Sedentary behaviour facilitates conditioned pain modulation in middle-aged and older adults with persistent musculoskeletal pain: a cross-sectional investigation

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Abstract
Introduction: Higher physical activity (PA) and lower sedentary behaviour (SB) levels have demonstrated beneficial effects on temporal summation (TS) and conditioned pain modulation (CPM) in healthy adults. This cross-sectional study investigated the relationships between PA and SB and TS/CPM responses in individuals with chronic musculoskeletal pain.

Methods: Sixty-seven middle-aged and older adults with chronic musculoskeletal pain were recruited from the community. Questionnaires measuring demographics, pain, and psychological measures were completed. Physical activity/SB levels were measured using the International Physical Activity Questionnaire—short form and Sedentary Behaviour Questionnaire, respectively. Semmes monofilament was used to assess mechanical TS (MTS) at the most symptomatic (MTS-S) and a reference region (MTS-R); change in the pain scores (baseline-10th application) was used for analysis. Conditioned pain modulation procedure involved suprathreshold pressure pain threshold (PPT-pain4) administered before and after (CPM30sec, CPM60sec, and CPM90sec) conditioning stimulus (2 minutes; ~12°C cold bath immersion). For analysis, PPT-pain4 (%) change scores were used.

Results: PPT-pain4 (%) change scores at CPM30sec and CPM60sec demonstrated significant weak positive correlations with SB levels and weak negative correlations with PA measures. After adjusting for confounding variables, a significant positive association was found between SB (h/d) and PPT-pain4 (%) change scores at CPM30sec and CPM60sec. No significant associations between MTS and PA/SB measures.

Conclusion: Sedentariness is associated with higher pain inhibitory capacity in people with chronic musculoskeletal pain. The observed relationship may be characteristic of a protective (sedentary) behaviour to enhance pain modulatory mechanism. Prospective longitudinal studies using objective PA/SB measures are required to validate the observed relationship in a larger sample size.

Keywords: Physical activity, Sedentary behavior, Conditioned pain modulation, Temporal summation, Boom-bust pain cycle, Older adults, Pain modulation, Pain mechanisms

1. Introduction
Physical activity (PA) is a commonly prescribed intervention to reduce pain in people with chronic pain. Population-level studies have found associations between regular engagement in PA and lower incidence of chronic pain. Mechanisms behind PA in modulating pain have been studied in various settings and populations. Preclinical studies demonstrated that regular engagement in PA influences a range of cellular mechanisms that are responsible for pain hypersensitivity, dysregulation of endogenous pain modulatory system, and chronic pain development.

Healthy older adults meeting PA recommendations (ie, moderate-vigorous PA levels) demonstrate better experimental pain responses (lower temporal summation [TS] of pain and greater conditioned pain modulation [CPM]). Individuals who perform endurance exercise and engage in vigorous activities...
have greater CPM effect than the control population.\textsuperscript{18,19,22,57,87} The positive impact of PA on pain sensitivity, nociceptive processing, and modulatory mechanisms in healthy individuals may not be similar in people with persistent pain due to altered nociceptive processing and negative psychosocial contexts associated with persistent pain.\textsuperscript{13,50,55}

Evidence indicates a nonlinear relationship between PA levels and pain.\textsuperscript{51} A large body of evidence suggests that engagement in PA/exercise by people with chronic widespread pain (CWP) often heightens their pain, potentially mediated through abnormal nociceptive processing and modulatory mechanisms associated with CS.\textsuperscript{14,55} Central sensitisation (CS) is considered a key pain mechanism responsible for the maintenance of several chronic musculoskeletal pain syndromes.\textsuperscript{17,71,72,81,85} Central sensitisation is characterised by amplification of peripheral nociceptive input\textsuperscript{56} and impaired descending inhibition of nociceptive inputs.\textsuperscript{56,81,96} Abnormal TS of pain and impaired CPM response are suggested to be surrogate markers of heightened nociceptive drive and poor nocostimulation and poor descending modulatory drive, respectively.\textsuperscript{2,13,24,81,96} In addition to CS, individuals with persistent pain possess negative pain cognitions about PA, which can adversely influence the pain modulatory systems, resulting in heightened pain experience during PA engagement.\textsuperscript{23,33,34} Moreover, no associations were found between pain processing measures and PA levels in individuals with chronic low back pain, suggesting a potential confounding of relationship by psychosocial factors.\textsuperscript{59} Therefore, it is essential to understand the PA relationships with various clinical markers of nociceptive processing and modulatory processes while taking into account a range of confounding factors such as pain catastrophizing and sleep quality.\textsuperscript{5,6,33,34,74,76}

