwise stated.

* Median (IQR).

KOOS, Knee injury and Osteoarthritis Outcomes Score; NRS, numeric rating scale.

3.2. Baseline pain sensitivity

There was a significant Site*Group interaction for PPTs ($F(2, 386) = 10.86$; $P < 0.001$) with PPTs being lower in PFP than controls in all sites (**Fig. 1**) with mean differences at the knee ($F(1, 188) = 33.99$; $P < 0.0005$; 178 kPa; 95% CI: 118-239 kPa), shin ($F(1, 188) = 7.40$; $P < 0.001$; 81 kPa; 95% CI: 22-139 kPa), and at the elbow ($F(1, 188) = 11.75$; $P = 0.001$; 89 kPa; 95% CI: 38-139 kPa).

Pressure pain thresholds in the control group ($F(2, 98) = 10.11$; $P < 0.0005$) were lower at the shin (mean difference = 82 kPa; 95% CI 39-125 kPa; $P < 0.0005$) and the elbow (mean difference = 88 kPa; 95% CI: 54-122) compared with the knee (**Fig. 1**).

For cuff pain sensitivity measures, there was a significant main effect for group for PDT ($F(1, 177) = 25.73$; $P < 0.0005$) and PTT ($F(1, 177) = 6.67$; $P = 0.011$), with both lower in PFP participants compared with controls (**Table 2**). There was no significant interaction between Limb and Group for PDTs ($F(1, 177) = 1.834$); $P = 0.177$) or PTTs ($F(1, 177) = 0.041$; $P = 0.840$).

3.3. Baseline temporal pain summation and conditioning pain modulation

Visual analogue scale scores for each of the 10 stimuli of the TSP paradigm are presented in **Figure 2**. Overall, there was a difference between groups for the TSP effect ($F(1, 170) = 74.8$; $P = 0.028$), with the PFP having a higher TSP effect compared with controls (PFP 1.5 95% CI 1.2-1.5 vs control 1.0 95% CI 0.8-1.3).

For CPM, there was a significant condition*group interaction ($F(1, 182) = 5.098$; $P = 0.025$). Post hoc analysis showed that the control group had an increase in PDT ($F(1, 45) = 5.191$; $P = 0.028$) during painful conditioning stimulus compared to without conditioning (mean difference = 5.4 kPa; 95% CI: 0.6-10.2), indicating a CPM response (**Fig. 3**). However, there was no significant change in PDT during conditioning for the PFP group ($F(1, 137) = 0.47$; $P = 0.495$) indicating no efficient CPM response in the PFP group.

3.4. Changes in pain sensitivity during and after treatment

Linear mixed models showed a significant effect of time with PPTs increased at 4 and 12 weeks at the patella ($F(2, 264.6) = 101.1$; $P < 0.0005$), shin, ($F(2, 262.2) = 57.2$; $P < 0.0005$), and the elbow ($F(2, 263.4) = 32.5$; $P < 0.005$) compared with baseline (**Fig. 4**). The linear mixed model of the TSP effect showed a significant effect ($F(2, 267.6) = 3.4$; $P = 0.035$; **Table 3**) with TSP effects increased at 4 weeks compared with baseline, but no difference from baseline at 12 weeks. There was no significant effect of time for the CPM effect ($P > 0.05$; **Table 3**).

Table 2

Mean (95% CI) of cuff pressure detection thresholds (PDT) and tolerance thresholds (PTT) for adolescents with patellofemoral pain (PFP) and controls at baseline.

	PFP	Control
	Mean (95% CI)	Mean (95% CI)
CUFF PDT (KPa)	25.3 (23.3-27.3)*	35.9 (32.3-39.5)
CUFF PTT (KPa)	63.9 (59.9-67.9)#	74.7 (67.5-82.0)

Significantly different from controls (*$P < 0.001$; #$P < 0.05$).

Pain intensity decreased with a mean of 3.5 (3.2) NRS points from baseline to 12-week follow-up. Decreases in pain NRS scores were correlated with increases in average PPT ($r = 0.316$, $P < 0.001$) from baseline to 12 weeks. No correlations were found between decreases in pain NRS scores during the 12 weeks and the change in the TSP effect ($r = 0.054$; $P = 0.586$) or CPM effect ($r = -0.033$; $P = 0.721$).

