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Young females with long standing patellofemoral pain display impaired conditioned pain modulation, increased temporal summation of pain and widespread hyperalgesia

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ABSTRACT

Patellofemoral pain (PFP) is a common recurring knee condition in young females, characterized by pressure hyperalgesia and reduced pain inhibitory control. This study investigated anti-nociceptive and pro-nociceptive pain profiles in young females with long-standing (>5 years) PFP (current-PFP), to those who recovered from adolescent PFP (recovered-PFP), and pain-free controls. This pre-registered, assessor blinded, cross-sectional study, included 87 females younger than 25 years: 36 current-PFP, 22 recovered-PFP, and 29 pain-free controls. The primary outcome was conditioning pain modulation (CPM) assessed by the increase of cuff pain tolerance thresholds assessed during painful cuff conditioning on the contralateral leg. Secondary outcomes included pressure pain thresholds at the knee, shin and forearm, and temporal summation of pain (TSP), assessed by pain intensity recordings on a visual analogue scale (VAS) during repeated cuff pressure pain stimulations on the leg. Compared to the recovered-PFP, the current-PFP had impaired CPM (mean-difference: 11.6%; P=0.004) and reduced pressure pain thresholds at the knee, shin and forearm (mean-difference: 85-225 kPa; P<0.05). There were no differences between current-PFP and controls in CPM. Current-PFP and recovered-PFP demonstrated facilitated TSP, compared to controls, (mean-difference: 0.7-0.8 VAS-change; P<0.05). Compared with controls the recovered-PFP had reduced pressure pain thresholds at the knee, which were higher than the current-PFP (mean-difference: 110-225 kPa; P<0.05). In conclusion, both current-PFP and recovered-PFP displayed altered pain mechanisms compared to controls with no history of knee-pain, despite resolution of symptoms in the recurrent-PFP group. The implications of these findings in the recurrent nature of PFP requires further studies.

Keywords: youth; Musculoskeletal Pain; pain recurrence; pain sensitivity

INTRODUCTION

Knee pain is common in youth, with patellofemoral pain (PFP) being the most common knee pain complaint, affecting one in fourteen adolescents with a prevalence twice as high in females [7;29] [6;24]. PFP is associated with decreased quality of life, and reduced physical activity due to pain[29]. PFP is a persistent and recurrent condition, with up to 50% of adolescents reporting pain one [27], and two years [29] after being offered evidence-based treatment. The reasons underlying pain recurrence are unknown. In other recurrent musculoskeletal pain conditions such a low back pain[11], and adolescents with musculoskeletal pain [12;36] a previous history of pain is associated with an increased risk of new pain episodes. Previous research has not been able to explain this, but one hypothesis is involvement of neuroplasticity of central pain mechanisms during pain-free periods.

Individuals with PFP have been characterized by lower pressure pain thresholds around the knee, at the tibialis anterior muscle and the elbow, indicating widespread hyperalgesia [28;32;33;38]. Widespread hyperalgesia is common in other painful knee disorders such as severe knee osteoarthritis [4;5], and indicates the spreading of sensitisation beyond the local painful area [3], and facilitation of central pain mechanisms may be implicated. Temporal summation of pain (TSP) and conditioning pain modulation (CPM) are two psychophysical tests, often used to evaluate pro-nociceptive and anti-nociceptive central mechanisms respectively. Facilitated TSP, evaluated as the change in pain response to subsequent stimuli of the same intensity, is believed to represent central pain facilitation when integrating the incoming nociception [2]. CPM is thought to reflect descending inhibition at the brainstem level [21], although it may be considered the net effect of pain inhibitory and facilitory mechanisms in the descending pain control system. It is evaluated by changes in perception of test stimuli from before, to during application of a painful conditioning stimuli [40;41]. Despite these mechanisms are altered in both chronic and recurrent musculoskeletal pain conditions, including knee osteoarthritis and low back pain [3;5;18], only one explorative study in female adolescents with PFP demonstrated impaired CPM response relative to controls

[28], and the question remains how these mechanisms behave during recovery. It is unclear if the central pain mechanisms return to the level of healthy controls when pain-free, or whether some degree of sensitisation may be present even when recovered.

