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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 pro-nociceptive and anti-nociceptive 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 to age-matched controls (N=50) and subsequently tracked while participating in an intervention focussed on activity modification.

They underwent quantitative sensory testing at baseline (pre-intervention), four weeks (during initial treatment), and twelve weeks (following 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 ten 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). PPTs increased at both follow-ups (P<0.001), and

the PPT-increase 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 pro-nociceptive mechanism as a prognostic factor in young adolescents with PFP.

INTRODUCTION

Musculoskeletal pain is one of the most frequent causes of years lived with disability among 10-14 year-old adolescents [24]. One in every four 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 the majority of children are diagnosed with an unspecific condition termed patellofemoral pain (PFP) condition. 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 longstanding knee pain conditions, psychophysical pain assessment has demonstrated altered pro-nociceptive and anti-nociceptive 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 longstanding pain. In adolescents, those with chronic musculoskeletal pain demonstrate lower pain thresholds compared to pain free controls, with no differences in CPM [21].[21]. While there is evidence of maturing somatosensory and pain perception during adolescence (i.e. decreased pain sensitivity and

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increased pain inhibition) [4;39], it is unknown if longstanding exposure to pain influences these developments.

Young adults in their early twenties with longstanding PFP demonstrate widespread pressure hyperalgesia (i.e. 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 longstanding 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 if younger adolescents (i.e. <15 years) with PFP display alterations in pro-nociceptive and anti-nociceptive mechanisms, and 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 (i.e. in younger adolescents).

The aim of the current investigation was to 1) compare mechanistic pain profiles (pressure pain sensitivity, TSP and CPM) in adolescents with PFP compared to pain free controls, 2) evaluate the association between baseline mechanistic pain profiles and improvements in pain intensity following treatment, and 3) examine the temporal mechanistic pain profile during and post 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 to controls, 2) improvements in self-reported pain intensity is associated with normalisation of the mechanistic pain profile, and 3) that increased pro-nociceptive and decreased anti-nociceptive mechanisms at baseline would predict less improvement in pain intensity during treatment.

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METHODS

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 multi-centre (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 prior to inclusion for all participants, and it was conducted in accordance with the Helsinki Declaration.

Participants

Adolescents between the ages of 10-14 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 one of two physiotherapists. The diagnosis of PFP was made in line with previously accepted criteria [7], and included: 1) Insidious onset of anterior knee or retro-patellar pain of more than 6 weeks duration. 2) Pain provoked by at least two 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 ten, 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

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Schlatter, iliotibial band syndrome, Sinding-Larsen-Johansson, 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.

Intervention

All participants were exposed to an intervention, consisting of activity modification, education and graded return to sport. The intervention was delivered by one of two physiotherapists over four 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].

Procedure

At baseline, prior to 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 (KOOS)[35], which participants completed with the help of their parents.

The mechanistic pain profiling was conducted by one of two 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 10-14 years. All procedures and

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instructions were piloted in adolescents of the same age-range, in order to ensure comprehension of instructions, and not elicit fear in the participants with regards to being exposed to painful stimuli. A pre-determined 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 temporal summation of pain (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 post treatment, at four 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.

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, Sweden) placed perpendicular to the skin, applying an increasing pressure at a rate of 30kPa/s. Participants were fitted with a hand-held 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 two was used for analysis. The average of all PPT across locations was used as surrogate for the overall sensitivity (Average-PPT).

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Cuff pain sensitivity

Cuff pressure pain sensitivity was assessed using an automated cuff algometer (Nocitech, 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/s. 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 which 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.

Temporal summation of pain

Temporal summation of pain was assessed with the computerised cuff algometer. The TSP paradigm consisted of 10 sequential stimulations (1s stimulation, 1s interval without stimulation) inflated rapidly (100 kPa/s) to the level of the PTT. To familiarise participants to the sensation of the rapid inflation, participants were first exposed to four stimulations (at 60%, 80%, 90% and 100% PTT, respectively), with longer intervals in-between (5 s). After the fourth, the TSP paradigm of ten 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. VAS scores from each stimulus were extracted, and the four training stimuli were not used for analysis. The VAS scores for the remaining ten 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

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effect was defined as the difference between VAS-I and VAS-II (i.e., VAS-II minus VAS-I) as per previous research[10;13] (i.e. greater difference indicating more facilitated TSP).

