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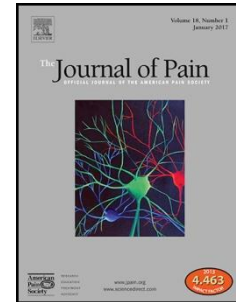
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Pain adaptability in individuals with chronic musculoskeletal pain is not associated with conditioned pain modulation

Running title:

Pain adaptability in MSK participants

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Highlights

- The dichotomy of pain adaptability exists in individuals with chronic musculoskeletal pain.
- Pain adaptability is dissociated with the potency of conditioned pain modulation.
- Pain adaptability could reflect the temporal aspect of pain inhibition.

Abstract (199 words)

Healthy humans can be divided into the pain adaptive (PA) and the pain non-adaptive (PNA) groups; PA showed a greater decrease in pain rating to a cold pressor test (CPT) than PNA. This study examined if the dichotomy of pain adaptability existed in individuals with chronic musculoskeletal pain (MSK). CPTs at 2°C and 7°C were used to assess the status of pain adaptability in participants with either chronic non-specific low back pain or knee osteoarthritis. The participants' potency of conditioned pain modulation (CPM) and local inhibition were measured. The strengths of pain adaptability at both CPTs were highly correlated. PA and PNA did not differ in their demographics, pain thresholds from thermal and pressure stimuli, or potency of local inhibition or CPM. PA reached their maximum pain faster than PNA ($t_{41} = -2.76$, $p < 0.01$), and had a gradual reduction of pain unpleasantness over seven days whereas PNA did not ($F_{(6,246)} = 3.01$, $p = 0.01$). The dichotomy of pain adaptability exists in MSK patients. Consistent with the healthy human study, the strength of pain adaptability and potency of CPM are not related. Pain adaptability could be another form of endogenous pain inhibition which clinical implication is yet to be understood.

Perspective

The dichotomy of pain adaptability was identified in healthy humans. The current study confirms that this dichotomy also exists in individuals with chronic musculoskeletal pain, and could be reliably assessed with cold pressor tests at 2°C and 7°C. Similar to the healthy human study, pain adaptability is not associated with conditioned pain modulation, and may reflect the temporal aspect of pain inhibition.

Keywords

Cold pressor test, conditioned pain modulation, musculoskeletal pain, pain adaptability, pressure pain threshold.

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1 Introduction (554 words)

2 The ability of the body to modulate pain without the help of medical interventions is known as
 3 endogenous pain inhibition. Conditioned pain modulation (CPM) is one of the well-studied
 4 endogenous pain inhibitions. It involves the reduction of pain from a painful stimulus when a second
 5 painful stimulus is applied distantly or heterotopically⁶³. Potency of CPM is defined by percentage
 6 change in pain threshold or pain rating at baseline to that during or after cold pressor. However, the
 7 relationship between potency of CPM and chronic pain is inconclusive; some studies showed that
 8 patients with high intensity of chronic pain displayed poorer CPM whereas^{4,17} other studies found no
 9 association between pain intensity and potency of CPM^{10,14,18}. Due to those inconsistent results and
 10 not well-understood clinical implications, the clinical use of CPM, as the only test of pain inhibition in
 11 quantitative sensory test (QST), is limited⁶².

12
 13 Pain adaptability could be another form of pain modulation. It is assessed using a similar method to
 14 that used in the measurement of the potency of CPM^{15,67}: the cold pressor test (CPT). When healthy
 15 humans were subjected to a cold pressor of 2°C for five minutes, all of them reported moderate to
 16 severe pain. After about two minutes, one group experienced significant pain reduction in the
 17 remaining three minutes from the cold water, i.e., the pain adaptive group (PA); whereas the other
 18 group experienced no changes or a slight increase in pain over time, i.e., the pain non-adaptive
 19 group (PNA)⁶⁷. This dichotomy in response to noxious stimulation was also found in another study
 20 where cold water at 7°C or hot water at 47.5°C was used¹⁵. When CPT was used to assess CPM, all
 21 tests were completed within two minutes. It is important to note that the dichotomy of PA and PNA
 22 only appeared after two minutes or longer into CPT, when everyone has nearly reached their peak
 23 pain. More importantly, PA reached their peak pain within a significantly shorter time than the PNA
 24 did. This confirms that pain adaptability measures a form of pain inhibition that differs from CPM. It

reflects the intensity as well as the temporal aspects of pain inhibition, which is not measured in CPM. Indeed, in their healthy human study, Zheng⁶⁷ found an association between pain adaptability and the potency of local inhibition, but not between pain adaptability and potency of CPM.

So far, pain adaptability has not been studied among clinical samples. It is unclear whether this dichotomy exists among patients with chronic musculoskeletal pain (MSK), who are considered to have a compromised CPM^{5,31,35,49,53}, and whether pain adaptability is related to CPM in those individuals and what its clinical implications are.

This study examined whether PA and PNA could be identified in MSK participants. More specifically, it aimed (1) to compare the feasibility of CPTs in two temperature settings in MSK participants, in assessing pain adaptability status and the potency of CPM. Feasibility was defined as the CPT with a higher rate of completion and a lower frequency of adverse events. (2) To investigate if PA could be differentiated from PNA using demographics, clinical pain history (years in pain), thermal detection and pain thresholds, pressure pain threshold (PPT), and potency of CPM and local inhibition. (3) To explore the association between pain adaptability and potency of CPM and between pain adaptability and local pain inhibition.

Methods

Study procedure

This study was conducted at RMIT University, Australia, with the approval of the RMIT Human Research Ethics Committee (HREC No 18892). All participants gave written consent to be in the study.

Previous studies used five-minute CPTs at temperatures of 1-4°C⁶⁷ or 7°C¹⁵ to determine the pain adaptability of healthy humans. Such temperatures have also been used in other studies to test CPM or cold pain tolerance in chronic pain participants without any adverse events^{18,42,45,48,60}. It is known that for CPT, water of lower temperatures is perceived as more painful than that of higher temperatures⁶¹. In a healthy humans study, one out of 42 participants could not complete a CPT at 1-4°C⁶⁷. It was speculated that a CPT at 2°C might be too painful for MSK participants. On the other hand, a CPT at 8°C could not induce CPM³². A CPT at 7°C might be suitable to identify PA and PNA and to induce CPM in individuals with MSK. Thus, a comparison of both temperatures should be explored.

