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Impaired conditioned pain modulation in young female adults with long-standing patellofemoral pain – a single blinded cross sectional study

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ABSTRACT

Objective: Patellofemoral pain (PFP) is common among young individuals. Female adolescents with PFP present typically with localised mechanical hyperalgesia around the knee but the effect of central pain mechanisms are unknown. This study aimed to compare temporal summation of pain, conditioned pain modulation (CPM), and widespread hyperalgesia in young female adults with PFP and age-matched pain-free controls.

Design: Cross-sectional study.

Setting and subjects: Twenty young female adults (19 - 21 years) with long-standing PFP were compared with 20 pain-free controls from the same population-based cohort

Methods: Cuff algometry was used to assess the pain detection threshold. Temporal summation of pain was assessed by recording the pain intensity on a visual analogue scale during repeated cuff pressure stimulations at pain tolerance intensity on the lower leg. CPM was recorded as the increase in cuff pain detection threshold in response to experimental conditioning pain imposed on the contralateral arm. Handheld pressure algometry was used to assess pressure pain thresholds (PPT) on the knee, shin, and forearm. The examiner was blinded to the type of subject assessed.

Results: Compared with pain-free controls, young females with PFP did not show a decrease in cuff pain thresholds ($P<0.40$) or facilitated temporal summation ($P<0.15$), but had a lower CPM response ($P<0.04$) and lower PPTs ($P<0.005$).

Conclusions: Young female adults with long-standing PFP demonstrated impaired CPM. This is important as PFP, a peripheral pathology, might have important central

components which need to be studied in order to understand its extent and therapeutic implications.

Key words: patellofemoral pain; central sensitization; CPM; hyperalgesia**;** experimental pain

INTRODUCTION

Patellofemoral pain (PFP) is a common knee condition among individuals who participate in repetitive knee loading activities (1, 2). The prevalence of PFP is more than twice as high among females compared to males and data from sports medicine clinics suggest that PFP is the most common knee condition and may account for 25% of all consultations regarding knee pain (3, 4). PFP is defined as pain anteriorly around the patella with pain that increases during prolonged sitting, squatting, kneeling, and stair climbing (5). Prospective studies have highlighted a poor long-term prognosis with only 1/3 being pain free 12 months after initiation of treatment (6).

Mechanical hyperalgesia was recently demonstrated by reduced pressure pain thresholds (PPTs) assessed around the knee and on the tibialis anterior muscle in female adolescents with PFP compared with pain free controls (7). The distal hyperalgesia observed at the tibialis anterior muscle may reflect segmental spreading of hyperalgesia (8). In some chronic musculoskeletal pain conditions with widespread hyperalgesia such as osteoarthritis (OA) and fibromyalgia, temporal summation of the pain perception to repetitive pressure pain stimulations appears to be facilitated compared with pain free controls, which is thought to be the result of facilitated central mechanisms (9, 10). Furthermore, studies have demonstrated reduced sensory perception to thermal stimulation and vibration (11, 12), indicating altered sensory function in patients with PFP.

Painful stimulation evokes a multisegmental hypoalgesia often referred to as conditioned pain modulation (CPM); a manifestation of the descending modulatory

effects characterised by attenuated pain response to a painful test stimulus when another painful conditioning stimulus is applied (13). CPM is a proxy of the effectiveness of the endogenous analgesia system. Previous studies have shown impaired CPM in both knee and hip OA (9, 10, 14) as well as other non-arthritic chronic pain conditions (15, 16). Impaired CPM is clinically important as it may be associated with a higher risk of developing chronic post-operative pain (17). Collectively, identification of sensitised central mechanisms and widespread hyperalgesia appears to be clinically important and may be associated with higher risk of long-standing pain (17-21). However, it has never been investigated among young female adults with PFP.

The aims of this study were to assess 1) temporal summation of cuff-induced pressure pain, 2) CPM assessed by cuff-algometry, and 3) widespread mechanical hyperalgesia in young female adults with PFP compared with age matched healthy pain-free controls. It was hypothesised that young adults with PFP would have increased temporal summation of pain and impaired CPM compared with pain-free controls and that PPTs around the knee and at sites remote from the area of self-reported knee pain would be lower among young female adults with PFP compared with pain-free controls.