The aim of this study was to compare CPM, TSP, as well as localised and widespread pain sensitivity in young females: 1) with current longstanding PFP (current-PFP), 2) self-reported as 'recovered' but with a history of adolescent PFP (recovered-PFP), and 3) without pain. It was hypothesised that in comparison to current-PFP, both recovered-PFP, and pain-free controls, would demonstrate more efficient CPM, higher pressure pain thresholds, and less faciliated TSP. It was further hypothesized that recovered-PFP would have impaired CPM and decreased pressure pain thresholds and facilitated TSP compared to pain-free controls.

METHODS

Participants

This study was pre-registered (ClinicalTrials.gov: NCT03051412), and designed as an assessor blinded, matched cross-sectional study of three groups: 1) Young female adults with a history of long-standing PFP (>5 years), 2) age-matched females with a history of adolescent PFP who currently self-report as recovered, and 3) age-matched female controls with no history of pain. The primary outcome in this study was CPM; based on detecting a mean difference in CPM response of 36% between PFP and controls, with common standard deviation of 50% (corresponding to an effect size of 0.72) [28] and power of 85%, the sample size equation was used to estimate inclusion of 36 young female adults in each group.

All participants were recruited from the Adolescent Pain in Aalborg 2011 cohort (APA2011)[31], a population based cohort which included adolescents from schools in Aalborg. The APA 2011 cohort consists of 504 adolescents with knee-pain, of whom 151 was diagnosed with PFP by a rheumatologist at inclusion, and a control group of 250 adolescents from the same schools' population with no musculoskeletal pain at inclusion. The 5-year follow-up of this

prospective cohort, was conducted in September 2016 (NCT02873143). In September 2016, participants were contacted and requested to fill out an online questionnaire regarding current pain. From this questionnaire, a list of potentially eligible participants for the current investigation was generated as follows; current-PFP were randomly contacted from those diagnosed with PFP at baseline, and reporting knee-pain in both the previous week and month in September 2016; participants potentially eligible as recovered-PFP were selected from those diagnosed with PFP at baseline, reporting 'No' to knee-pain in both the previous week and month. The control group were selected from those who had no knee-pain at baseline (2011), or at follow-up. To eliminate selection bias, participants from each of these groups were randomly selected to be invited to participate, by assigning them an ID number, and sequentially selecting ID's to invite using a random number generator (Excel).

In 2016 the inclusion criteria applied at the time of testing for the current PFP-group were: current anterior knee or retro-patellar pain since adolescence of insidious onset; pain provoked by at least two of the following knee loading activities: squatting, running, hopping, or stair walking[10]; female, and age between 18 and 30 years. Exclusion criteria was: Traumatic injury to the hip, knee, ankle or the lumbar spine within the past 3 month, other diagnosable pathologies that can cause pain around the kneecap (patellar tendinopathy, Osgood-Schlatter, iliotibial band syndrome, Sinding-Larsen-Johansson syndrome, reverse jumpers knee, if they occur in isolation (without patellofemoral pain). The inclusion criteria for the recovered PFP- group were: Previous history of patellofemoral pain; self reporting as having no current knee-pain; female and age between 18 and 30 years. Exclusion criteria: Any type of current knee-pain. The inclusion criteria for the control group were: Free from current or previous chronic musculoskeletal pain complaints; female, between 18 and 30 years of age.