The steps of this study are summarised in Fig 1. All participants underwent three sessions with an interval of one week. Baseline data such as demographics, body mass index, quality of life, sleep quality, pain catastrophizing, clinical pain history, and thermal detection and pain thresholds were collected at session 1. After session 1, participants were given a pain diary to record their time courses (in hours) of the average daily pain and intensity of the average daily pain (0-10 numerical rating scale), highest daily pain (0-10 numerical rating scale), as well as unpleasantness of clinical pain (0-20 scale, 20 being intolerable unpleasantness) over 7 days. At each of the sessions 2 and 3, the participants received a CPT. They were randomly allocated to receive a CPT at 2°C (2-4°C, for five minutes) at session 2 followed by a CPT at 7°C (7-9°C, for seven minutes) at session 3 or a CPT at 7°C followed by CPT at 2°C (Fig 1) by drawing a sealed envelope containing a number which corresponded to a random number sequence generated in Excel by an independent assessor (ZZ). The strength of pain adaptability and potency of CPM were assessed in both sessions. The participants were informed that the test would be painful but would not cause any harm. They were also informed that they could remove their foot from the cold pressor at any time without prejudice.

Water and skin temperatures prior to each CPT were measured. Any adverse event due to the tests was recorded. Participants were in a seated position during all testing.

Selection criteria

Participants were enrolled by the outcome assessor (DWLW) and an independent clinician (SH).

Non-specific low back pain and knee osteoarthritis are two highly prevalent chronic musculoskeletal conditions^{2,40,58}. Thus, these two types of chronic musculoskeletal pain were chosen for the current study. Furthermore, they both share similar mechanisms such as central sensitization and abnormal/weaker CPM when compared with healthy individuals^{13,17,52}.

Inclusion criteria

Those aged between 20 and 65 years, with non-specific low back pain for more than three months (diagnosed based on the Guideline from the American College of Physicians and the American Pain Society¹¹) of intensity of 2 or more on a 0-10 numerical rating scale, and with adequate conversational English were included in the study.

Individuals within the age range of 40 to 80 years, with adequate conversational English, with knee OA diagnosed based on the guideline of the American college of Rheumatology on the criteria for idiopathic osteoarthritis of the knee³ and knee pain of intensity of 2 or more on a 0-10 numerical rating scale were included.

Exclusion criteria

Participants were excluded if pregnant, intending to become pregnant or breast feeding, had thermal sensitivity deficits (two Standard deviations less or more than the normal range of corresponding age), had brain tumour, cancer or haemophilia, uncontrolled hypertension or had injuries at the testing sites. Also, individuals with recreational drug use, excessive alcohol use, anti-convulsant use, anti-depressant or opioid medication use for pain, or previously diagnosed mental illnesses were excluded. Since there are no standard guidelines for the diagnosis of chronic non-specific low back pain, the participants were selected based on the recommendations of previous studies, which is by an elimination process^{11,34}. Low back pain caused by radicular neuropathy, osteoporosis, surgery or previous fractures of the spine, acute trauma in the spine, inflammation, malignant or autoimmune disease were not included¹¹. Individuals suffering from both chronic low back pain and knee osteoarthritis were excluded.

Test sites

The participants' thermal detection (cold and warm) and pain thresholds (cold and heat) were assessed at the knees, wrists and lower back bilaterally (Fig S1). Their PPTs and pain ratings to suprathreshold pressure stimulus (SUPRA) were also assessed bilaterally at these sites before the CPTs. During the CPTs, PPT was measured at the wrist (contralateral to the most painful knee/side of the lower back) and on the knee (ipsilateral).

Outcome measures

Pain intensity from cold water

While their foot (ipsilateral to the most painful knee/side of the lower back) was immersed in cold water (mixture of ice and water), participants were asked to rate their pain continuously using a 0-10

electronic visual analogue scale (eVAS, Aalborg university, Aalborg, Denmark), where 0 indicated no pain at all and 10 the worst pain possible. For the CPT at 2°C, participants were asked to immerse their foot for five minutes and for the CPT at 7°C (7-9°C \pm 0.1°C), seven minutes. If a participant could not complete the CPT, the last value carried forward method was used for missing data of the maximum and end pain. The time for each participant to reach their maximum pain from the cold water was recorded.

PPT and potency of endogenous pain controls

The PPTs were measured using a hand held algometer with a circular probe of surface area 1 cm² (Algomed, Medoc, Ramat Yishai, Israel). Participants were given a switch to press as soon as they started to feel pain from the pressure applied at the testing sites. The algometer was applied perpendicularly to the sites, and pressure was gradually increased at a rate of 30KPa/s⁶⁷ until the participant pressed on the switch. The average of two PPT readings at each site was recorded.

To measure the potency of endogenous pain controls, CPT was used as conditioning stimulus and PPT as the testing stimulus. The parallel paradigm⁶³ was used. The change in PPT at the contralateral wrist reflected the potency of CPM, while the change in PPT at the ipsilateral knee reflected the potency of local inhibition. The PPTs were measured before and at two minutes after the start of the CPTs. The assessor was blinded to the pain history and the pain adaptability status of the participants.

Confounding factors

Thermal detection and pain thresholds

The cold and warm detection thresholds and cold and heat pain thresholds of the participants were measured using the Thermal Sensory Analyser II (TSA-II, Medoc, Ramat Yishai, Israel) at all six sites.

Three consecutive cold or warm stimuli were applied using the method of limits (thermode size 30x30mm²) starting from a baseline temperature of 32°C and a temperature returning rate of 4°C/s. For the assessment of the cold and warm detection thresholds, the temperature was decreased or increased at a rate of 1°C/s, with an inter-stimulus interval ranging from 3 to 5s^{7,51}. The temperature was changed at a rate of 3°C/s with an interval of 20s for the assessment of cold pain and heat pain thresholds^{24,26}. The safety cut-off temperatures were set at 0°C and 50°C. For participants whose pain thresholds were beyond this range, 0°C and 50°C were recorded as their cold and heat pain thresholds respectively.