3.5. Predictive of outcome of baseline mechanistic pain profiling

The univariate regression analysis of baseline parameters (average PPT, TSP effect, and CPM effect) and change in pain NRS scores at 12 weeks are found in **Table 4**. The baseline TSP effect was the only variable associated with changes in pain NRS scores ($F(1, 16) = 7.9$; $P = 0.006$; $R^2 = 0.065$), with those having a higher TSP effect having a poorer outcome (ie, less reduction in pain NRS scores). Adjusting for sex did not change the association with TSP effect on pain NRS outcome, and sex did not improve model fit and were not significant in the model (Supplementary appendix; Table S1, available at http://links.lww.com/PAIN/A938).

4. Discussion

These results demonstrate that young adolescents (age 10-14 years) with long-standing PFP have widespread pressure hyperalgesia, facilitated TSP, and impaired CPM, compared to controls without pain. In adolescents with PFP, PPT increased over a 12-week intervention reaching a similar level as pain-free controls),

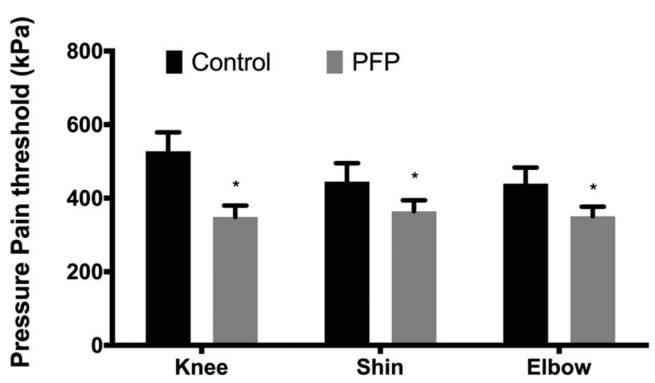

Figure 1. Mean (+95% CI) pressure pain thresholds at baseline in patellofemoral pain (PFP) and control participants. Significantly different from controls (*$P < 0.001$).

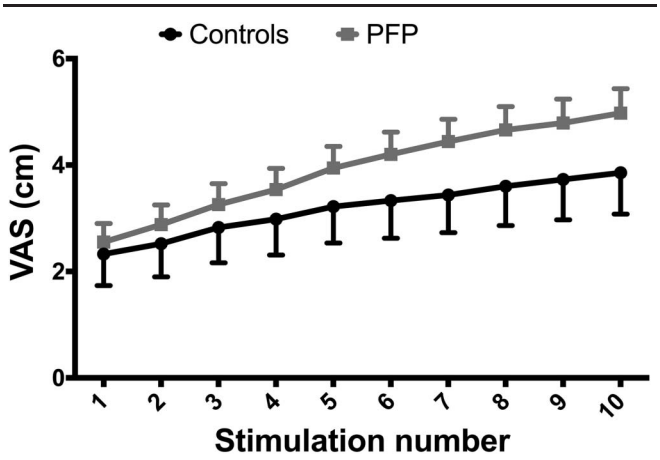

Figure 2. Mean (±95% CI) visual analogue scale (VAS) scores at baseline during the temporal summation of pain paradigm (10 stimulations) for healthy controls and those with patellofemoral pain (PFP).

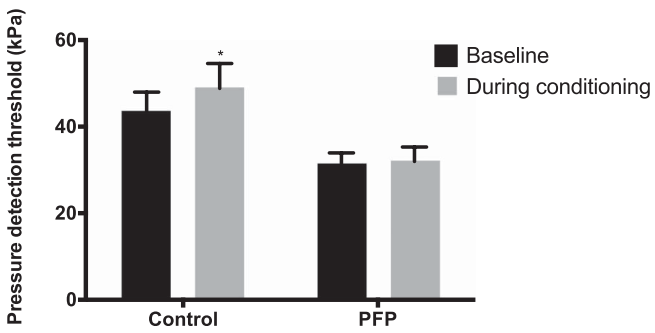

Figure 3. Mean (+95% CI) baseline pressure detection thresholds before and during painful conditioning for those with patellofemoral pain (PFP) and controls. Significantly different from preconditioning recordings (*$P < 0.05$).

whereas CPM did not change. Although TSP appeared facilitated in PFP at 4 weeks, it returned to baseline levels at 12 weeks. Facilitated TSP at baseline was predictive of less improvements in pain intensity at 12 weeks, although the proportion of variance explained was low.