METHODS

Subjects

The design was a cross-sectional study nested within a population-based cohort. Young female adults diagnosed with PFP were matched to a gender- and age-matched comparison group of pain-free controls. Both young adults with PFP and pain-free controls were recruited from the same population-based cohort (the Adolescent Pain in Aalborg 2011) (22). This cohort has been followed since 2011 and consisted of 2200 adolescents between 15 and 19 years of age. From these, 153 were diagnosed with PFP using previously described inclusion and exclusion criteria (23, 24). In short, the patients with PFP were required to have an insidious onset of anterior knee or retropatellar pain of more than 6 weeks duration and provoked by at least two of the following daily activities: prolonged sitting or kneeling, squatting, running, hopping, or stair walking; tenderness on palpation of the patella, pain when stepping down or double leg squatting; and worst pain during the previous week of more than 3 cm on a 10 cm visual analogue scale (VAS). Exclusion criteria were concomitant injury or pain from the hip, lumbar spine, or other knee structures; previous knee surgery; self-reported patellofemoral instability; knee joint effusion. From the 153 adolescents with PFP, 121 were enrolled in a randomised trial (24). Participants who were previously diagnosed with PFP in the original trial (23) were included in a telephone interview to inquire if they still had knee pain and if so they were invited to participate in the current study. Pain-free controls were randomly recruited from the same population-based cohort by telephoning a random sample with approximately the same age, gender, and sports participation as the PFP group. The inclusion criteria for pain-free controls were: No current self-reported

musculoskeletal pain; no self-reported prior surgery in the lower extremity; no self-reported neurological or other medical conditions. The study was conducted in accordance with the Helsinki Declaration and was approved by the local ethics committee in the North Denmark Region (N-20110020).

Protocol

All parameters were collected by an examiner who was blinded towards group allocation (PFP vs. pain-free controls). Data was collected from the side of the most painful knee among those with PFP and the same side matched on dominance on pain-free controls. Manual pressure algometry, cuff pressure algometry, temporal summation of pain, and CPM were assessed in a sequence on a single day with approximately 3-5 minutes between each test. The reliability of manual PPT measurements performed on pain-free young adults has previously been investigated and found to be acceptable for sites around the hand and head (intraclass correlation coefficients (ICC) ranging from 0.69 to 0.88) (25) In pain-free adults, the reliability of computer controlled cuff-algometry for assessing pressure algometry, temporal summation of pain, and CPM has been found to be good to excellent with ICCs ranging from 0.60-0.89 (26). The primary outcome was temporal summation of pain measured as the change in VAS during repeated cuff stimulations on the lower leg. Secondary outcomes included 1) cuff pressure pain sensitivity recorded on the lower leg, 2) CPM with the outcome being the change in cuff pain sensitivity on the lower leg after cuff-induced arm pain (the conditioning stimulus), and 3) PPTs at the patella, the tibialis anterior muscle, and the lateral epicondyle.

Pressure algometry

PPTs were assessed using a hand-held pressure algometer (Somedic Sales AB, Sweden) with a stimulation area of 1 cm^2 placed perpendicular to the skin. Pressure was applied at a rate of 30 kPa/s which was verified using the inbuilt digital indicator on the algometer. The individuals were instructed to indicate when the sensation changed from a sensation of pressure to the first sensation of pain. Measurements were done with the individuals resting in a reclining position and the knee slightly flexed at 15 degrees. PPT was measured at sites close to the knee to reflect localised hyperalgesia and on the contralateral site distant to the knee to investigate widespread hyperalgesia (8-10). The PPTs were measured twice at each site and the average was calculated and used for the analyses. Three assessment sites were located on: 1) The knee at the centre of the patella. 2) The muscle belly of the tibialis anterior muscle 5 cm distal to the tibial tuberosity. 3) The elbow, on the lateral epicondyle of the humerus.

Computer-controlled cuff pressure algometry

Cuff pressure pain detection thresholds (PDT) and cuff pressure pain tolerance (PTT) were assessed by a computer-controlled cuff pressure algometer (Nocitech, Denmark and Aalborg University, Denmark). Computer controlled cuff algometry have previously been widely used to study central pain mechanisms (9, 10, 27, 28) and has the advantage of being user independent. A 13-cm wide silicone tourniquet cuff (VBM, Germany) with an equal-sized proximal and distal chamber was wrapped around the lower leg on the side with the worst knee pain. The cuff was mounted with a 5 cm distance between its upper rim and the tibial tuberosity. The cuff pressure was increased with a rate of 1 kPa/s simultaneously in both chambers and the maximal pressure limit of the system was 100 kPa which may cause some

participants to reach 100 kPa before reaching PTT. The participants used an electronic VAS to rate their pressure-induced pain intensity and a button to release the pressure. The electronic VAS was sampled at 10 Hz. Zero and ten cm extremes on the VAS were defined as “no pain” and “maximal pain”, respectively. The participants were instructed to rate the pain intensity continuously on the electronic VAS from the first sensation of pain and to press the pressure release button when the pain was intolerable. The pressure value when the subject rated the sensation of pain as 1 cm on the VAS was defined as the PDT and the pressure recorded when the subject terminated the cuff inflation was defined as the PTT.