Pain catastrophizing

Pain catastrophizing scale (PSC), which is a validated questionnaire^{46,47}, was used to assess the participants' feeling and thoughts when they were in pain⁵⁴. Participants were asked to rate how often they experienced the 13 thoughts and feelings listed when they were in pain. The total score was calculated, a higher score indicates a higher extent of catastrophizing.

Level of depression, anxiety and stress

The Depression Anxiety and Stress Scale- 21 items (DASS-21)³⁹ was used. This questionnaire, with proven psychometric properties⁸, consists of three subscales, each containing seven items for depression, anxiety and stress, respectively. Higher scores represent more severe depression, anxiety or stress.

Functional status

A validated modified Roland Morris Questionnaire (RMQ) was used^{30,50}. This questionnaire contains 24 items of which participants chose those that applied to them. The total number of items chosen was calculated; the greater the score, the more severe the disability^{6,30}.

Sleep quality

The sleep quality was measured using the validated questionnaire, Pittsburgh Sleep Quality Index (PSQI)^{9,21,41}. Participants were asked about their sleep pattern in the last month. A score of five or less was associated with a good sleep quality, otherwise a score greater than five was associated with poor sleep quality.

Skin and water temperatures

The skin temperature of the foot was recorded by taking thermal snapshots using an infrared camera with 0.1°C accuracy (Testo 890, thermal imager, Testo, Germany) prior to the CPT. The temperature of the foot to be immersed in the cold pressor was measured at the midpoint between the tip of the middle toe and the anterior aspect of the ankle level with the malleoli. This point was chosen as it was fully immersed in the cold pressor, and the malleoli are easily identified on thermal images. The water temperature was measured using an external probe immersed in the water bath (external probe, Thermo Scientific, USA).

Adverse events

The participants were monitored for any adverse events associated with CPT such as fainting, and the frequency of adverse events were recorded.

Sample size calculation

It was hypothesised that the proportions of PA (39%) and PNA (61%) found in healthy participants⁶⁷ would be applicable to the MSK sample. Based on these proportions, with 80% power and 5% level

of significance (2-sided) a total of 42 participants were required. Considering that 15% of the participants might not be able to complete the three sessions, we recruited 49 participants.

Data analysis

SPSS version 23.0 (IBM corporation, USA) was used for all analyses. The status of pain adaptability was determined following the protocol from Zheng's study⁶⁷. The strength of pain adaptability was measured by subtracting the pain rating (to the cold water) at the end the CPT from the maximum pain during the CPT. A decrease of two or more on a 0-10 pain scale from the maximum pain at the end of CPT was categorised as PA; a decrease of less than two in pain was categorised as PNA. The potency of CPM and local inhibition was assessed by calculating the percentage change in PPT before and at two minutes after the start of the CPTs at the wrist and knee respectively. The correlations of the experimental pain characteristics between the two CPTs were investigated using Pearson correlation to assess the consistency of the measurements of the strength of pain adaptability and potency of CPM across the two CPTs. Paired t-tests were used to compare the strength of pain adaptability and potency of CPM assessed at the CPTs at 2°C and 7°C. The proportions of PA and PNA, and the proportions of participants who completed and those who could not complete the CPTs at 2°C and 7°C were compared using McNemar's chi square test. The baseline characteristics, PPT and SUPRA of the PA and PNA were compared using independent t-tests and chi square tests. Three-way (group, site and sides) mixed analysis of variance (ANOVA) with two repeated measures (sites, 3 levels and sides, 2 levels) were used to analyse their cold detection threshold, warm detection threshold, cold pain threshold and heat pain threshold. Mixed-design ANOVAs with one repeated measures (time, 7 levels) were used to examine the change in daily average pain, highest daily pain, daily hours in pain, and unpleasantness of pain over seven days in PA and PNA. The correlations between the strength of pain adaptability and baseline clinical pain, thermal pain thresholds and pressure pain thresholds were explored using Pearson correlations. The

Holm-Bonferroni adjustment was used for multiple comparisons²⁷. The hypotheses were arranged in ascending order according to their p-value, and the p-values were compared with the Holm-Bonferroni adjusted significance. A p-value that was smaller than the Holm-Bonferroni adjusted significance was considered significant. The data in the text and tables are reported as mean and standard deviation (SD) and in figures as mean and standard error of mean (SEM).

Results

Recruitment of MSK participants

Recruitment was between February 2015 and February 2016. After screening 138 individuals, 49 were eligible and were included in the study. Out of the 49 included participants, 25 participants were chronic non-specific low back pain participants and 24 knee osteoarthritis participants (Fig 1). After the first session, the baseline measurements and thermal tests, six participants (five chronic non-specific low back pain and one knee osteoarthritis) dropped out: four due to work or study commitment, one for medical reasons and one for unknown reasons. Their data were excluded from the analysis.

Forty-three (43) participants completed the study. The comparison between participants with chronic non-specific low back pain or knee osteoarthritis resulted in no significant differences in any outcome measures, including strength of the pain adaptability and potency of CPM at both 2°C and 7°C CPTs, thermal detection and pain thresholds, PPT, SUPRA, sleep quality and psychological factors (Supplementary materials Tables S1-S5). Therefore, the data presented here are the combined data of participants with chronic non-specific low back pain or knee osteoarthritis, with a total sample of 43. All analyses were performed for the 43 MSK participants with a majority of them being male,

middle aged, overweight, and suffering from moderate pain with a pain history over seven years (Table 1).

CPT 2°C vs CPT 7°C

All 43 pain participants were tested with both CPTs (2°C and 7°C) in a random order. Pain induced by the CPT at 2°C was moderately correlated with that induced at 7°C (average pain, $r=0.53$, $p<0.01$; maximum pain, $r=0.70$, $p<0.01$) (Table 2). There was a statistically significant difference in the maximum pain between the two CPTs, however the difference was very small (0.54 ± 1.31). Strong correlations were found in the time to reach maximum pain ($r=0.77$, $p<0.01$) and strength of pain adaptability ($r=0.74$, $p<0.01$) between the two CPTs. PA and PNA were identified during both tests. Out of the 43 participants 34 (79%) were consistent in their pain adaptability status, that is, they were either PA or PNA for both CPTs. The remaining 21% (nine participants) were not consistent in their pain adaptability status, meaning these participants were PA in one CPT and PNA in the other. Although there were nine participants who were inconsistent in their pain adaptability status, there was no significant difference in any measure between them and the rest of the participants. The proportions of the PA and PNA, and those who completed the CPTs and those who could not were not statistically different across the two CPTs either (Table 2). No statistically significant difference was observed in the potency of CPM between the two CPTs. Although not all of participants could successfully complete the five minutes at 2°C ($n=11$, 25.6% could not complete) or seven minutes at 7°C ($n=8$, 18.60% could not complete), no adverse events were reported.