Conditioned pain modulation

The PDT was re-assessed 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/s 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/s. 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 (i.e. an increase in PDT indicates an efficient CPM).

Statistics

Data are presented as mean and standard deviation (SD) for descriptive purposes, and mean 95% confidence interval (95%CI) for inferential statistics, with median (inter-quartile 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 subjects' 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 subjects' factor. A one-way ANOVA with Groups as a factor was run to determine if TSP was different between groups, with TSP-effect as the dependant variable. To evaluate the CPM paradigm, a mixed-model

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ANOVA, with *Group* (PFP, Control) as the between subjects' factor, and *Condition* (before versus during conditioning) as the within subjects as 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, four 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 (AIC). 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 multi-variable 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.

RESULTS

Participants

One hundred and fifty-one adolescents diagnosed with PFP were recruited and included at baseline (Flowchart; Figure S1), and 50 pain free control adolescents aged 10-14 years (Table 1). Data on cuff pain sensitivity, TSP and CPM were available at baseline for 138 PFP

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participants and 48 controls. Data from eighteen 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

to 4.1; P<0.001).

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 to 239 kPa), shin (F$(1,188)$=7.40;

P<0.001; 81 kPa; 95%CI: 22 to 139 kPa), and at the elbow (F$(1,188)$=11.75; P=0.001; 89

kPa; 95%CI: 38 to 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 to 125 kPa; P< 0.0005) and the elbow (mean

difference =88 kPa; 95%CI: 54 to 122) compared to 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) 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).

Baseline temporal pain summation and conditioning pain modulation

VAS scores for each of the ten 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 to controls (PFP 1.5 95%CI 1.2 to 1.5

versus control 1.0 95%CI 0.8 to 1.3).

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For CPM, there was a significant condition*group interaction (F1,182) =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 to 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.

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 to 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 four weeks compared to baseline, but no difference at 12-weeks. There was no significant effect of time for the CPM-effect (P>0.05; Table 3).

Pain intensity decreased with a mean of 3.5 (3.2) NRS points from baseline to 12 weeks 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).

Predictive of outcome of baseline mechanistic pain profiling

The univariate regression analysis of baseline parameters (Average-PPT, TSP-effect and CPM-effect) predicting the 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;

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P=0.006; $R^2 = 0.065$), with those having a higher TSP-effect having a poorer outcome (i.e. 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).

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, pressure pain thresholds increased over a twelve-week intervention reaching a similar level as pain-free controls), whereas CPM did not change. While TSP appeared facilitated in PFP at four weeks, it returned to baseline levels at twelve weeks. Facilitated temporal summation of pain at baseline was predictive of less improvements in pain intensity at 12 weeks, although the proportion of variance explained was low.

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 pro-nociceptive and anti-nociceptive 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 following treatment which indicates that early, efficient treatment, may counteract deleterious effects of long-lasting

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pain complaints on the pain system. This is substantiated by the fact that improvements in self-reported pain were correlated to increases in PPTs. This may indicate that the observed increases in PPTs are partially driven improvement in pain, or vice versa. Together, this data indicates that increased pain sensitivity appears to be closely linked with the PFP pain condition, and not just at the knee (painful area).

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 pro-nociceptive 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 pro-nociceptive 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 which have shown similar prognostic effects in adults (e.g. 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 temporal summation of pain 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

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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 four weeks) during the 12-weeks 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 longstanding pain [13].

One consideration is whether the intervention impacted TSP at four 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 temporal summation of pain in humans [25], and animal studies show that regular exercise reduces excitability in the central nervous system [38]. Interestingly, as 12-weeks, when the majority of adolescents were returning to sports [29], TSP returned to similar level as baseline. It is not implausible that the initial activity restriction had unintended impacts on pro-nociceptive mechanisms. While, this may question the use of activity restriction in youth with musculoskeletal pain this is an avenue which could be examined in future research, for example when adolescents are sedentary/ resting from physical activity due to injury or seasonal changes.

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

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adolescence could similarly 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 to 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 to 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, i.e an individual can have a higher pain tolerance and lower pain rating during every one of the ten stimulations due to decreased pain sensitivity, but no change in the magnitude of the TSP effect. In this case, the pre-conditioning 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 warrants further investigation.

Limitations

Assessors were not blinded to the status of patients (PFP versus control). However, the majority of outcomes were collected with an assessor-independent technology. This was an

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exploratory analysis of prognostic factors, and future research needs to validate our findings in this patient population.