Self-reported measures

In addition to height, weight and age, the following clinical self-reported measures were collected from participants during the physical assessment of eligibility: 1) Knee Injury and Osteoarthritis Outcome Score (KOOS) with scores ranging from 0 (worst) to 100 (best) and covers the five domains: Pain, symptoms, function in daily living, function in sport and recreation, and knee-related quality of life [34]; 2) Numerical Rating Scale (NRS) scores of worst pain intensity during the last week and average pain last week; 3) Pain frequency of knee-pain; 4) Symptom duration (from recall); 5) If they no longer suffered from knee-pain, the symptom-free duration (from recall); 6) The pain localisation collected by the Navigate Pain (Aglance Solution, Aalborg, Denmark) application [8], as well as unilateral or bilateral pain (if bilateral pain was indicated, participants were asked to indicate the most painful knee), and pain in other locations.

Protocol

Participants were assessed using a quantitative sensory testing battery. Participants were familiarised with procedures on the day of testing, with standardised instructions given to all participants by a native Danish speaker. Instructions and procedures were pilot tested for comprehensibility with ten healthy individuals prior to recruitment of the first participant. If the tester for some reason believed the instructions were not understood, they were explained again until the tester was confidant in the participants understanding. The testing session took approximately 30 minutes per participant. The assessor performing assessments was blinded to group allocation (current-PFP, recovered-PFP, or control).

The protocol included assessment of CPM (primary outcome), as well as temporal summation of pain and pressure pain thresholds as secondary outcomes (outlined in detail below). These methods have demonstrated reliability [16;17] and collection of outcomes followed the same approach as previously [28]. For the current-PFP group, the leg with knee-pain, or the 'most painful knee' was selected as the test leg for those who had bilateral pain. To ensure blinding, two assessors were

present for all participants: One who was unblinded to group status greeted participants, and collected the self-report data, which was used to assign the test leg, prior to participants being introduced to a second assessor who conducted the algometry measures. The same method was used for the recovered-PFP group who reported a history of bilateral pain. Control participants were randomly assigned a leg to act as the test leg. The success of the blinding was calculated by asking the experimenter to guess which group the participants belonged to (current-PFP, recovered-PFP, or controls). If group status was adequately concealed, it would be likely that a correct guess would be made 33% of the time. All participants were tested in the same sequence (Figure 1), first with pressure pain threshold assessments by pressure algometry at the knee, shin and elbow, and subsequently assessment of leg pain sensitivity to cuff pressure detection and tolerance thresholds, temporal summation of pain, and CPM by cuff algometry.

Single-point pressure pain sensitivity

Pressure pain thresholds were assessed using a hand-held algometer (Somedic, Hörby, Sweden) with a 1-cm^2 probe (covered by a disposable latex sheath). The pressure algometer was place perpendicular to the skin and pressure was manually increased at a rate of 30 kPa/s. Participants were instructed to indicate when the sensation first changed from a sensation of pressure, to a sensation of pressure pain. The participant was fitted with a hand–held switch and instructed to press the switch as soon as the pressure triggers pain. This was done on the following sites: 1) On the knee at the centre of the patella on the test-leg [32]; 2) on the tibialis anterior muscle 5 cm distal to the tibial tuberosity on the test-leg; and 3) on the contralateral elbow, on the lateral epicondyle of the humerus.

Cuff pressure pain sensitivity

A computer-controlled cuff pressure algometer [16;17] (Nocitech, Aalborg, Denmark) with an air-filled tourniquet cuff (VBM, Germany) was used to assess the cuff pressure detection threshold and

pressure tolerance threshold. The cuff was applied just below the heads of the gastrocnemius muscle and the pressure was increased automatically at a rate of 1 kPa/s to a maximum of 100 kPa. Subjects were instructed to rate the first onset of pain, and continuously thereafter, using an electronic 10 cm visual analogue scale (VAS; “0 cm” representing “no pain” and “10 cm” representing “maximal pain”), and to push a hand-held switch when they could not tolerate the pressure (defined as pressure tolerance threshold). If tolerance was not reached before 100 kPa, the pressure tolerance threshold was defined as 100 kPa for the further analysis. The cuff pain detection threshold was defined as the cuff pressure when the VAS was 1 cm [17]. This procedure was repeated bilaterally. Cuff algometry is considered reliable with interclass coefficients (ICCs) of 0.79 to 0.87[17].