Characteristics of PA and PNA in MSK participants

Since a strong correlation was shown between the strengths of pain adaptability across the two CPTs, and the proportion of PA and PNA between the two CPTS did not differ, in the following sections, PA and PNA identified using the CPT at 2°C will be used to explore the differences between PA and PNA.

Baseline characteristics

Among the 43 participants, 18 PA and 25 PNA were identified using a CPT at 2°C. No significant difference was found between PA and PNA in their demographics, pain history, sleep quality, function, quality of life and psychological factors (Table 3). Similarly, no statistically significant difference was observed between the PA and PNA in room temperature, water temperature or foot temperature. There was a trend that PNA had more comorbidity than PA did ($t_{41} = -2.16$, $p = 0.02$), there was however no statistically significant difference between the two groups (adjusted criterion of statistical significance < 0.01).

Pain adaptability and clinical pain

No significant correlations were found between the strength of pain adaptability and features of clinical pain (daily average pain, highest pain, hours in pain, and unpleasantness of pain). No main effect of group were observed for daily average pain, highest pain, hours in pain, and unpleasantness of pain over a 7-day period. However, a statistically significant group by time interaction for the unpleasantness over seven days ($F_{(6,246)} = 3.01$, $p = 0.01$) was found (Fig 2). The unpleasantness reduced from 7.12 ± 3.22 to 6.06 ± 3.47 over 7 days in the PA group whereas it oscillated and stayed relatively high in PNA group (from 9.04 ± 3.89 to 8.80 ± 2.78).

Pain adaptability and QST

Thermal and mechanical pain thresholds

The PPTs and SUPRAs of PA and PNA at all sites before the CPT showed no statistically significant difference between the two groups, although the PNA appeared to have lower PPTs than the PA (Table 4). Mixed-design ANOVAs resulted in no main effect for groups in either the cold and warm detection thresholds or their cold and heat pain thresholds at all sites (Table S6).

Correlations between the strength of pain adaptability and baseline thermal detection and pain thresholds and pressure pain thresholds were explored. Significant correlations between the strength of pain adaptability and warm sensation threshold at the right knee ($r = 0.37$, $p = 0.02$) and heat pain threshold at the left wrist ($r = 0.045$, $p < 0.01$) were observed. The higher the warm detection threshold or heat pain threshold, the stronger the strength of pain adaptability was.

CPT induced pain

The analysis of the experimental pain parameters during the CPT showed no difference in the average ($p=0.43$) and maximum ($p=0.60$) pain between PA and PNA (Table 5). A statistically significant difference was found between the PA and PNA in their time to reach maximum pain during the CPT (Table 5), with the PA ($65.81 \pm 31.54s$) reaching their maximum pain faster than the PNA ($142.28 \pm 133.63s$). A significant difference was also observed in their pain difference (strength of pain adaptability) between the maximum experimental pain and the experimental pain at the end of the CPT (Table 5). The PA had a higher pain difference (5.32 ± 1.96) than PNA (0.19 ± 0.47), which is expected as it was based on this outcome measure that PA and PNA were categorized. The time course for pain intensity from the CPT at $2^{\circ}C$ is shown in Fig 3.

Pain adaptability and potency of endogenous pain controls

There was no significant difference in the percentage PPT changes at the knee ($t_{41}=-1.04$, $p=0.30$) and wrist ($t_{41}=0.70$, $p=0.50$) during the CPT between the PA and PNA, thus no difference between the PA and PNA in their potency of either local inhibition or CPM. Further, no significant correlation was found between the strength of pain adaptability and potency of local inhibition ($r=0.04$, $p=0.79$) (Fig S2), and strength of pain adaptability and potency of CPM ($r=0.23$, $p=0.14$) (Fig S3).

Discussion (1499 words)

The dichotomy of PA and PNA exists in MSK participants. Both the CPTs at 2°C and at 7°C could be used to identify PA and PNA. Pain adaptability was highly correlated between the two sessions. No adverse events were observed. The time to reach the maximum experimental pain was shorter in the PA than PNA. The PA, but not PNA, reported a gradual reduction in clinical pain unpleasantness over seven days. The two groups did not differ in other measures. The strength of pain adaptability and potency of CPM were not correlated, indicating potentially two forms of endogenous pain controls were involved during the CPT.

Pain adaptability is reliable and is not temperature dependent

PA and PNA exist in healthy humans^{15,67}. This is the first study showing that this dichotomy also exists in MSK individuals. Indeed, about 40% and 60% of PA and PNA individuals were identified in the current study, which is agreement with previous studies in healthy participants, with the proportions of PA and PNA being 39% and 61% respectively in one study⁶⁷ and 35% and 65%

respectively in another¹⁵. A similar proportion (31% PA, 69% PNA) was also found when a hot water immersion at 47.5°C for five minutes was used in healthy participants¹⁵. This shows that pain adaptability does not seem to be temperature dependent.

The pain adaptability status was inconsistent in 21% of participants between CPT at 2°C and 7°C. A strong correlation of the strength of pain adaptability between the two sessions implies however that status of pain adaptability is stable and can be reliably assessed. A previous healthy human study¹⁵ reported that 65% of the participants were consistent and 35% were not.

Both CPTs could also be used to induce CPM, although very weak. This can be explained by the impaired CPM in MSK individuals³⁷. The completion rates and the percentage differences in the strength of pain adaptability and potency of CPM did not differ between the two CPTs. No adverse events were reported, being consistent with previous CPT studies^{18,45}. Thus, two CPTs can be used to assess both the strength of pain adaptability and potency of CPM, and are safe for MSK populations.