Temporal summation of cuff-induced pressure pain

Temporal summation was assessed by the computer-controlled cuff algometer (Nocitech, Denmark). Ten cuff pressure stimuli (1-s duration and 2-s interstimulus interval) were delivered to the lower leg by simultaneous inflation of both cuff chambers at an intensity equivalent to PTT recorded during the assessment of the cuff pain sensitivity. In the period between stimuli, a constant non-painful pressure of 5 kPa was kept, thus ensuring that the cuff did not move. The participants were instructed to rate the pain intensity continuously on the electronic VAS. The mean VAS score during the 1-s interval between stimulations after each of the 10 stimuli was extracted and then normalised by subtraction of the mean VAS scores from the first stimulation.

Conditioned pain modulation

Experimental tonic pain was induced in the contralateral arm by cuff-induced pain (conditioning stimulation), and assessment of cuff PDT and PTT was performed on

the lower leg before and during the conditioning stimulus on the arm. A 7.5-cm-wide tourniquet cuff (VBM, Germany) was wrapped around the left arm with the lower rim of the cuff placed 3 cm proximal to the cubital fossa. The computer-controlled cuff algometer maintained a constant pressure at 60 kPa. The CPM effect was expressed as the percentages increase of PDT and PTT, respectively, from baseline to the conditioning assessments. If subjects reached 100 kPa as PTT before conditioning cuff-pain these were excluded from further analysis. A-priori it was expected that some subjects would reach 100 kPa and therefore the CPM effect using PTT was only included as an explorative outcome.

Self-reported outcomes

The following clinical self-reported measures were used: 1) Patellofemoral Osteoarthritis Outcome Score (KOOS)(29), worst pain intensity during the last four weeks, and current pain measured on a 0-10 numeric rating scale (NSR), 2) symptom duration (months), 3) most painful knee (right/left), 4) uni- or bilateral pain (yes/no), and pain localisation measured using the Navigate pain app (30).

Statistical analysis

The sample-size was based on the primary outcome of detecting a difference in normalized VAS during temporal summation from stimuli 1 to stimuli 10 of 1.5 cm(10). Common standard deviation was estimated to be 1.5 cm and with a power 0.80 and alpha at 0.05 this corresponds to a sample-size of minimum 16 in each group.

All analyses were defined a-priori. The primary analysis was a comparison between groups in the change in VAS during temporal summation. Secondary analyses

included comparisons of cuff PDT, cuff PTT, CPM, and PPTs at the centre of the patella, m. tibialis anterior and the lateral epicondyle. Unpaired t-tests were used for all comparisons except for the PPTs where a two-way ANOVA was used with group and site as factors. All calculations were performed using Stata version 11 (StataCorp, College Station, Texas, USA). Mean values and 95% confidence intervals (CI) are reported if data were normally distributed and otherwise they are presented as median and interquartile range (IQR). P-values less than 0.05 were considered significant.

RESULTS

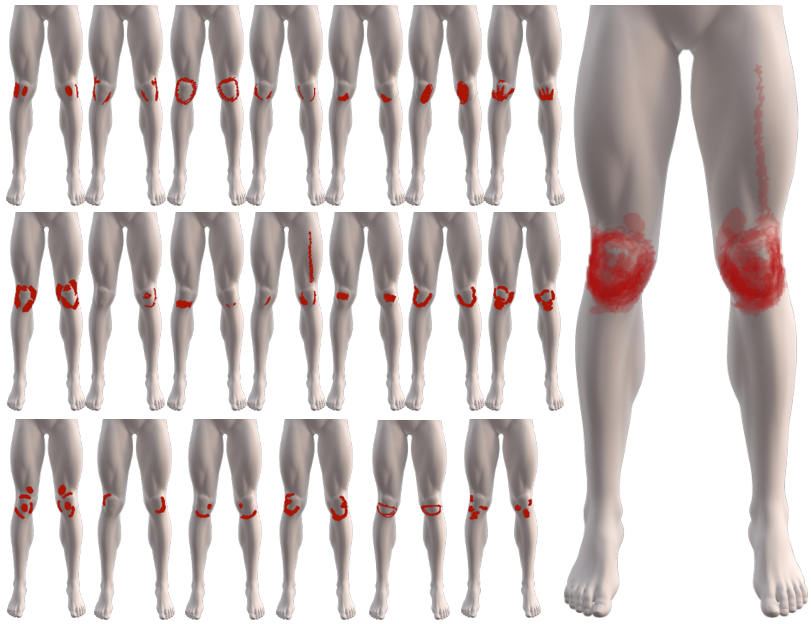
The female adults with PFP had a median symptom duration of 6 years and reported in general intermittent episodes (Table 1) of peri-patellar pain (Figure 1).