4.1. Not just a simple overuse injury in adolescents

Patellofemoral pain has long been assumed to be a simple localised pain complaint affecting the knee and caused by repetitive biomechanical loading of the knee joint.[28,34] This study provides evidence of altered pronociceptive and antinociceptive mechanisms in young adolescents with PFP underlining that this pain condition may be more complex than previously assumed. At baseline, participants demonstrated significantly decreased PPTs locally, and widespread, which increased during treatment. In the current study, PPTs normalised to the same extent as the age-matched controls after treatment, which indicates that early, efficient treatment, may counteract deleterious effects of long-lasting pain complaints on the pain system. This is substantiated by the fact that improvements in self-reported pain were correlated with increases in PPTs. This may indicate that the observed increases in PPTs are partially driven by improvements in pain, or vice versa. Together, these data indicate that increased pain sensitivity seems to be closely linked with the PFP pain condition, and not just at the knee (painful area).

4.2. Temporal summation of pain could potentially be a trait for a more sensitive central pain system

In addition to widespread pressure hyperalgesia young adolescents with PFP also demonstrated a more facilitated TSP, which may be indicative of pronociceptive alterations in the central nervous system. Greater facilitation of TSP at baseline was associated with less improvements in pain during treatment, which underlines the potential importance of pronociceptive factors in the PFP presentation. This association remained significant when accounting for sex and pain duration. This extends previous findings by Holley et al.[14] who demonstrated that lower CPM efficiency was associated with an increased risk of transitioning from acute to chronic pain. There are studies that have shown similar prognostic effects in adults (eg, osteoarthritis).[16] Two systematic reviews have previously evaluated the predictive capacity of QST—albeit neither included adolescent populations. The first was in peripheral musculoskeletal injuries and found in 5 small exploratory studies QST parameters were associated with more pain or disability.[26] A second review found that TSP was most consistently associated with acute or chronic pain after surgery.[36] More recently, Bauemer et al.[3] demonstrated that TSP was associated with the immediate analgesic response to acupuncture in chronic pain patients. Combined this evidence indicates the potential role of mechanistic pain profiling in understanding prognosis and response to treatment, particularly as pain duration has been shown to play role in other MSK populations.[23]

In the current study, TSP remained facilitated (and even more facilitated at 4 weeks) during the 12-week follow-up. This raises the question if TSP is a trait for a more sensitive nervous system in recurrent musculoskeletal pain conditions such as PFP, or it is a residual effect of experiencing long-standing pain.[13]

One consideration is whether the intervention impacted TSP at 4 weeks. Previous research has shown regular exercise can modulate central pain mechanisms and neuroimmune function,[5,27,37] which could therefore explain a more pronounced facilitation during the period of restricted sports participation.[22,37] More vigorous physical activity has been linked to lower TSP in humans,[25] and animal studies show that regular exercise reduces excitability in the central nervous system.[38] Interestingly, at 12-weeks, when most adolescents were returning to sports,[29]

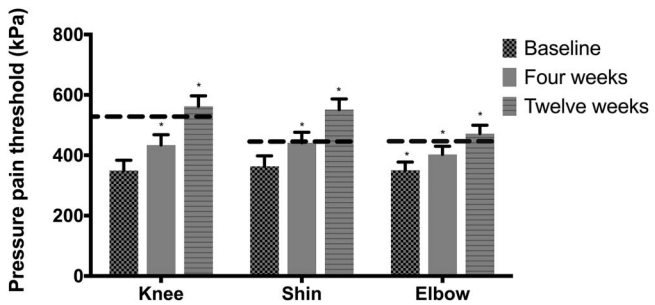

Figure 4. Mean (95% CI) pressure pain thresholds before, during (4 weeks), and after (12 weeks) treatment for the patellofemoral pain group. Dashed black line indicates baseline levels of controls (for visual purpose only). Significantly different from baseline (*$P < 0.05$).