Conclusions

This study found alterations in pro-nociceptive and anti-nociceptive pain mechanisms in young adolescents suffering from what was previously considered a localised pain complaint. The observed widespread hyperalgesia reversed during and following treatment, to be comparable to 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 pro-nociceptive characteristics in during adolescent development.

Acknowledgements

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

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Figure legends

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 pre-conditioning recordings (*, P<0.05).

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 difference from baseline (*, P<0.05).

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Tables

	PFP	Control
Age (years)	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 (months)*	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)	-

Table 1. Demographics of patellofemoral pain (PFP) and control participants. Values presented as mean (SD) unless otherwise stated. *Median (IQR). KOOS: Knee injury and Osteoarthritis Outcomes Score.

	PFP	CONTROL
	Mean (95% CI)	Mean (95% CI)
CUFF PDT (KPA)	25.3 (23.3 to 27.3)*	35.9 (32.3 to 39.5)
CUFF PTT (KPA)	63.9 (59.9 to 67.9)[#]	74.7 (67.5 to 82.0)

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. Significantly different from controls (*, P<0.001; [#] ,P<0.05).

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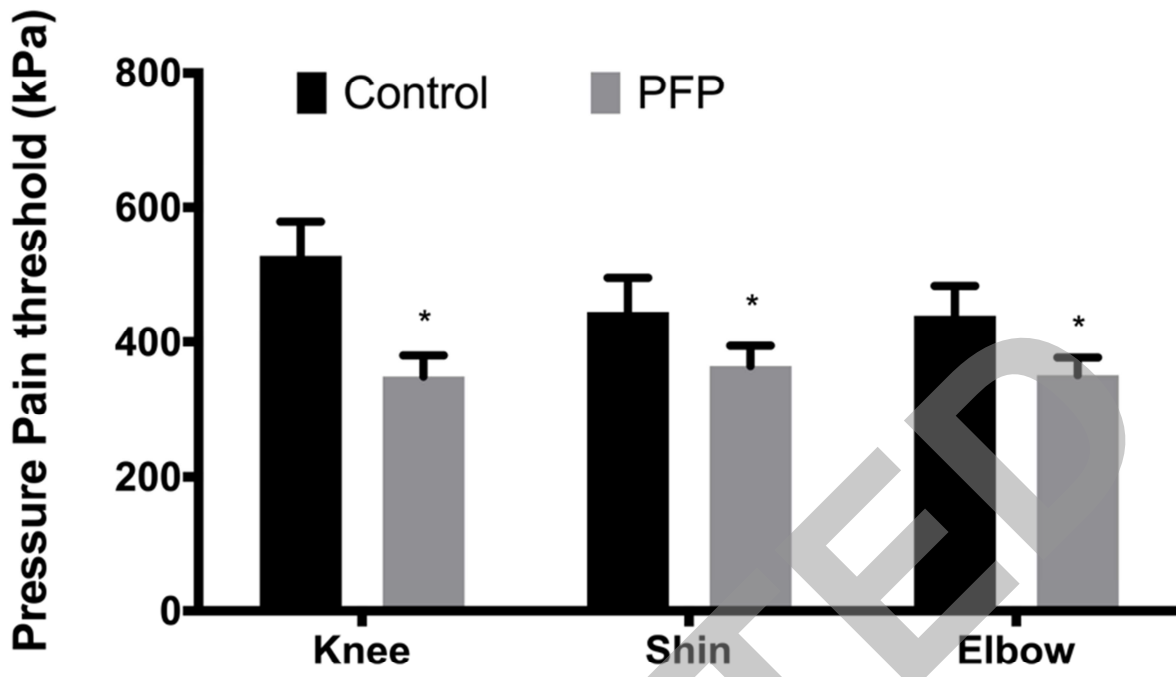| Baseline variable	B	95%CI B	Beta	P-value
Average-PPT	-0.001	-0.01 to 0.002	-0.63	0.487
CPM	-0.015	-0.07 to 0.04	-0.051	0.579
TSP	-0.73	-1.24 to -0.22	-0.254	**0.006**

Table 3. Univariable linear regression of baseline general pressure pain sensitivity (Average-PPT), conditioning pain modulation (CPM), and temporal summation of pain (TSP) predicting reduction in pain numerical rating scale (NRS) scores from baseline to 12 weeks.