Pain adaptability is not associated with CPM

In the current study, CPT was used to assess both pain adaptability and potency of CPM. CPM is usually transient or lasts the same duration as the conditioning stimulus⁵⁵. However, some other studies reported that CPM lasted after the conditioning stimulus terminated, and the duration ranged from 5 minutes to one hour^{19,23,36,57}. One could argue that the decrease in pain rating at the end of the CPT seen in the PA could be the effect of CPM. However, in the current study, the potency of CPM in the PA did not differ from that in the PNA, and no significant correlation was observed between the strength of pain adaptability and potency of CPM. Therefore, the status of pain adaptability was not impacted by the potency of CPM. This observation is consistent with the

healthy human study⁶⁷. This shows that these two endogenous pain controls could operate through different mechanisms.

CPM is the only QST assessing endogenous pain inhibition. Limited studies show that a poorer CPM is related to increased number of pain sites²⁰ in MSK population, and its potency predicts the outcomes of anti-depressants or surgery^{16,64,65}. However, CPM and its association with pain are far from clear. Inefficient CPM does not always lead to more severe pain. Patients with a longer duration of pain history have a more efficient CPM than those with a shorter-pain history²². This observation is resonated with other studies where even within chronic pain patients, the efficiency levels of CPM varied¹⁷. Other forms of endogenous pain inhibition may contribute to those variations. Pain adaptability could be one of them.

Clinical implications of pain adaptability

Consistent with the previous healthy human study⁶⁷, the PA and PNA did not differ in any demographic data, or QST. The only two significant differences were that the PA reached their maximum pain faster than PNA did and reported a gradual reduction of pain unpleasantness over a 7-day period. It is likely the association between pain adaptability status and latency to the maximum pain could be due to the time to process the nociceptive input from the noxious CPT and to activate the descending inhibition. Such an inhibition is likely to be sustained in PA individuals contributing to a continuous reduction of pain during the CPT, and a gradual reduction of pain unpleasantness over seven days, which is in contrast to a fluctuation of pain unpleasantness in PNA. This temporal aspect of pain and related inhibition is not assessed in the current QST paradigm. Yet temporal characteristics of pain are important as illustrated in the following two examples.

1 A previous study, comparing capsaicin-induced hyperalgesia between younger and older healthy
 2 participants, found a delayed report of maximum experimental pain in the older group⁶⁶. Both
 3 groups had similar pain ratings and flare response to topical capsaicin. However, there was a trend
 4 that the older participants were slower in reaching their maximum experimental pain. Further, the
 5 secondary hyperalgesia induced by capsaicin (area of punctate hyperalgesia) was maintained for a
 6 significantly longer duration in the older than in the younger participants, and was not reversed by
 7 local anaesthesia⁶⁶. This means that the younger participants reached their maximum pain faster,
 8 and also presented with pain inhibition sooner than the older participants. It was proposed that
 9 those differences in the latency of reporting maximum pain and maintained hyperalgesia might be
 10 due to reduced capacity of the central nervous system to activate the inhibition systems in the older
 11 participants⁶⁶. Similarly, the PNA could have a reduced capacity to activate the inhibitory systems,
 12 hence the longer time to reach the maximum pain and the lack of pain inhibition during the CPT.

13
 14 This lack of pain inhibition might impact on the capability of individuals to cope with a new episode
 15 of pain. A recent study²⁸ followed up the day to day pain experience of post-surgical patients for 60
 16 days and found significant individual variations in how post-operative pain was reduced and at which
 17 time point. Significant pain reduction varied from day 10 to day 21 post-surgically, with some
 18 patients presenting with a fast reduction whereas others a slow reduction. The authors commented
 19 that currently there is no way to predict who would be in which category. Previous research shows
 20 the potency of pre-surgical CPM may predict the severity of post-surgical pain. It is unknown if pre-
 21 surgical pain adaptability might help predict the time course of post-surgical pain.

22
 23 Compared with PA, PNA tended to suffer from more comorbidities, which might interfere with this
 24 activation-inhibition loop. A recent study on knee osteoarthritis identified a subgroup of patients

with more comorbidities and more severe pain³³, suggesting that comorbidity indeed could be related to pain sensitivity and hence pain adaptability. However, this hypothesis should be debated as pain adaptability was also identified in healthy participants without comorbidities^{15,67}.

Pain sensitivity and pain modulation are physiological responses that are influenced by psychological behaviours^{1,12,44,59} and genetics and environment⁴³. PA and PNA did not however differ in anxiety, depression, stress and pain catastrophizing measured in the current study. Further studies exploring the influence of psychological factors, such as suggestibility, coping strategies or expectations, are needed.

Limitations

This study has a few limitations. Firstly, the sample size might not be large enough to achieve statistical differences in some outcome measures. Using the PPT results at the wrists from the current study with 80% power and α level of 0.05, the minimum required total sample size to achieve significance was 84. Secondly, some participants could not complete the CPTs and did not have a PPT measurement at the two minutes time point. Their PPT was considered unchanged at the two minutes time point and thus the potency of their CPM could have been underestimated. However, removing such participants from the analysis did not change the results. Lastly, two participants reported a low level of pain rating to CPT and the rating did not change during the whole test. They were categorized as PNA. It is possible that this lack of change might be another form of adaptive behaviour. This could be the reason why not much difference was found between the PA and PNA. However, when those participants were removed from the analysis, this did not impact on the current findings.

Conclusions

The pain adaptive and pain non-adaptive exist in patients with chronic musculoskeletal pain. A cold pressor test at either 2°C or 7°C is a reliable method to measure this form of inhibition. Pain adaptability is dissociated with the potency of CPM; and could reflect the temporal aspect of pain inhibition that is not explained by CPM. It would be important to replicate this study with less painful stimuli than CPT, while controlling for psychological factors during the stimulation. The relevance of pain adaptability in predicting the time course of post-operative pain and in treatment response should be further explored.