Table 1: Demographics and patient reported outcomes

	Pain free (n=20)	Patellofemoral pain (n=20)	P-values
Age [years]*	20.5 (20.0-21.0)	20.0 (19.0-21.0)	0.26
Weight [kg]	61.7 (7.4)	63.8 (8.3)	0.40
Height [cm]	169 (5)	170 (5)	0.53
Sports participation (% yes)	75%	80%	0.61
Duration of symptoms (years)*	N/A	6 (4.5-7)	-
Worst pain last four weeks [NRS]	0 (0-0)	7 (5.5-8.0)	<0.0001
KOOS symptoms	96 (5)	79 (11)	<0.0001
KOOS pain	99 (2)	74 (11)	<0.0001
KOOS activity	100 (1)	84 (10)	<0.0001
KOOS Sport	98 (3)	59 (23)	<0.0001
KOOS QoL	97 (7)	55 (18)	<0.0001
PainDetect*	0 (0-0)	7.5 (4.5-11.0)	<0.0001
Self-reported description of pain from PainDetect			
Persistent pain with slight fluctuations (n)		4	
Persistent pain with pain attacks (n)		3	
Pain attacks without pain between them (n)		12	
Pain attacks with pain between them (n)		1	

* Median and interquartile range. 0 to 100, best to worst scale. PFOOS: Patellofemoral Osteoarthritis Outcome Score

Figure 1: The 20 small figures show the participants usual self-reported pain, while the large picture show the average pain location of the 20 young adults with patellofemoral pain.

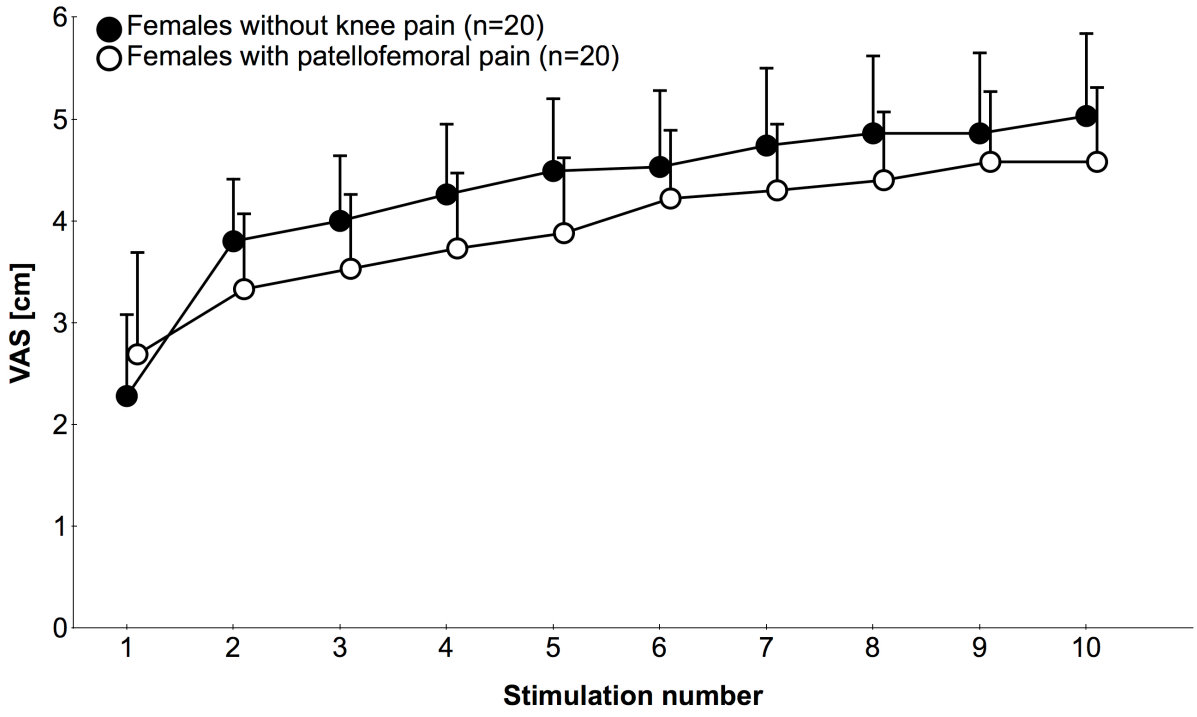


Temporal summation of pain

The VAS scores following the ten repeated cuff stimulations showed a progressive increase in both groups illustrating the temporal summation of pain.