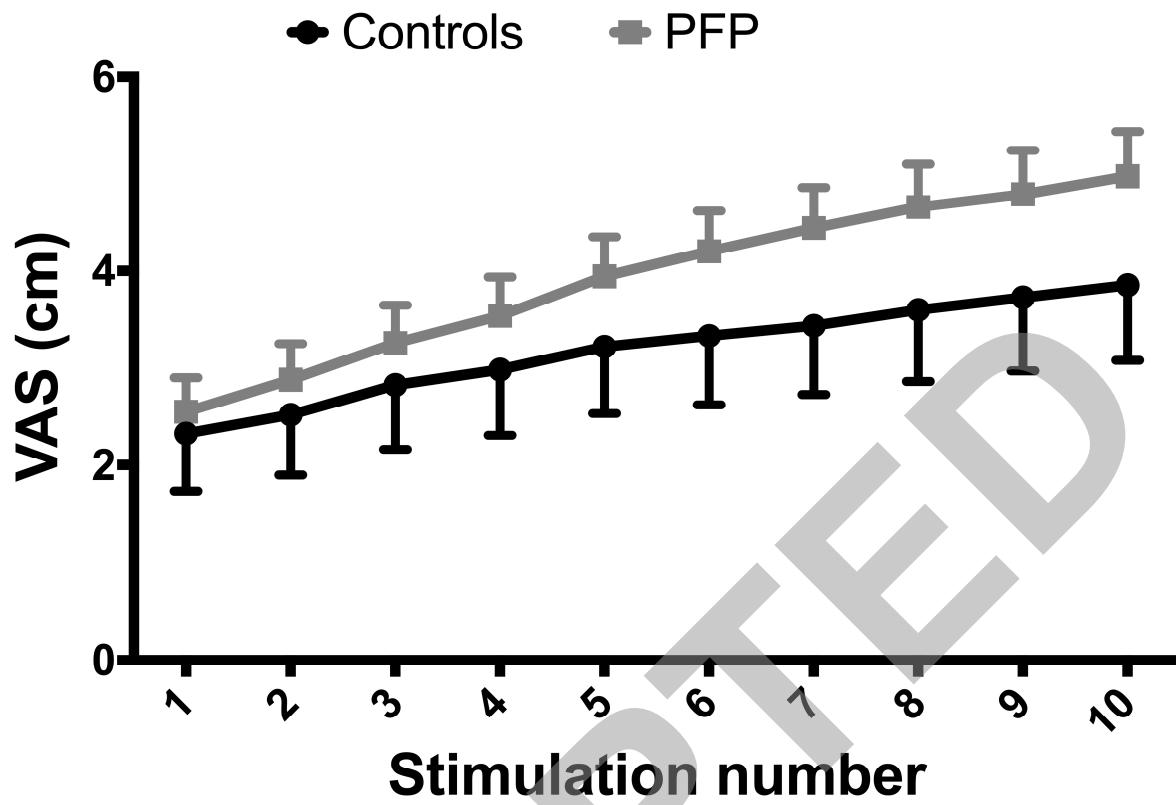| Baseline variable	B	95% CI B	Beta	P-value
Widespread PPT	-0.001	-0.01 to 0.002	-0.63	0.487
CPM	-0.015	-0.07 to 0.04	-0.051	0.579
TSP	-0.73	-1.24 to -0.22	-0.254	**0.006**