Temporal summation of pain

The computer controlled cuff algometer (NociTech, Denmark) was used to assess TSP. Ten short-lasting stimuli (1 s each) at the level of the cuff pressure tolerance threshold were given with a 1 s break in between stimuli. Participants were instructed to continuously rate the pain intensity of these sequential 10 stimuli using the electronic VAS, and not to return to zero in the breaks. For each cuff stimulus a VAS score was extracted and the ten VAS scores were normalised by subtracting the VAS score of the first stimulus. For analysis of TSP, the average VAS score was calculated in the interval from the first to the fourth VAS score (VAS-I) and for the final three VAS scores (VAS-II). The TSP-effect was defined as the difference between VAS-I and VAS-II (i.e. VAS-II minus VAS-I), which has been use in similar studies previously [26]. This method has demonstrated reliability (VAS I-II ICCs 0.7-0.77)[37].

Conditioning pain modulation

Conditioning pain modulation was assessed by the changes in cuff pressure pain sensitivity at the leg, from baseline (outlined above) to during the presence of a painful conditioning stimulus applied

to the contralateral leg, by cuff algometry, which has proven reliable [16]. The conditioning stimulus was induced by inflation of a tourniquet around the lower leg contralateral to the test leg at a pressure level corresponding to 70% of the pressure tolerance threshold. This was inflated immediately at the beginning of the test to this constant pressure, while simultaneously the cuff on the test leg inflated at a rate of 1k/Pa to reassess the pain detection and tolerance thresholds. Both tourniquets began simultaneously and were released once all measurements were finished, or if the subject terminated the collection of outcomes using the hand switch (maximum 100s). The CPM-effect was calculated as the percentage change in pressure detection and tolerance thresholds from baseline, compared with the recordings during the conditioning stimulus (i.e. a positive CPM-effect indicate an efficient CPM)[41]. Participants were excluded from analysis this if pressure tolerance was not reached before 100 kPa, as a CPM response would not be detectable.

Statistics

Data are presented as mean and standard deviation or median and inter-quartile range unless otherwise stated. All data were assessed for approximate normal distribution by visual inspection of Q-Q plots. The primary analysis was done using a one-way analysis of variance (ANOVA) with the categorical dependent variable as group (current-PFP, recovered-PFP, control). The dependent variables were CPM-effect (on both pressure detection and tolerance thresholds), TSP, pressure pain thresholds (knee, tibia, elbow).

In addition to comparing differences in CPM-effect across groups, a repeated measures ANOVA was run with factors time (baseline *versus* conditioning) and groups (current-PFP, recovered-PFP, control) in order to validate if the conditioning paradigm induced CPM in the groups (i.e. had a significant increase in PDT and PTT from baseline).

For cuff pain sensitivity (pressure detection and tolerance thresholds), a two way between-within subject ANOVA was run, with the categorical dependent factor as group (current-PFP, recovered-PFP, control), and the within-subject's factors as side (test leg, contra-lateral leg). With significant

factors or interactions, the Least Significant Difference (LSD) post-hoc tests were used. Secondary analyses were done using Pearson correlation to explore the association between duration of recovery and local pain sensitivity (pressure pain threshold at the centre of the patella). Statistical significance was set at $P<0.05$.

RESULTS

Eighty-seven young females were recruited, tested and included in analysis of QST measures. Thirty-six in the current-PFP group, 22 in the recovered-PFP group, and 29 controls. Current-PFP had a median pain duration of 8 years, while those who no longer experienced knee-pain, were recovered for a median of 2 years (Table 1). The assessor blinding was considered reasonable, with the blinded assessor guessing correctly identified correct allocation for 49% of the participants in the correct group. All participants completed all quantitative sensory testing procedures.