Table 3

Mean (95% CI) values for effects of conditioned pain modulation (CPM-effect; change in PDT k from pre-conditioning to during conditioning) and temporal summation of pain (TSP-effect; VAS-II minus VAS-I representing summation) at baseline, 4 and 12 weeks during intervention in the patellofemoral pain group.

	CPM-effect	TSP-effect
	Mean (95% confidence interval)	Mean (95% confidence interval)
Baseline	0.6 (−1.5 to 2.7)	1.5 (1.3-1.7)
4-week	−0.3 (−2.4 to 1.8)	1.8* (1.6-2.0)
12-week	−2.1 (−4.2 to 0.1)	1.5 (1.3-1.7)

Significantly difference from baseline (*$P < 0.05$).

Table 4

Univariable linear regression of baseline quantitative sensory testing predicting change in pain from baseline to 12 week.

Baseline variable	B	95% CI B	Beta	*P*
Widespread PPT	−0.001	−0.01 to 0.002	−0.63	0.487
CPM	−0.015	−0.07 to 0.04	−0.051	0.579
TSP	−0.73	−1.24 to −0.22	−0.254	**0.006**

CPM, conditioned pain modulation; PPT, pressure pain thresholds; TSP, temporal summation of pain.

TSP returned to similar level as baseline. It is not implausible that the initial activity restriction had unintended impacts on pronociceptive mechanisms. While this may question the use of activity restriction in youth with musculoskeletal pain, this is an avenue that could be examined in future research, for example, when adolescents are sedentary/resting from physical activity due to injury or seasonal changes.

4.3. Implications of long-standing pain during adolescence

Intense or long experiences of pain during early life may influence the developing central nervous system. Neonatal pain during surgical procedures negatively impacts the normal development of endogenous pain responses, which has been observed when following such children into adolescence.[8] Potentially, long experiences of pain in late childhood/early adolescence could impact pain modulation and/or susceptibility to pain across the lifespan. Research has shown that there seems to be an age-related developmental improvement in central pain inhibitory mechanisms, evidenced by greater CPM efficiency in older adolescents.[39] In our study, there was no efficient pain response in the PFP group at baseline, while controls showed much smaller CPM responses compared with the magnitude observed in pain-free older adolescent/young adults when using the same methodology.[13,31]

Similarly, previous research show that young adults who have "recovered" from long-standing knee pain since adolescence have higher PPTs and greater CPM effects than those with currently suffering from PFP.[13] The "recovered" participants displayed localised pressure pain hyperalgesia and facilitated TSP compared with controls.[13] This suggests that after long-standing knee pain during adolescence, there are long-lasting alterations that could increase susceptibility to future pain complaints.[13] However, it must be considered that TSP and CPM are relative measures. That is, an individual can have a higher pain tolerance and lower pain rating during every one of the 10 stimulations due to decreased pain sensitivity, but no change in the magnitude of the TSP effect. In this case, the preconditioning and PDT during conditioning both increase over time, leading to no net change in the CPM effect (as was the case in the current study). This is contrary to other musculoskeletal conditions in older adults where some amount of "normalisation" of the mechanistic pain profiles has occurred.[11,12,19] The implications of these differences and whether it is due to long-term periods of pain exposure during developmental periods warrant further investigation.

4.4. Limitations

Assessors were not blinded to the status of patients (PFP vs control). However, most outcomes were collected with an assessor-independent technology. This was an exploratory analysis of prognostic factors, and future research needs to validate our findings in this patient population.

5. Conclusions

This study found alterations in pronociceptive and antinociceptive pain mechanisms in young adolescents suffering from what was previously considered a localised pain complaint. The observed widespread hyperalgesia reversed during and after treatment, to be comparable with pain-free adolescents, indicating some of these characteristics are receptive to changes in pain. This mechanistic pain profiling may provide some insight into those who are at risk of a worse prognosis. Further research should aim to understand the implications of maintained pronociceptive characteristics during adolescent development.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A938.

Supplemental video content

A video abstract associated with this article can be found at http://links.lww.com/PAIN/A939.