The analysis showed no signification difference between groups in the increase in VAS from stimulus 1 to 10 (0.9 cm (95%CI: -0.5; 2.3 cm, t(38)=1.48, P=0.15) (Figure 2).

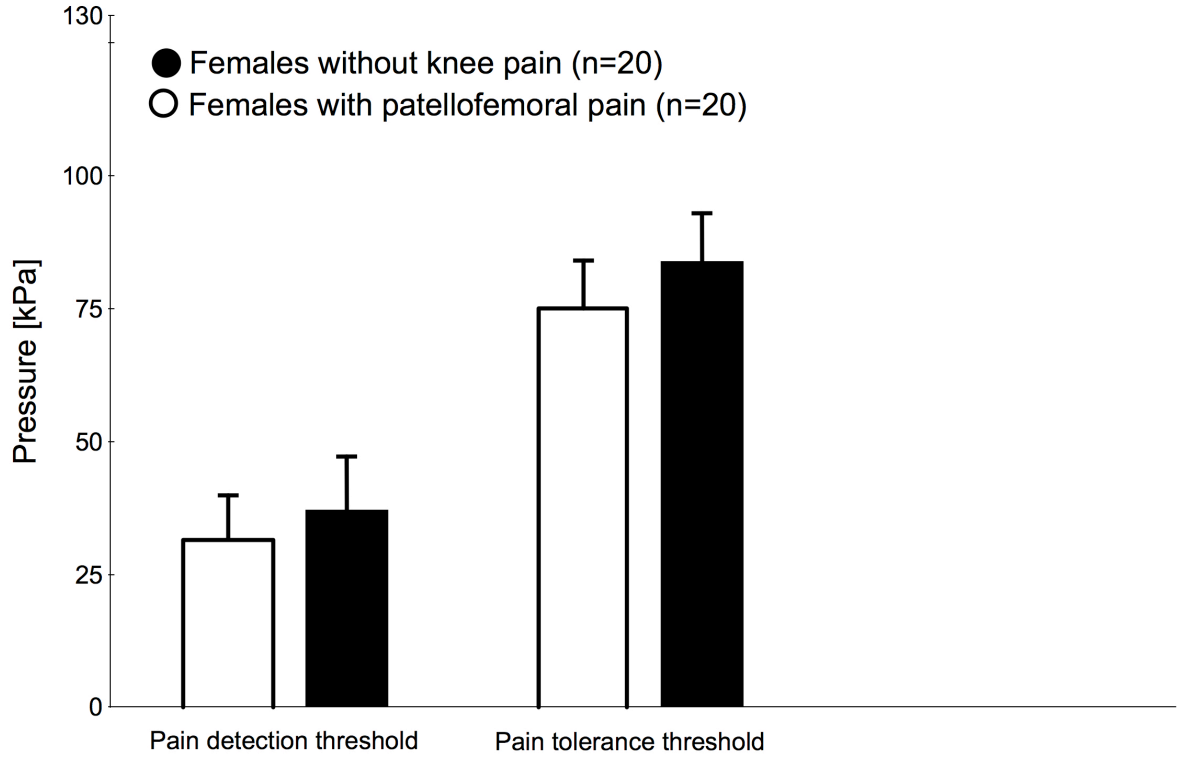
Figure 2: Mean (+1.96*SE, N=20) of the visual analogue scale (VAS) scores after 10 cuff pressure pain stimulations at the pain tolerance intensity in females with patellofemoral pain (open symbols) and pain free controls (solid symbols).



Cuff pain sensitivity

There were no significant differences in PDT (-5 kPa (95%CI: -18; 7 kPa, t(38)=0.85, P=0.40)) or PTT (-8 kPa (95%CI: -21; 6, t(38)=1.11, P=0.27) between young female adults with PFP and pain-free controls (Figure 3).