Evidence of the relationship between PA levels and nociceptive modulatory mechanisms in chronic musculoskeletal pain is scarce.\textsuperscript{41,59} Insights on these mechanistic relationships may help to design solutions to optimize PA in individuals with musculoskeletal pain. Therefore, this cross-sectional study aimed to investigate the association between self-reported PA and SB levels and measures of nociceptive processing and modulatory mechanisms in a cohort of adults with chronic musculoskeletal pain.

2. Methods

2.1. Study design

A cross-sectional observational study.

2.2. Sampling strategy

Adults with chronic musculoskeletal pain from an urban community were invited to participate in this study. Convenience sampling, a type of nonprobability sampling method, was used.\textsuperscript{75} Study advertisements were published periodically (September 2016–June 2017) in a local (free) newspaper and social media (Facebook); study invitation emails were sent out to the members of the community organisations including Age Concern Otago, Arthritis New Zealand, and University of the Third Age (NZ). Interested volunteers contacted the research team through either telephone or email and underwent eligibility screening by a research team member with a health professional background.

2.3. Eligibility criteria

Adults who had chronic musculoskeletal pain, ie, pain persisted for more than 3 months, were eligible for study participation.\textsuperscript{15,89} Volunteers who have had any of the following conditions/situations were excluded: autoimmune diseases (rheumatoid arthritis, gout, systemic lupus erythematosus, and ankylosing spondylitis), underwent joint replacement surgery, history of angina, peripheral vascular disorders, and any neurological conditions or cognitive disorders that would influence sensory testing procedures. The Mini-Mental State Examination was used to ensure the participants were free of any cognitive impairment.\textsuperscript{3,6} Ethical approval was obtained from the University of Otago Human Ethics Committee, and all participants provided written consent before study participation.

2.4. Procedure

All participants completed self-reported clinical and psychological questionnaires and underwent quantitative sensory testing (QST). Participants’ age, sex, ethnicity, and anthropometric measures (height, weight, and waist and hip circumference) were collected. Hand and foot dominance was determined using the Edinburgh Handedness Inventory,\textsuperscript{58} and Otago Footedness Inventory,\textsuperscript{79} respectively. Participants also reported whether they had consumed any pain medications for pain relief on the day of testing.

2.5. Pain measures

2.5.1. Pain distribution

Participants specified the location(s) of pain by ticking the relevant boxes of a blank body chart (front and back views) indicating specific body regions (shoulde/rs, arms/elbows, wrist/hands, hip, knee, legs/ankle/feet, neck, chest, or low back). Participants marked an “X” on the body region/joint that hurts the most (ie, the most painful region). Presence of CWP was identified using the 4 items about the “pain subscale” from the London Fibromyalgia Epidemiology Symptom Screening Questionnaire (LFESSQ).\textsuperscript{15,86,92} To be classified as having CWP, participants had to respond “yes” to all 4 pain criteria of the LFESSQ with either “both a right- and left-side positive response” or a positive response for the presence of pain at both sides. If the data were not satisfying the LFESSQ CWP criteria, then it was classified as regional pain syndrome.

2.5.2. Pain intensity and interference

Brief Pain Inventory (BPI), a standardized, validated assessment tool, was used to capture pain intensity of the most painful region (average, least, and worst pain intensity in the past 24 hours and 4 weeks) and interference in daily activities.\textsuperscript{56} Participants reported the presence of pain in the area that was nominated to have the worst pain and rated the intensity of pain on an 11-point numeric pain rating scale (NPRS).