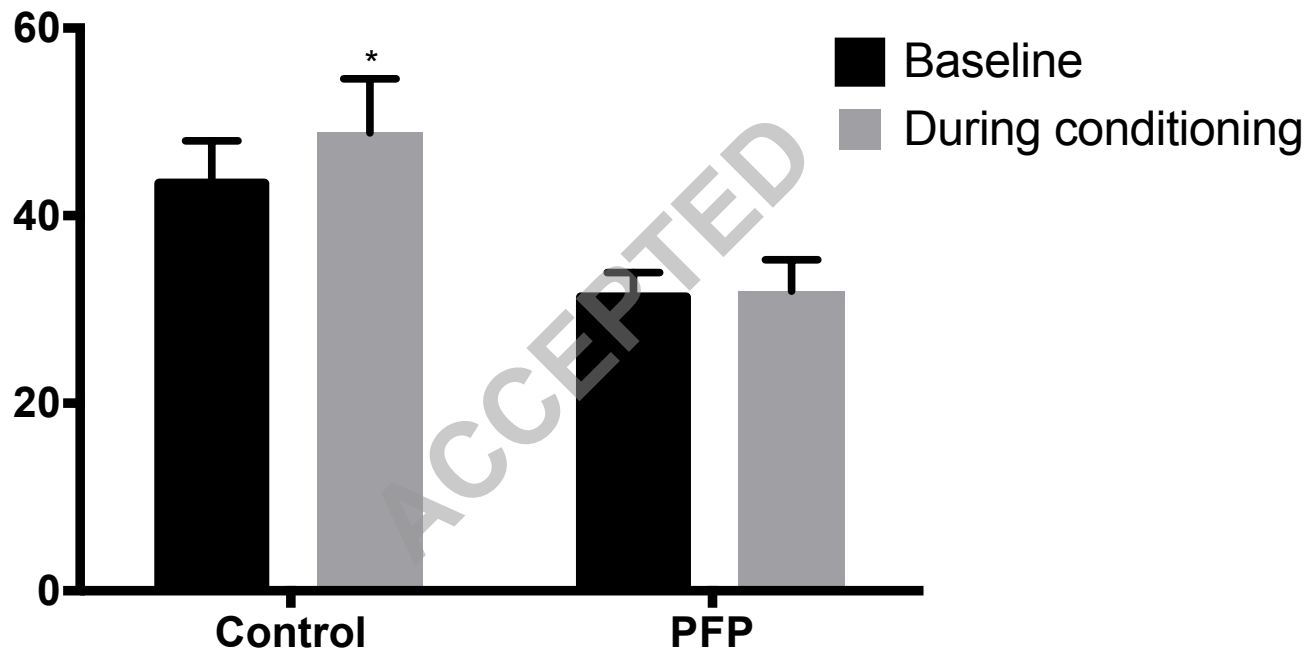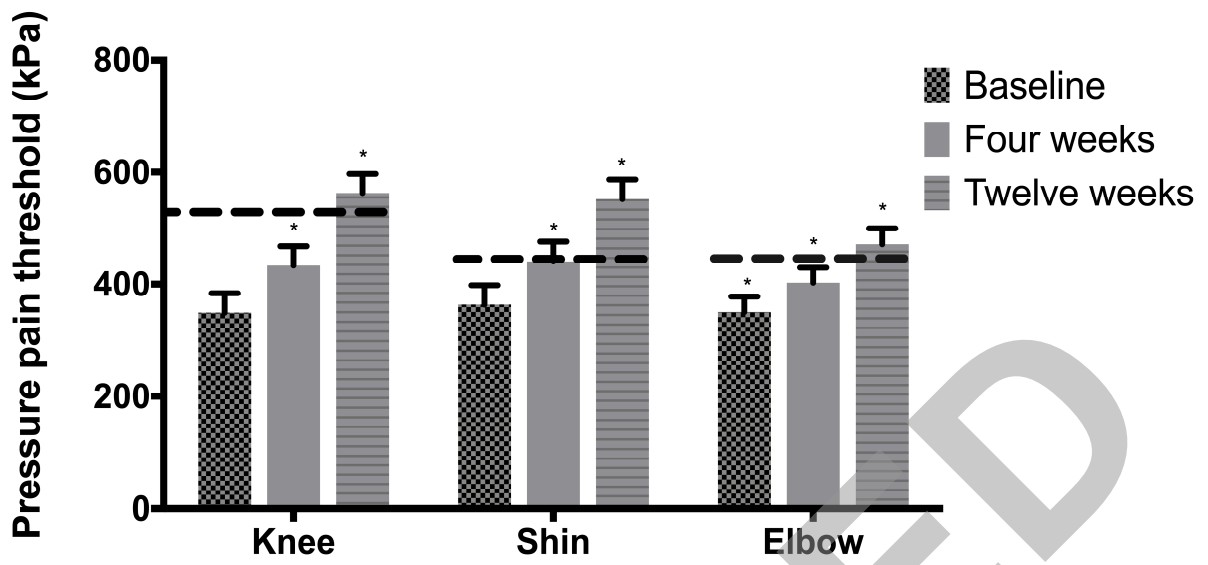**Table 4.** Univariable linear regression of baseline quantitative sensory testing predicting change in pain from baseline to 12 weeks.