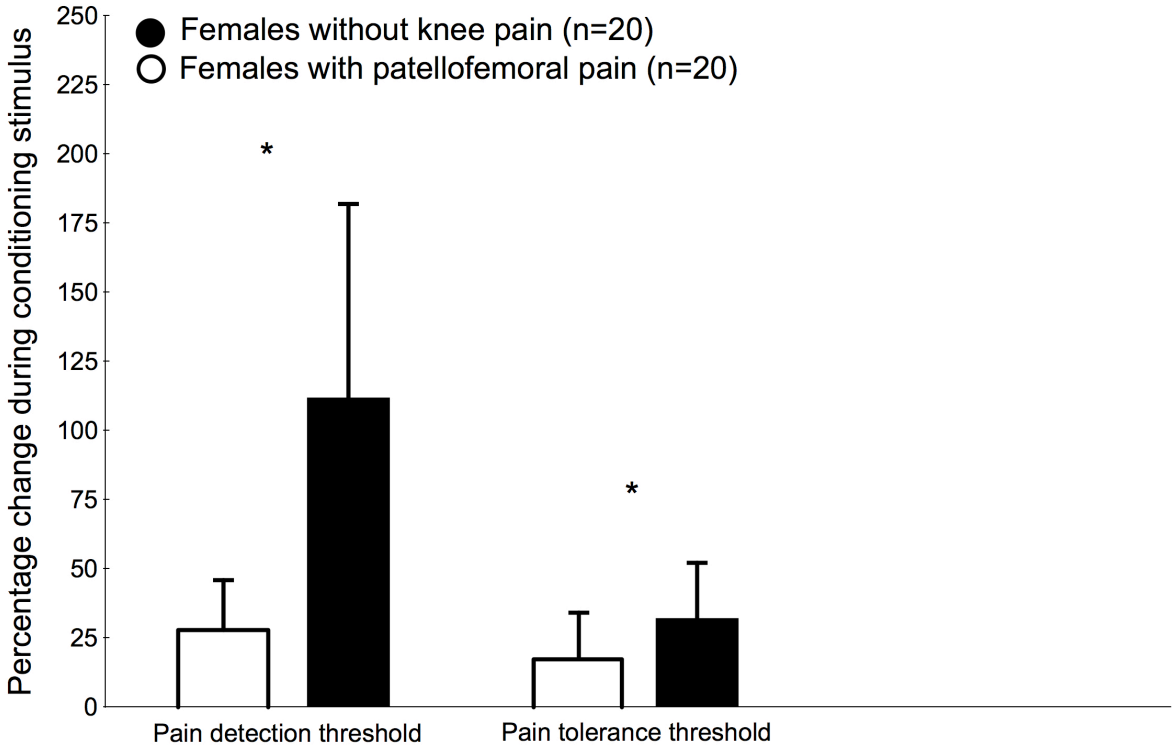
Figure 3: Mean ((+ 1.96*SE, N=20) cuff pain detection threshold (PDT) and pain tolerance (PTT) threshold in females with patellofemoral pain (open symbols) and pain free controls (solid symbols). here.



Conditioning pain modulation

Young female adults with PFP had a 78% (95%CI: 4; 151%, t(38)=2.15, P<0.04) lower CPM response in their PDT (Figure 4). The explorative CPM assessments based on PTT measurements excluded 11 pain-free controls who reached 100 kPa before experimental cuff-pain tolerance was reached but showed a 20% lower PTT response among young female adults with PFP compared to pain-free controls (95%CI: 1; 39%, t(27)=2.24, P<0.04) (Figure 4).

Figure 4: Percentage increase (+1.96*SE, N=20) in pain detection threshold (PDT) and pain tolerance (PTT) from before, to during (CPM) the experimental tonic pain was induced in the contralateral arm in female with patellofemoral pain (open symbols) and pain-free controls (solid symbols). The PDT includes 18 individuals in each group as the measurement system malfunctioned during collection of data. * denotes significant differences (P<0.04).