2.5.3. Neuropathic pain

The painDETECT questionnaire was used to identify the presence of a neuropathic pain component in the most painful area. The chosen tool has superior diagnostic accuracy when compared with other screening tools.\textsuperscript{40} The questionnaire consists of 12 items that measure pain quality rated on a 5-point Likert scale (1 = “never” to 5 = “very strongly”), pain radiation from the primary area of pain (yes or no), and pain course pattern (scored from −1 to 2). The total score ranges from −1 to 38 points with a score of ≥19 indicative of a likely neuropathic pain (≤12: nociceptive pain and 13–18: possible neuropathic pain component [or mixed type]).
2.6. Psychological variables and sleep quality

2.6.1. Depression, anxiety, and stress scale (DASS-21)
The depression, anxiety, and stress scale (DASS-21) was used to measure 3 psychological constructs: depression, anxiety, and stress over the past week. The DASS-21 consists of 21 items rated on a 4-point Likert scale and has adequate validity (Cronbach’s alpha = 0.70–0.90) in older adults with persistent pain.44 The total score ranges from 0 to 80, with higher scores indicating greater levels of depression, anxiety, and stress.

2.6.2. Pain catastrophizing scale
The pain catastrophizing scale (PCS) was used to measure the extent of catastrophic thoughts about their pain. The PCS consists of 13 items rated on a 5-point Likert scale that measures 3 dimensions of catastrophizing: rumination, magnification, and helplessness.44 The total score ranges from 0 to 52, where higher scores indicate greater levels of catastrophic thoughts about pain.77

2.6.3. Pain vigilance and awareness questionnaire
The pain vigilance and awareness questionnaire (PVAQ) was used to measure the frequency of habitual “attention to pain” over the past 2 weeks.47,48 The PVAQ has 16 items rated on a 6-point Likert scale, and the total score ranges from 0 to 80. Higher scores indicate greater levels of pain vigilance and awareness, which has shown associations with higher pain severity.67

2.6.4. Central sensitization inventory
Central sensitization inventory (CSI) was used to identify participants with central sensitivity syndromes (eg, fibromyalgia, irritable bowel syndrome, chronic headache, temporomandibular disorders, and pelvic pain syndromes).53 The CSI consists of 2 parts—part A assesses 25 health-related symptoms common to central sensitivity syndromes, with a total score ranging from 0 to 100, and part B (is not scored) asks about previous diagnoses of 1 or more specific disorders, including central sensitivity syndromes. The CSI has demonstrated high level of test–retest reliability and internal consistency (Pearson r = 0.817; Cronbach’s alpha = 0.879).46

2.6.5. Sleep quality
Sleep quality was assessed using a single item of the Pittsburgh Sleep Quality Index. All participants responded to the question: During the past month, how would you rate your sleep quality overall? (very good, fairly good, fairly bad, and very bad). For purposes of this study, the response categories were collapsed to good (“very good” and “fairly good”) and bad (“fairly bad” and “very bad”) sleep quality.

2.6.6. Pain self-efficacy
A 2-item validated questionnaire was used to assess pain self-efficacy (PSE) beliefs.45 Participants rated their confidence on a scale of 0 to 6 with 1 being not at all confident and 5 being completely confident, with the mean score taken as the final score for PSE.

2.7. Assessment of physical activity and sedentary behaviour
Physical activity levels were assessed using the International Physical Activity Questionnaire—short form (IPAQ-SF).43 The IPAQ-SF is a commonly used questionnaire in research settings for quantifying self-reported levels of PA and has been widely used in chronic pain populations. The IPAQ-SF consists of 9 items which provides information on the time spent doing walking, moderate- to vigorous-intensity activities, and sedentary activities. Also, an additional item of the IPAQ-SF was used to estimate time spent in sitting on a typical weekday. The data processing and scoring of the IPAQ-SF was conducted as per the guidelines (www.ipaq.ki.se). A Microsoft Excel spreadsheet that enables automatic scoring of the IPAQ-SF was used.10 Both categorical (low, moderate, and high based on PA recommendations) and continuous variables (walking MET-min/wk, moderate MET-min/wk, vigorous MET-min/wk, total PA MET-min/wk, total activity min/wk, and total days of activity) were calculated as per the recommendation for scoring the IPAQ-SF. For all analysis, we have used continuous scores of PA variables.