In the current-PFP group, 33 of 36 participants completed the pain drawings. Participants with current-PFP had a median of 2 (IQR 1-2.5) pain-sites (all including knee pain), with 60% reporting pain in another location than the knee; most commonly back (N = 11), neck (N = 7) and hip/pelvis (N = 7) pain. Seven of the 33 fulfilled the American College of Rheumatology criteria for widespread pain[39].

Conditioning pain modulation

Two participants (one current-PFP, and one control) reached the 100 kPa limit (both on the test and contralateral leg) and were excluded from the CPM analysis. A significant group effect was found for the CPM-effect assessed by the percentage increase in pressure tolerance threshold (Figure 2; ANOVA: $F(2,84) = 4.402$; $P < 0.05$). Post-hoc test revealed that those with current-PFP pain had a reduced CPM-effect relative to the recovered-PFP (mean difference 11.2%; 95% CI 3.4-19.0; $P < 0.005$; effect size Cohen's $d = 0.7$[9] (95% CI 0.2 to 1.3)). There was no significant difference between the current-PFP group and those who were pain free ($P > 0.05$; effect size Cohen's $d = 0.4$

(95% CI -0.1 to 0.9) or the recovered and those who were pain-free (P>0.05; effect size Cohen's d = 0.4 (95% CI -0.9 to 0.2)). There were no significant differences between groups for CPM assessed by percentage change of pressure detection threshold during conditioning (Figure 2; F(2,84) = 1.052; P = 0.35; effect sizes Cohen's d current PFP versus control =0.3 (-0.2 to 0.8), current-PFP versus recovered = 0.2 (95% CI -0.3 to 0.8), recovered-PFP versus control = 0.0 (95% CI -0.5 to 0.6) .

In the repeated measures ANOVA, to determine which groups had a significant increase in PDT/ PTT from baseline, there was a significant interaction for both PDT ($F(4.2,2)$ $p<0.05$) and PTT($F(8.0,2)$; $p <0.05$). All three groups had a significant increase in both PDT and PTT from baseline ($p<0.05$; Table 3) i.e. a conditioning effect despite the between group differences in how much CPM they experienced (CPM-effect).

Temporal summation of pain

Mean VAS scores normalised relative to the first stimulation for each group over the ten repeated stimulations are displayed in Figure 3. The ANOVA of TSP-effects showed a difference between groups ($F(2,84) = 5.0$; $P < 0.05$). Post hoc testing revealed the current-PFP group had a facilitated TSP-effect (1.7 cm, 95% CI 1.3 to 2.2 cm) compared to controls (0.9 cm, 95% CI 0.5 to 1.3 cm; mean difference = 0.8 cm; 95% CI 0.3 to 1.4 cm; $P < 0.01$) but not when compared to the recovered-PFP (1.6 cm 95% CI 1.2 to 2.0 cm; mean difference = 0.1 cm; 95% CI -0.7 to 0.6 cm; P=0.5). Similarly, the recovered-PFP showed facilitated TSP compared to pain-free controls (mean difference 0.7 cm; 95% CI 0.08 to 1.4 cm; $P < 0.05$).

Cuff pressure pain sensitivity

There was a significant main effect for group for pressure tolerance threshold ($F (2,84) = 4.818$, $P < 0.01$). The current-PFP group had reduced pressure tolerance threshold compared to both the recovered-PFP ($P < 0.029$) and the pain-free controls ($P < 0.01$). Main effects for pressure detection

and tolerance threshold are presented in Table 2. No significant group effect was found for the pressure detection threshold ($F(2,84) = 1.285$, $P = 0.12$).