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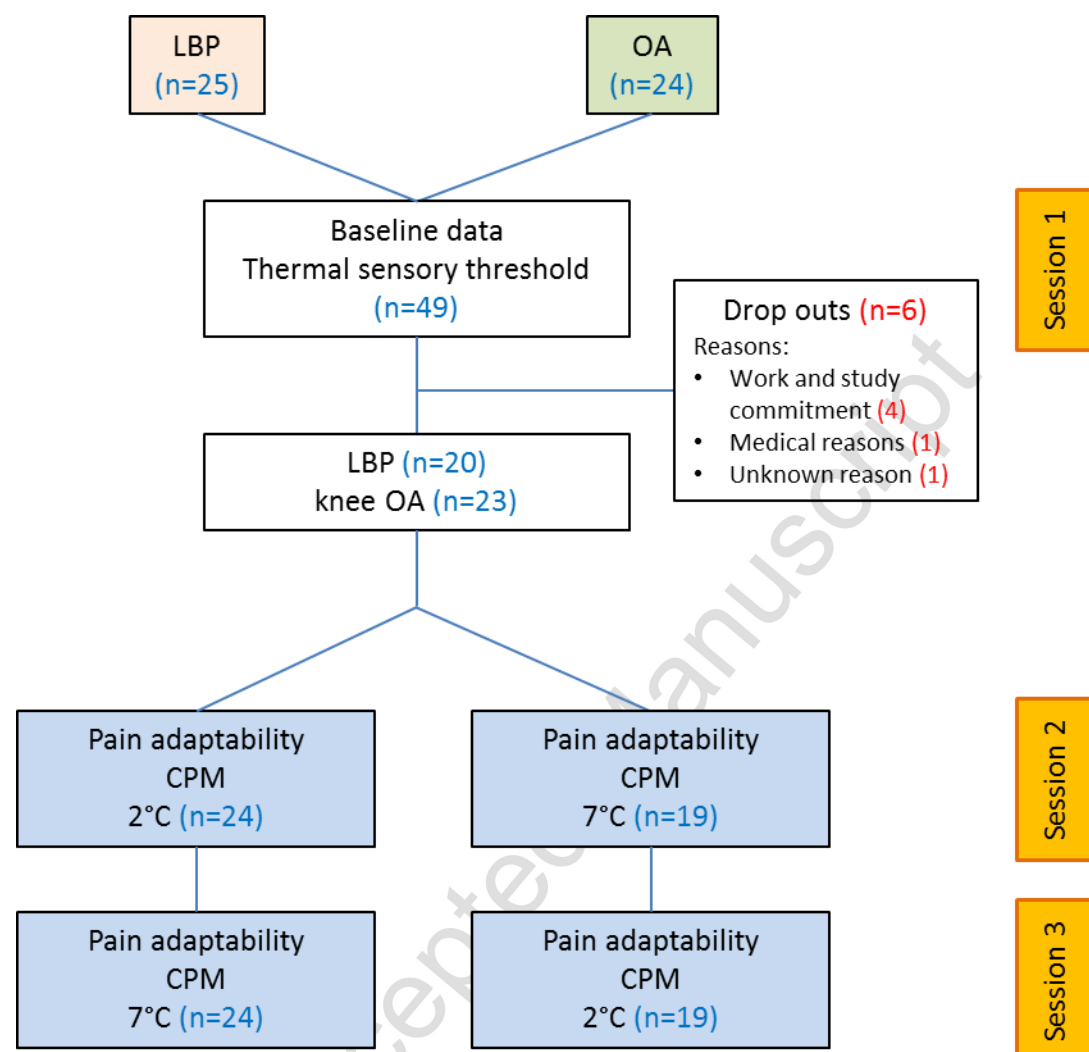
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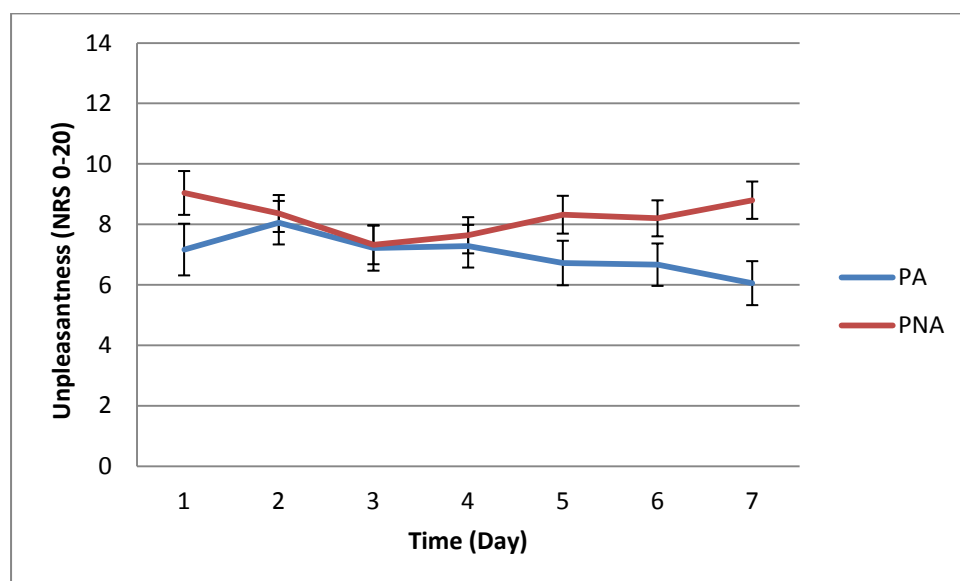
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Figure legends