Sedentary behaviour was assessed using the self-reported Sedentary Behaviour Questionnaire, which has demonstrated acceptable psychometric properties.44,69 The SBQ consists of 9 items that determine the amount of time spent doing 9 sedentary activities during a typical weekday and typical weekend day. Response categories ranged from “none” to “6 hours or more” for sedentary activity. The mean duration (hours per day) spent on individual sedentary activities on a typical weekday and weekend day was computed. A weighted daily estimate of sedentary time (hours per day) was calculated as \((\frac{2\times(\text{sedentary time during a typical weekday}) + \text{(sedentary time during a typical weekend day)}}{2})\).44 As an “a priori” decision, the daily estimate of sedentary time based on the SBQ was used as a primary measure of SB in the analysis.

2.8. Quantitative sensory testing
Quantitative sensory testing procedures are commonly used to assess these somatosensory abnormalities in musculoskeletal pain. This study administered 2 dynamic QST procedures (ie, TS of pain and CPM).24,68,98

2.8.1. Mechanical temporal summation
Temporal summation procedure is a commonly used sensory psychophysical testing that may produce heightened pain experience, due to the facilitation of central nociceptive drive.82,83 Abnormal TS in humans has been proposed as a clinical signature of enhanced summation of central neurons, a feature of CS.62,83,96 In this study, we used the mechanical TS protocol to induce TS. Mechanical TS (MTS) has been shown to predict pain severity,92 including movement-evoked pain associated with knee osteoarthritis.53 Moreover, ethnicity interacted with TS responses in predicting higher clinical knee pain ratings.54 Mechanical TS was assessed using a nylon monofilament (Semmes monofilament 6.65, 300 g).24 Brief 10 repetitive contacts were delivered at a rate of 1 Hz, externally cued by auditory stimuli. The participants rated the level of pain experienced on the NPRS immediately after the first contact and rated their greatest pain intensity after the 10th contact. Three trials were conducted at the index area and remote site, with the order of testing randomised. The index area included the nominated most painful joint, and the remote area included either the dorsal opposite wrist (in cases of lower back/upper limb joints as an index area) or the opposite shin, ie, 5 cm below the tibial tuberosity over the belly of tibialis anterior muscle (in cases of the neck/upper limb as an index area). For each trial, the MTS was calculated as the difference between the NPRS rating after the
first contact and the highest pain rating after the 10th contact. This score presents the maximum amount of MTS across the 10 contact points. The average of the 3 trials was calculated for each participant for each site (ie, most symptomatic joint (MTS-S) and a remote site (MTS-R)), with a positive score indicating an increase in MTS.

### 2.8.2. Conditioned pain modulation procedure

Conditioned pain modulation is the most frequently administered procedure for exploring the endogenous pain modulatory system. Conditioned pain modulation test procedure is always administered at least 15 to 20 minutes after the MTS procedure, and it was administered according to the previously published recommendations of testing.

#### 2.8.2.1. Conditioning stimulus

Conditioning stimulus consisted of a cold pressor task, where the participants immersed their hand (until midforearm) in a thermos containing cold water for a maximum period of 2 minutes. The hand opposite to the side of the most painful area was used unless that hand was also symptomatic (eg, the left hand was immersed when the testing joint is right-sided knee pain). The temperature of the cold water was maintained at $-12^\circ$ centigrade and was confirmed immediately before and after the immersion procedure.

Participants continued hand immersion until the end of the trial (ie, 2 minutes) or until it was too uncomfortable to be immersed (NPRS $\geq 8$). Similar conditioning stimulus (ie, cold water) protocol has been used in previous studies showing significant CPM effect.

#### 2.8.2.2. Test stimulus

A computerised, handheld digital algometer (AlgoMed; Medoc, Ramat Yishai, Israel) was used to measure suprathreshold pressure pain threshold (pain4) at the most painful area in the most symptomatic region. Two familiarisation trials were performed at the midforearm before the formal trials. The 1-cm² algometer probe was pressed over the marked test sites perpendicularly to the skin at a rate of 30 kPa/s. The participants were instructed to press the algometer trigger button in the patient control unit when the pressure sensation changed to a pain intensity of 4 out of 10 on the NPRS. Once the patient-controlled unit was activated, the trial was automatically terminated, and the amount of pressure (kPa) was recorded. If participants did not report pain at the maximum pressure level which was set at 1000 kPa for safety reasons, the procedure was terminated by the assessor, and a score of 1000 kpa was assigned for that trial. Two PPT (pain4) trials were recorded before the conditioning stimulus and were averaged (preaverage score) to obtain a baseline score for each participant. Three PPT (pain4) trials were recorded in the same region at 30, 60, and 90 seconds immediately after the conditioning stimulus.