Single-point pressure pain sensitivity

There were significant differences between groups for pressure pain thresholds at the centre of patella (ANOVA: $F(2,84) = 13.6$; $P < 0.001$), the tibialis anterior muscle (ANOVA: $F(2,84) = 6.5$; $P < 0.002$), and the contralateral elbow (ANOVA: $F(2,84) = 3.1$; $P < 0.049$). Post-hoc analysis demonstrated the current-PFP group had lower pressure pain thresholds at the knee compared to both the recovered-PFP group ($P < 0.05$) and the control group ($P<0.0001$), and lower pressure pain thresholds at the tibialis anterior muscle and contralateral elbow compared to the control group ($P < 0.001$; Table 2). The recovered-PFP group had lower pressure pain thresholds at the knee compared to controls ($P < 0.027$).

Pain sensitivity and time since recovery

Pearson correlation was run to determine whether there was any association between local pain sensitivity (pressure pain threshold at centre of patella) and time since recovery in the recovered group. There was no significant relationship between the time since recovery and pressure pain threshold ($P>0.05$; $r = -0.049$).

DISCUSSION

This assessor blinded quantitative study, found that young females with long-standing PFP since adolescence were characterized by impaired CPM (reflecting less descending pain inhibition) compared to the recovered-PFP group, facilitated TSP, and local and widespread pressure hyperalgesia compared to controls with no history of knee-pain. The recovered-PFP had a greater CPM effect compared to the current-PFP group. Interestingly, they had greater pressure pain sensitivity at the knee compared to controls with no history of knee-pain, which was significantly

decreased compared to the current-PFP group. Similarly, those with a history of knee-pain displayed as much temporal summation of pain as those currently experiencing persistent pain, which was increased relative to controls.

Current Patellofemoral Pain

Previous smaller studies have demonstrated that patients with PFP are characterized by widespread pressure hyperalgesia and impaired CPM compared to healthy individuals [28;32]. Interestingly, our results demonstrate that the recovered-PFP had a more efficient CPM compared to those with PFP. There were no differences for either of these groups from the healthy controls. Despite not reaching the intended sample size, small effect sizes between the current-PFP and controls (0.3 and 0.4 for CPM by detection and tolerance thresholds respectively) supports the lack of differences in this cohort. The differences in CPM between recovered-PFP and current-PFP had a moderate effect size (0.7) supporting the statistical difference between these groups. The more efficient CPM in recovered-PFP compared to those who continue to suffer from pain is interesting and one could speculate if this could potentially be protective, acting as a 'buffer' against pain, despite they display similarly facilitated TSP as those who have current-PFP. Indeed this study is the first to also document facilitated temporal summation of pain in female youth with PFP. TSP has extensively been investigated in older chronic pain populations [3], but only one previous smaller study evaluated this in younger subjects with knee pain [28]. Despite participants were recruited from the same population based cohort (APA 2011) but at an earlier time-point and not the same individuals (random selection), there was not a facilitated TSP profile in this earlier study. One reason for the differences may be relatively longer (2 years) symptom duration, and greater disability in the current investigation, since measures of facilitated central pain mechanisms have been found to worsen with increasing pain duration [5]. Participants in the present study scored worse on all subscales on the KOOS than the previous study (most notably the sport subscale, which was 11

points lower) [28], and reported median pain duration of 8 years, which may be considered long (considering it is around 1/3 of their lives).

Previous research also indicates an association between pain duration and TSP in patients with knee osteoarthritis [4]. In PFP patients, the lowest pressure pain thresholds were observed in those with the highest pain intensity and longest pain duration [30]. Further research is warranted to investigate 'how long' PFP patients need to have pain, before changes in pain sensitivity start to manifest, and if early treatment affects the pain sensitivity, and recurrent trajectory of pain.

The presence of long-standing pain, underpinned by increased pain sensitivity in these young adults may also explain the high prevalence of additional pain sites in the current study (with 60% reporting pain in more than one location, and nearly one in four fulfilling the criteria for widespread pain). Having chronic musculoskeletal pain in one location, is an independent risk factor for developing pain in subsequent other pain-free locations [1]. While there are many potential contributors, central pain mechanisms are one potential reason thought to play a role [15]. Together this may explain the mechanisms underpinning the unfavourable longer-term prognosis, and trajectory toward more pain locations after developing PFP during adolescence.