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References

[1] Arendt-Nielsen L, Morlion B, Perrot S, Dahan A, Dickenson A, Kress HG, Wells C, Bouhassira D, Mohr Drewes A. Assessment and manifestation of central sensitisation across different chronic pain conditions. Eur J Pain 2018;22:216–41.
[2] Arendt-Nielsen L, Skou ST, Nielsen TA, Petersen KK. Altered central sensitization and pain modulation in the CNS in chronic joint pain. Curr Osteoporos Rep 2015;13:225–34.
[3] Baeumler PI, Conzen P, Irnich D. High temporal summation of pain predicts immediate analgesic effect of acupuncture in chronic pain patients-A prospective cohort study. Front Neurosci 2019;13:498.
[4] Blankenburg M, Boekens H, Hechler T, Maier C, Krumova E, Scherens A, Magerl W, Aksu F, Zernikow B. Reference values for quantitative sensory testing in children and adolescents: developmental and gender differences of somatosensory perception. PAIN 2010;149:76–88.
[5] Bobinski F, Teixeira JM, Sluka KA, Santos ARS. Interleukin-4 mediates the analgesia produced by low-intensity exercise in mice with neuropathic pain. PAIN 2018;159:437–50.
[6] Boudreau SA, Kamavuako EN, Rathleff MS. Distribution and symmetrical patellofemoral pain patterns as revealed by high-resolution 3D body mapping: a cross-sectional study. BMC Musculoskelet Disord 2017;18:160.
[7] Crossley KM, Stefanik JJ, Selfe J, Collins NJ, Davis IS, Powers CM, McConnell J, Vicenzino B, Bazett-Jones DM, Esculier JF, Morrissey D, Callaghan MJ. 2016 Patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 1: terminology, definitions, clinical examination, natural history, patellofemoral osteoarthritis and patient-reported outcome measures. Br J Sports Med 2016;50:839–43.
[8] Goffaux P, Lafrenaye S, Morin M, Patural H, Demers G, Marchand S. Preterm births: can neonatal pain alter the development of endogenous gating systems? Eur J Pain 2008;12:945–51.
[9] Graven-Nielsen T, Izumi M, Petersen KK, Arendt-Nielsen L. User-independent assessment of conditioning pain modulation by cuff pressure algometry. Eur J Pain 2016;21:552–61.
[10] Graven-Nielsen T, Vaegter HB, Finocchietti S, Handberg G, Arendt-Nielsen L. Assessment of musculoskeletal pain sensitivity and temporal