Fig 1: Study procedure

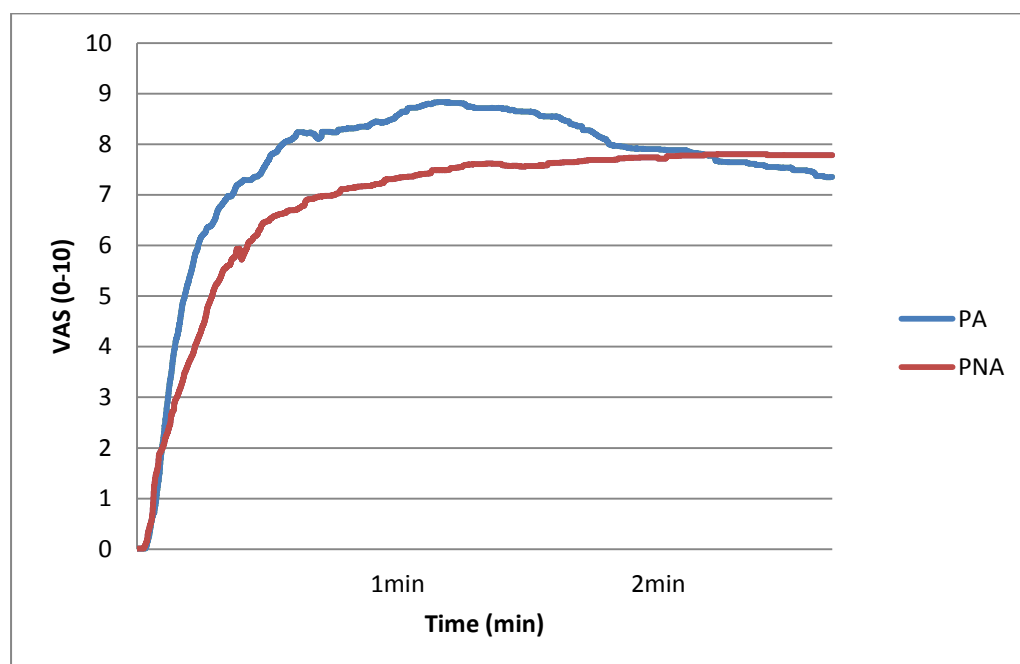


LBP= chronic non-specific low back pain participants; OA=knee osteoarthritis participants; 2°C= 2-4°C cold pressor test; 7°C=7-9°C cold pressor test; CPM=conditioned pain modulation; Sessions 1, 2 and 3 were one week apart.

Fig 2: Time courses for unpleasantness of clinical pain for PA and PNA groups

PA=pain adaptive; PNA=pain non-adaptive; NRS=numerical rating scale; *=significant group by time interaction.

Fig 3: Time courses for pain intensity from the CPT at 2°C for PA and PNA groups



PA=pain adaptive; PNA=pain non-adaptive; VAS=visual analogue scale.

Table 1: Demographics and pain data of all participants (n=43)

Demographics and pain history	Mean \pm SD / frequency
Age (yrs)	56.40 \pm 13.27
BMI	28.45 \pm 6.62
Gender M/F	26/17
History of pain (yrs)	7.17 \pm 8.17
Average Pain in the last week (NRS)	4.43 \pm 1.55
Maximum Pain in the past week (NRS)	5.73 \pm 2.34
Maximum Pain in the last 24Hr (NRS)	4.39 \pm 2.16
No. of painful areas	2.56 \pm 1.39
No. of comorbidities	0.79 \pm 1.08
medication/ no medication	23/20
LBP/knee OA	20/23

BMI=body mass index; M=male; F=female; NRS=numerical rating scale 0-10, 0 being no pain at all and 10 the worst pain possible; medication=participants taking pain medication; no medication=participants not taking pain medication; LBP=chronic non-specific low back pain; knee OA=knee osteoarthritis.

Table 2: Pain parameters during CPT and items to assess the feasibility of CPT at 2°C and CPT at 7°C (mean ± SD)

Pain parameters and items to assess feasibility	CPT2 (n=43)	CPT7 (n=43)	% difference	Pearson correlation, r	p-value	t ₁ -value	p-value	Adjusted significance ¹
Average pain from CPT (VAS)	6.08 ± 1.97	5.76 ± 1.83	5.40	0.53	<0.01*	1.14	0.26	0.03
Maximum Pain from CPT (VAS)	8.88 ± 1.77	8.34 ± 1.60	6.27	0.7	<0.01*	2.72	0.01*	0.02
Time to reach Maximum Pain (s)	110.27 ± 109.83	153.68 ± 143.48	32.89	0.77	<0.01*	-3.08	<0.01*	0.01
Strength of Pain adaptability (Max-End)	2.34 ± 2.87	2.27 ± 2.81	3.04	0.74	<0.01*	0.22	0.83	0.05
No. of PA/PNA	18/25	17/26	-	McNemar's test	1.00	-	-	0.05
No. of completed/ not completed	32/11	35/8	-	McNemar's test	0.45	-	-	0.05
Potency of CPM (%PPT Change)	4.99 ± 27.52	4.34 ± 28.36	13.93	0.11	0.48	0.12	0.91	0.05
No. of adverse events	0	0	-	-	-	-	-	0.05

CPT2= cold pressor test at 2°C; CPT7=cold pressor test at 7°C; VAS= visual analogue scale 0-10, 0 being no pain at all and 10 the worst pain possible; Max-End= difference between maximum pain and pain at the end of the cold pressor test; PA=pain adaptive; PNA=pain non-adaptive; completed=participants who completed the cold pressor test; not completed=participants who did not complete the cold pressor test; PPT=pressure pain threshold; % difference= $|CPT2-CPT7| * 100 / \text{average of CPT2 and CPT7}$; *=significant p values; 1= Holm-Bonferroni adjusted criterion of statistical significance (significant p values are less than these values).

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Table 3: Baseline characteristics of PA and PNA (mean \pm SD)

Baseline characteristics	PA (n=18)	PNA (n=25)	χ^2_1 / t_{41} -test	p value	Adjusted significance ¹
Age (yrs)	55.67 \pm 14.07	56.92 \pm 12.93	-0.3	0.76	0.01
BMI	28.01 \pm 3.58	28.77 \pm 8.21	-0.37	0.72	0.01
Gender M/F	12/6	14/11	0.5	0.48	0.01
History of pain (yrs)	5.51 \pm 6.72	8.37 \pm 9.01	-1.14	0.26	<0.01
Average Pain over past 7 day (NRS 0-10)	3.27 \pm 1.61	3.92 \pm 1.81	-1.23	0.23	<0.01
Maximum Pain over past 7 day (NRS 0-10)	4.44 \pm 1.75	5.02 \pm 1.80	-1.04	0.31	0.01
Unpleasantness of pain over past 7 day (NRS 10-20)	7.00 \pm 2.86	8.11 \pm 2.43	-1.37	0.18	0.01
Daily duration of pain over past 7 day (hrs)	6.19 \pm 6.17	6.88 \pm 4.36	-0.41	0.68	0.01
Maximum Pain in the last 24Hr (NRS)	3.76 \pm 2.13	4.84 \pm 2.11	-1.64	0.11	<0.01
No. of painful areas ²	2.33 \pm 1.41	2.72 \pm 1.37	-0.9	0.37	<0.01
No. of comorbidities ³	0.39 \pm 0.50	1.08 \pm 1.29	-2.16	0.02	<0.01
Sleep quality (PSQI)	6.67 \pm 3.87	6.56 \pm 3.49	0.09	0.93	0.03
Function (RMQ)	6.72 \pm 4.73	6.96 \pm 4.35	-0.17	0.87	0.01