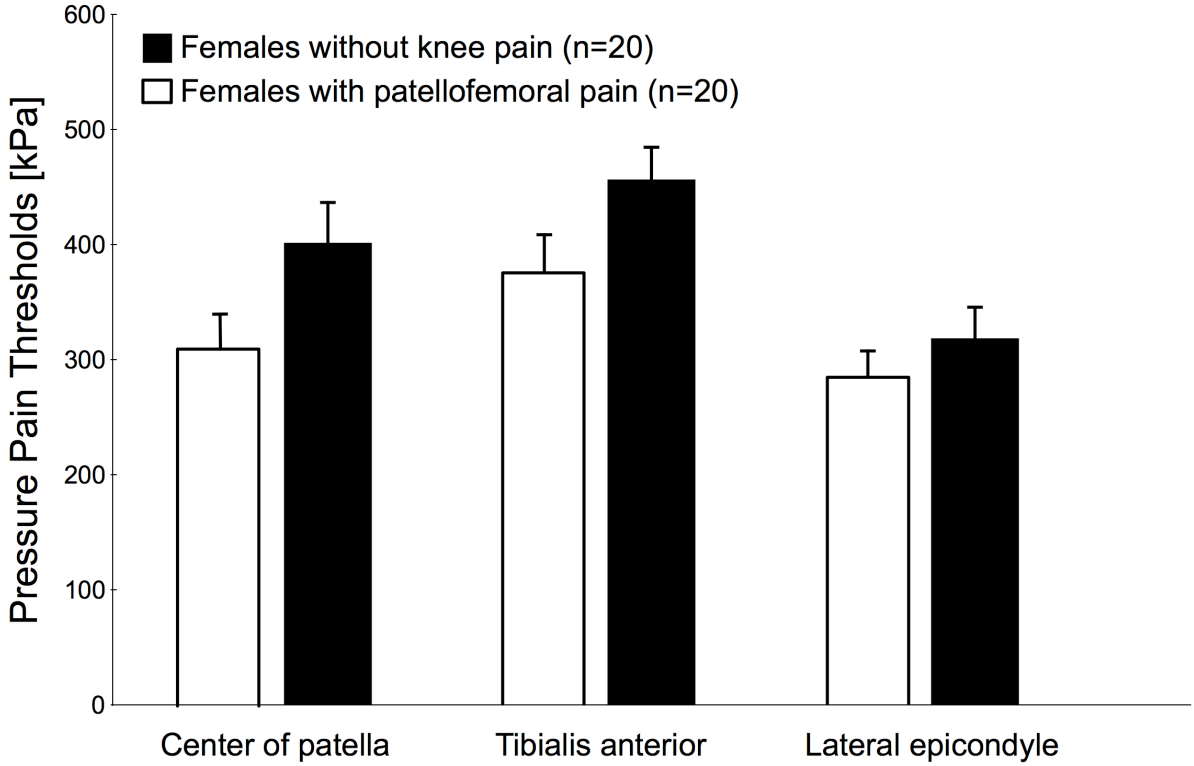


Pressure pain sensitivity

There was a significant effect of group (PFP vs. pain-free controls) on PPTs ($F_{1, 114}$ = 8.2, P < 0.005) (-68 kPa, (95%CI: -115; -21 kPa)) and PPT site ($F_{2, 114}$ = 7.1, P < 0.001), (Figure 5).

292 Figure 5: Mean (+1.96*SE, N=20) handheld pressure pain threshold (PPT) on the center of the

293 patella, tibialis anterior and the lateral epicondyle.



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Discussion

Young female adults with long-standing PFP were characterised by impaired CPM assessed by PDT and spreading hyperalgesia, but contrary to our main hypothesis, they showed no signs of facilitated temporal pain summation. This is the first study to provide evidence for an altered pain processing among young adults with PFP.

Temporal summation of pain

Contrary to the a priori hypothesis, young female adults with long-lasting chronic PFP did not have facilitated temporal summation. Previous studies have shown a facilitated temporal summation of pain in patients with knee OA and in other musculoskeletal pain disorders such as fibromyalgia, chronic low back pain and whiplash (31-34). The difference in results may potentially be explained by the difference in study populations. The current study population reported knee pain for an average of six years, which is similar to previous studies on knee OA (10), but they are indeed much younger (≈45 years younger). The young adults with PFP developed knee pain while they were in their early teens while patients with knee OA developed knee pain in their mid-50s. Likewise the young adults with PFP presented slightly lower peak pain intensities compared to sensitised adult patients with knee OA typically reporting peak pain during the last 24 hours of 8 on a NRS (10). This is important because higher peak pain is associated with a more facilitated temporal summation (10). The pain reported by young adults with PFP is normally associated with patellofemoral joint loading (e.g. stair walking or squatting) and rarely they report pain at rest (35). Patients with knee OA often report pain at rest and also during walking. Collectively the lack of facilitating temporal summation may suggest

that long pain duration is not the only factor, which is required to cause changes in temporal summation.