Recovered from patellofemoral pain

The recurrent nature of PFP could be explained by increased pain sensitivity in the recovered-PFP group found in the current study. Despite being pain-free, it appears that changes in pain sensitivity and central pain mechanisms do not completely return to the level of controls, despite being recovered for a median of 24 months.

In knee osteoarthritis, a peripheral nociceptive drive has been considered important for maintaining facilitated central pain mechanisms, evidenced by the 'normalisation' of mechanism after 'removal' of peripheral nociception by joint replacement surgery [19;20;25]. Contrary to this, the current investigation indicates that increased sensitivity persists in PFP patients, despite self-reporting no current pain. This in line with basic science indicating that development of central pain

mechanisms initially depends on nociceptive inputs from peripheral injury, but that change can continue to persist in the absence peripheral input [1].

Research from other recurrent musculoskeletal pain complaints provide alternative models/theories of pain recurrence, which have primarily focussed on biomechanics and altered motor control and postural stability in those with e.g. recurrent back pain [22;23], showing alterations despite symptom remission of symptoms. There is lack of data examining other factors, (including pain sensitivity), in recurrent low back pain patients, and it is unclear if they display altered pain mechanisms relative to controls [14;35]. No studies have evaluated biomechanics in PFP patients despite no current pain.

This study is the first to demonstrate altered pain mechanisms in those with a prior history of adolescent PFP who are currently pain-free, providing the first potential mechanism for explaining their recurrent knee-pain episodes. The increased pain sensitivity and facilitated pro-nociceptive mechanisms in the recovered-PFP group, means that minimal/reduced nociceptive input would be required for subsequent pain episodes to occur in this group. Dynamic processes influenced by past pain inputs or 'somatosensory pain memories' may play a role [13]. Longitudinal research is needed to confirm this, and future research should try to prospectively elucidate the temporal profiles of pain mechanisms during recovery.

Strengths and limitations

Study strengths are the recruitment from a population-based cohort, increasing the generalizability of the results, and the use of a blinded assessor, reducing the risk of detection bias. A potential limitation is the cross-sectional nature of the study, preventing conclusions regarding causality of the observed findings. Exploring whether changes in local pain sensitivity were associated with time since recovery was not significant in the current investigation, but this analysis was limited by the small sample of recovered participants. Further we did not account for pain in other locations in the recovered group. The study was powered for 36 individuals per group. Unfortunately, few were

recovered from knee-pain explaining the reduced recruitment and underlining the persistent nature of this pain complaint. Despite a lower sample-size than expected, the data demonstrates clear findings, with the recovered group falling between controls and current pain on almost all outcomes.

Conclusion

Young females with long-standing patellofemoral pain were characterized by widespread single-point pressure hyperalgesia and impaired descending pain control, while those who were currently pain free displayed increased localised pressure hyperalgesia, and facilitated temporal summation of pain, compared to young pain-free females with no history of knee-pain. Despite being recovered for a median of 2 years, those with a history of adolescent knee-pain continue to demonstrate altered pain processing. These findings are particularly interesting due to the potential effects of such maintained effects on central pain mechanisms for recurrence of pain symptoms, despite reporting no current pain.

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FIGURE LEGENDS

Figure 1. Schematic representation of testing procedures.

Figure 2. Mean (+ 95% CI) conditioning pain modulation (CPM)-effect for the current-patellofemoral pain (current-PFP, solid bars), recovered-PFP (grey), and controls (white) groups. Significantly different from recovered-PFP (*, $P < 0.005$). PDT = Pain detection threshold; PTT = pain tolerance threshold.

Figure 3. Mean (95% CI) normalised visual analogue scale (VAS) scores following the ten cuff pain stimulations with current-PFP (black symbols), recovered-PFP (grey) and pain free controls (dashed line). VAS scores are normalised to the VAS score of the first stimulus.