Physical health (SF-36)	45.79 ± 5.33	42.71 ± 8.27	1.48	0.15	<0.01
Mental health (SF-36)	53.70 ± 6.63	53.15 ± 7.53	0.25	0.81	0.01
Pain catastrophizing (PCS)	13.67 ± 10.37	16.24 ± 10.88	-0.78	0.44	<0.01
Depression (DASS21)	2.17 ± 2.62	2.64 ± 3.90	-0.45	0.66	0.01
Anxiety (DASS21)	1.44 ± 1.65	2.00 ± 2.16	-0.91	0.37	<0.01
Stress (DASS21)	4.06 ± 3.96	4.00 ± 4.12	0.04	0.96	0.05
Room temperature (°C)	22.61 ± 0.40	22.83 ± 0.45	-1.64	0.11	<0.01
Water temperature at start of CPT (°C)	2.69 ± 0.32	2.58 ± 0.27	1.22	0.23	<0.01
Foot temperature at start of CPT (°C)	21.95 ± 0.80 [^]	22.00 ± 0.71 [§]	-0.16 [#]	0.87	0.02
LBP/knee OA	7/11	13/12	0.29	0.59	0.01

PA=pain adaptive; PNA=pain non-adaptive; BMI=body mass index; M=male; F=female; NRS 0-10=numerical rating scale 0-10, 0 being no pain at all and 10 the worst pain possible; NRS 0-20=numerical rating scale 0-20, 0 being neutral and 20 intolerable unpleasantness; PSQI=Pittsburgh Sleep Quality index; RMQ= modified Roland Morris Questionnaire; SF-36= short form 36 items survey, to measure quality of life; PCS=Pain Catastrophizing Scale; DASS21=Depression, Anxiety and Stress Scale 21 items; [^]= sample size is 15; [§]= sample size is 20; [#]= degree of freedom is t_{33} ; LBP= chronic non-specific low back pain; OA=osteoarthritis; 1= Holm-Bonferroni adjusted criterion of statistical significance (significant p values are less than these values); 2=assessed based on the 10 body area method^{20,25,56}; 3=assessed using the Cumulative Illness Rating Scale^{29,38}.

Table 4: PPT and SUPRA in PA and PNA before CPT (mean \pm SD)

Psychophysical tests	Sites	Sides	PA (n=18)	PNA (n=25)	t ₄₁ -test	p value	Adjusted significance ¹	Cohen's d
PPT (Kgf/cm ²)	Knees	Right	3.83 \pm 1.32	3.01 \pm 1.23	2.08	0.04	<0.01	0.64
		Left	3.51 \pm 1.13	2.79 \pm 0.95	2.28	0.03	<0.01	0.69
	Wrists	Right	3.22 \pm 1.10	2.92 \pm 0.96	0.97	0.34	0.01	0.30
		Left	2.98 \pm 1.03	2.81 \pm 0.97	0.55	0.58	0.01	0.17
	Lower back	Right	4.28 \pm 1.91	3.42 \pm 1.39	1.69	0.10	0.01	0.51
		Left	3.74 \pm 1.71	3.41 \pm 1.36	0.59	0.48	0.01	0.22
	Knees	Right	4.42 \pm 1.95	3.82 \pm 2.24	0.91	0.37	0.01	0.28
		Left	3.92 \pm 1.80	3.80 \pm 2.30	0.18	0.86	0.01	0.06
SUPRA (NRS)	Wrists	Right	3.67 \pm 2.40	3.74 \pm 2.12	-0.11	0.92	0.05	0.03
		Left	3.22 \pm 1.82	3.12 \pm 2.45	0.15	0.88	0.02	0.05
	Lower back	Right	3.50 \pm 2.36	3.58 \pm 2.35	-0.11	0.91	0.03	0.03
		Left	3.11 \pm 2.19	3.68 \pm 2.53	-0.77	0.45	0.01	0.24

PA=pain adaptive; PNA= pain non-adaptive; PPT=pressure pain threshold; SUPRA=pain intensity from suprathreshold pressure stimulus; NRS= numerical scale 0-10, 0 being no pain and 10 the worst pain; K= knee; W= wrist; LB= lower back; *= significant p value; 1= Holm-Bonferroni adjusted criterion of statistical significance (significant p values are less than these values); The effect size was calculated as the Cohen's d, where d= 0.20 would be a small effect, d= 0.50 would be a medium effect, and d= 0.80 would be a large effect.

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Table 5: Pain characteristics of PA and PNA during the CPT at 2°C (mean \pm SD)

CPT Pain characteristics	PA (n=18)	PNA (n=25)	t ₄₁ -test	p value	Adjusted significance ¹	Cohen's d
Average pain from CPT (VAS)	6.37 \pm 1.53	5.88 \pm 2.24	0.80	0.43	0.03	0.26
Maximum Pain from CPT (VAS)	9.05 \pm 1.15	8.76 \pm 2.12	0.52	0.60	0.05	0.17
Time to reach Maximum Pain (s)	65.81 \pm 31.54	142.28 \pm 133.63	-2.76	0.01*	0.02	0.79
Strength of Pain adaptability (Max-End)	5.32 \pm 1.96	0.19 \pm 0.47	12.63	<0.01*	0.01	3.60

PA= pain adaptive; PNA= pain non-adaptive; CPT= cold pressor test; VAS=visual analogue scale 0-1, 0 meaning no pain at all and 10 the worst pain possible; Max-End= difference between maximum pain and pain at the end of the cold pressor test; *= significant p value; 1= Holm-Bonferroni adjusted criterion of statistical significance (significant p values are less than these values); The effect size was calculated as the Cohen's d, where d= 0.20 would be a small effect, d= 0.50 would be a medium effect, and d= 0.80 would be a large effect.