summation by cuff pressure algometry: a reliability study. PAIN 2015;156: 2193–202.
[11] Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. Arthritis Rheum 2012;64:2907–16.
[12] Henriksen M, Klokker L, Graven-Nielsen T, Bartholdy C, Schjodt Jorgensen T, Bandak E, Danneskiold-Samsoe B, Christensen R, Bliddal H. Association of exercise therapy and reduction of pain sensitivity in patients with knee osteoarthritis: a randomized controlled trial. Arthritis Care Res (Hoboken) 2014;66:1836–43.
[13] 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;159:2530–7.
[14] Holley AL, Wilson AC, Palermo TM. Predictors of the transition from acute to persistent musculoskeletal pain in children and adolescents: a prospective study. PAIN 2017;158:794–801.
[15] Imai Y, Petersen KK, Morch CD, Arendt Nielsen L. Comparing test-retest reliability and magnitude of conditioned pain modulation using different combinations of test and conditioning stimuli. Somatosens Mot Res 2016;33:169–77.
[16] Izumi M, Petersen KK, Laursen MB, Arendt-Nielsen L, Graven-Nielsen T. Facilitated temporal summation of pain correlates with clinical pain intensity after hip arthroplasty. PAIN 2017;158:323–32.
[17] Junge T, Runge L, Juul-Kristensen B, Wedderkopp N. Risk factors for knee injuries in children 8-15 years: the CHAMPS-Study DK. Med Sci Sports Exerc 2015;48:655–62.
[18] King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, MacDonald AJ. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. PAIN 2011;152:2729–38.
[19] Kosek E, Ordeberg G. Abnormalities of somatosensory perception in patients with painful osteoarthritis normalize following successful treatment. Eur J Pain 2000;4:229–38.
[20] Kosek E, Roos EM, Ageberg E, Nilsdotter A. Increased pain sensitivity but normal function of exercise induced analgesia in hip and knee osteoarthritis-treatment effects of neuromuscular exercise and total joint replacement. Osteoarthritis Cartilage 2013;21:1299–307.
[21] Lewandowski Holley A, Wilson AC, Cho E, Palermo TM. Clinical phenotyping of youth with new-onset musculoskeletal pain: a controlled cohort study. Clin J Pain 2017;33:28–36.
[22] Lima LV, Abner TSS, Sluka KA. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. J Physiol 2017; 595:4141–50.
[23] McPhee ME, Graven-Nielsen T. Recurrent low back pain patients demonstrate facilitated pro-nociceptive mechanisms when in pain, and impaired anti-nociceptive mechanisms with and without pain. PAIN 2019; 160:2866–76.
[24] Murray CJ, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, Bennett D, Bernabe E, Blencowe H, Bourne R, Braithwaite T, Brayne C, Bruce NG, Brugha TS, Burney P, Dherani M, Dolk H, Edmond K, Ezzati M, Flaxman AD, Fleming TD, Freedman G, Gunnell D, Hay RJ, Hutchings SJ, Ohno SL, Lozano R, Lyons RA, Marcenes W, Naghavi M, Newton CR, Pearce N, Pope D, Rushton L, Salomon JA, Shibuya K, Vos T, Wang H, Williams HC, Woolf AD, Lopez AD, Davis A. UK health performance: findings of the Global Burden of Disease Study 2010. Lancet 2013;381:997–1020.
[25] Naugle KM, Riley JL III. Self-reported physical activity predicts pain inhibitory and facilitatory function. Med Sci Sports Exerc 2014;46:622–9.
[26] O'Leary H, Smart KM, Moloney NA, Doody CM. Nervous system sensitization as a predictor of outcome in the treatment of peripheral musculoskeletal conditions: a systematic review. Pain Pract 2017;17: 249–66.
[27] Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol (1985) 2005;98:1154–62.
[28] Powers CM, Witvrouw E, Davis IS, Crossley KM. Evidence-based framework for a pathomechanical model of patellofemoral pain: 2017 patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester, UK: part 3. Br J Sports Med 2017;51:1713–23.
[29] Rathleff MS, Graven-Nielsen T, Holmich P, Winiarski L, Krommes K, Holden S, Thorborg K. Activity modification and load management of adolescents with patellofemoral pain: a prospective intervention study including 151 adolescents. Am J Sports Med 2019;47:1629–37.
[30] Rathleff MS, Holden S, Straszek CL, Olesen JL, Jensen MB, Roos EM. Five-year prognosis and impact of adolescent knee pain: a prospective population-based cohort study of 504 adolescents in Denmark. BMJ Open 2019;9:e024113.
[31] 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;17:980–8.
[32] Rathleff MS, Roos EM, Olesen JL, Rasmussen S. High prevalence of daily and multi-site pain-a cross-sectional population-based study among 3000 Danish adolescents. BMC Pediatr 2013;13:191.
[33] 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: 414–21.
[34] Rathleff MS, Vicenzino B, Middelkoop M, Graven-Nielsen T, van Linschoten R, Holmich P, Thorborg K. Patellofemoral pain in adolescence and adulthood: same same, but different? Sports Med 2015;45:1489–95.
[35] Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)-development of a self-administered outcome measure. J Orthop Sports Phys Ther 1998;28: 88–96.
[36] Sangesland A, Storen C, Vaegter HB. Are preoperative experimental pain assessments correlated with clinical pain outcomes after surgery? A systematic review. Scand J Pain 2017;15:44–52.
[37] Sluka KA, Frey-Law L, Hoeger Bement M. Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation. PAIN 2018; 159(suppl 1):S91–97.
[38] Sluka KA, O'Donnell JM, Danielson J, Rasmussen LA. Regular physical activity prevents development of chronic pain and activation of central neurons. J Appl Physiol (1985) 2013;114:725–33.
[39] Tsao JC, Seidman LC, Evans S, Lung KC, Zeltzer LK, Naliboff BD. Conditioned pain modulation in children and adolescents: effects of sex and age. J Pain 2013;14:558–67.