Table 1. Baseline demographics. Data are displayed as mean (SD) and median [inter-quartile range] unless otherwise indicated.

	Current-PFP	Recovered-PFP	Control
N	36	22	29
Age (years)	22.8 (1.1)	23.2 (1.2)	23.1 (1.2)
BMI (kg/m^2)	24.1 (4.1)	23.7 (4.0)	22.7 (4.1)
Height (m)	1.69 (0.08)	1.66 (0.06)	1.67 (0.06)
Weight (kg)	69.2 (13.8)	65.3 (10.5)	63.3 (11.1)
Test limb (% Dominant)	37	54	41
Bilateral pain (%)	89%	77%	
Pain Duration (Years)	8 [7-10]	5 [2.9-6.6]	-
Time since knee-pain (Years)*	-	2 (0.7-4.0)	-
KOOS Symptoms (0-100)	71 (16)	95 (5)	97 (3)
KOOS Pain (0-100)	67 (13)	97 (4)	100 (1)
KOOS activity (0-100)	78 (13)	98 (2)	100 (2)
KOOS Sport (0-100)	48 (21)	91 (11)	99 (2)
KOOS QoL (0-100)	51 (21)	85 (13)	98 (4)
Pain Frequency (%)	Daily: 34% Several times per week: 34% Weekly: 17% Monthly: 14% Rarely: 0% Never: 0%	-	-
Current Pain (NRS 0-10)	2 (2)	-	-
Worst Pain in the last 4 weeks (NRS 0-10)	7 (2)	-	-
Average pain in the last 4 weeks (NRS 0-10)	4 (1)	-	-

KOOS: Knee injury and Osteoarthritis Outcome Score. NRS: Numerical Rating Scale.

Table 2. Mean (95% CI) pressure pain thresholds (PPT), cuff pressure pain detection threshold (PDT), and pressure tolerance thresholds (PTT) for females with current-PFP, recovered-PFP, and pain-free control.

	Current-PFP	Recovered-PFP	Controls
Cuff PDT	21.1 (18.0 - 24.18)	24.5 (20.1 - 28.4)	25.8 (22.3 - 29.2)
Cuff PTT	42.2(36.3 - 48.1)*#	52.9 (45.3 - 60.4)	55.0 (48.5 - 61.6)
PPT Centre of Patella	377.3 (318.3 - 436.2) *#	492.3 (420.3 - 564.3)#	602.8(534.0 - 671.7)
PPT Tibialis anterior	323.2 (262.2-384.1) #	398.5 (332.1- 464.8)	479.8 (410.1 - 549.4)
PPT Contralateral elbow	363.3 (262.3 - 384.1) #	423.2 (332.1 - 464.8)	448.7 (410.1 - 549.4)

Significantly lower than Recovered-PFP (*, $P < 0.05$) and Controls (#, $P < 0.05$).

Table 3. Differences in threshold values at baseline and during conditioning, and in VAS during temporal summation paradigm.

	Pressure detection threshold		Pressure tolerance threshold		Temporal Summation of pain	
	Baseline	**During conditioning**	**Baseline**	**During Conditioning**	**VAS-I**	**VAS-II**
Current-PFP	19.3 (17.0-21.7)	25.4 (21.6-29.3)*	42.0(37.4 - 46.5)	47.2 (42.0-52.5)*	4.0 (3.4 - 4.7)	5.8 (4.9 - 6.69
Recovered-PFP	24.0 (19.9 - 28.1)	34.2 (28.2-40.2)*	53.0 (43.9-62.1)	65.8 (64.6-77.0)*	3.6 (2.8 - 4.5)	5.3 (4.5 - 6.1)
Controls	25.1 (21.4 - 28.1)	35.9 (30.6-41.2)*	54.8 (48.6 - 61.1)	65.3 (57.4-73.2)*	4.3 (3.5-5.1)	5.2 (4.3-6.1

*indicates significant increase from baseline.