Conditioned pain modulation

Young female adults with PFP had a less efficient CPM similar to what have been observed in older adults with knee OA (31). Less-efficient CPM mechanisms have previously been reported in patients with musculoskeletal pain conditions, such as myofascial temporomandibular disorders (36), chronic low back pain (37), and fibromyalgia (38) but this study is the first to report impaired CPM in a younger patient population. A reduced potency of the descending control makes the entire neuroaxis more vulnerable to pain (39). However, an important finding is that the CPM response was highly variable among the young female adults with PFP. Some had no change in PDT during the test stimulus while others had responses similar to pain-free controls. Earlier studies have linked a less efficient CPM response to poorer long-term outcome after thoracotomy (17). Although pure speculation, this may also be the case for young female adults with PFP who are known for having a high degree of chronicity with only 1/3 being pain-free one year after treatment (40, 41). Eleven pain-free controls reached maximum in their pain tolerance threshold assessment before the conditioning stimulus was applied which made it impossible to compare the effect of the conditioning stimulus on their pain tolerance threshold.

CPM and temporal summation of pain are both considered part of central pain processing but reflect two different mechanisms. Conditioned pain modulation originates from the activation of brainstem inhibitory projections that, in turn, act to postsynaptically inhibit spinal and trigeminal wide dynamic-range neurons (42). The

inability of the noxious conditioning stimulus to increase pain thresholds indicates a potential deficiency in the body's endogenous pain modulatory ability. Temporal summation is thought to be a facilitating mechanism that mimics the initial phase of the windup process in dorsal horn neurons seen in animals (43). Therefore, the data from this study suggests that mainly the inhibitory mechanism is affected in young female adults with PFP.

Pressure and cuff pain sensitivity

Young adults with PFP had lower PPTs but showed no difference in either PDT or PTT measured with the cuff algometer. The reason might be that cuff algometry primarily captures deep tissue hyperalgesia while mechanical PPTs measure hyperalgesia of superficial structures and muscles (8, 44). Reduced efficiency of the CPM system may explain the widespread hyperalgesia. However, the present population may have a lower degree of central sensitization compared to patients with knee OA who are often characterised by facilitated temporal summation, widespread hyperalgesia, and an inefficient CPM system (10). An important aspect when interpreting these results is that this population is much younger than previous studies on older adults with chronic pain. Although not heavily researched it appears that changes in pain processing is dependent on the age of the individual (45). Emerging evidence suggests that there might be some critical periods during adolescence and childhood where pain experiences might induce long-lasting and specific effects not observed among adults (45). However, it does appear that PPTs may change in response to recovery. A recent study demonstrated that adolescents with PFP deeming themselves as recovered after 3 months of exercise therapy had

a 68-76 kPa larger improvement in PPTs around the knee and tibialis anterior compared to adolescents with not recovered after treatment (46).

Strengths and limitations

A strength of the study is that all the participants were recruited from a large, well-defined, population-based cohort that have been followed for three years. Recruitment of a population-based sample suggests that our data may be generalizable to young female adults with long-standing PFP. An examiner blinded to group allocation was used to minimise the risk of detection bias which is a significant strength.

The present findings may not apply to the male population of young adults with PFP, as only females were included. The results may only apply to female adults with PFP who developed knee pain during their early teens and not those who develop knee pain during adulthood. Hormonal status of the participants was not assessed which may introduce an unsystematic bias and reduce the difference in pain sensitivity between groups. No reliability studies have been performed among this population and no data exist for the minimally clinically important change. This makes it difficult to interpret the relative difference between groups.

Clinical implications

Based on the large variation in CPM response among the young female adults with PFP it seems likely that altered central processing of pain is only present within a subgroup. It is known from a previous randomised trial among adolescents with PFP that there is a subgroup of adolescents who does not respond favourably to the

current best available evidence-based treatment, exercise therapy (23). It may be that this subgroup is characterised by facilitated central mechanisms and treatment among this subgroup should move away from the mechanical paradigm focusing purely on improving strength and restoring lower extremity alignment. Instead normalisation of the hyperexcitability of the nervous system should be targeted. Interestingly, exercise-induced hypoalgesia may be affecting the facilitated central mechanisms in the subgroup with efficient exercise therapy (47).

This study demonstrated that young female adults with long-standing patellofemoral pain were characterized by impaired conditioned pain modulation. This is the first study to provide evidence of an altered pain processing among young female adults with patellofemoral pain which is important as patellofemoral pain might have an important pain processing component which needs to be studied in order to understand its extent and therapeutic implications.

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