#### 2.8.2.3. Calculation of conditioned pain modulation:

A percent change score was calculated for each time point (ie, 30 seconds [CPM30sec], 60 seconds [CPM60sec], and 90 seconds [CPM90sec]) as below, with a positive score indicating an increase in PPTs (pain4) after the conditioning stimulus and thus presence of CPM effect. Conditioned pain modulation percent change score = ([post score - preaverage score]/preaverage score) $\times$ 100. The percent change score was calculated to overcome the inter-regional variability of recorded pain thresholds.

### 2.9. Data analysis

All statistical analysis was performed using SPSS (version 23.0). Descriptive statistics were calculated for all measured variables. Statistical assumption testing revealed that the measured variables of interest were non-normally distributed.

The Friedman analysis of variance was used to assess differences between (preconditioning and postconditioning PPT-P4 scores), thus evaluating the presence of overall CPM effect. The Wilcoxon signed-rank test was used to determine differences for the following pairwise comparisons: preconditioning PPT-P4 vs postconditioning PPT-P4 at 30 seconds; preconditioning PPT-P4 vs postconditioning PPT-P4 at 60 seconds; and preconditioning PPT-P4 vs postconditioning PPT-P4 at 90 seconds. In addition, the Wilcoxon signed-rank test was used to assess differences between pain rating scores after first application and 10th application at the symptomatic and remote sites, and differences between MTS-S and MTS-R pain rating change scores. Effect sizes were calculated for all pairwise comparisons. Spearman rank correlation statistics were used to determine the relationships between (1) MTS-S and MTS-R and pain severity and the level of interference and (2) MTS and CPM (dependent variables), and IPAQ-PA and SB (primary predictor/independent variables).

To assess for relationships between PA/SB and CPM/MTS response, a 2-step procedure was used as follows: Step 1 evaluated the correlations between dependent variables of MTS (MTS-S and MTS-R) and CPM (CPM30sec, CPM60sec, and CPM90sec) scores and the independent variables of PA, SB, demographics, pain-related clinical variables, and psychological variables, using Spearman rank correlation statistics ($P \leq 0.05$). No attempt was made to correct the statistical significance of multiple correlations between variables of interest. The following criteria were used to interpret the strength of association between variables of interest: very strong—0.8 to 1, strong—0.5 to 0.8, weak—0.2 to 0.5, and very weak—less than 0.2.

Subsequently, step 2 involved multiple linear regression analyses for each dependent variable (MTS and CPM) and primary independent variables (PA and SB measures) if they have demonstrated significant associations ($r$) with a $P$-value of $\leq 0.05$. Because no correlation exists between dependent variables (MTS and CPM measures), a multiple regression model for each dependent variable was built.

Due to modest sample size (CPM: $n = 60$; MTS: $n = 67$), a maximum of 4 confounder variables (ie, demographic, anthropometric, pain, and psychological variables) in addition to primary independent variables (PA and SB variables) were adjusted in the final multiple regression model. Because PA measures (except walking) demonstrated significant ($P < 0.05$) weak negative correlations with SB, multicollinearity effects of PA variables in the multiple regression models were assessed using variance inflation factor and tolerance functions. Confounding variables were included in the step 2 modelling if they have demonstrated significant relationships with the dependent variables. In addition to adjusted models, backward multiple linear regression analyses were performed. For all regression analysis, relevant statistical assumptions were assessed.

### 3. Results

#### 3.1. Participant characteristics

Table 1 presents the descriptive statistics of the demographics, clinical features, and key outcome of interests (change scores of TS and CPM) for all participants.
| **Table 1**  
**Summary of demographics, pain, psychological, and predictor and outcome variables.** |
| --- | --- |
| **Domains and variables** | **Descriptive scores (mean (SD) or n [%]) and/or median (percentiles)** |
| **Demographics** |  |
| Age (in years) | 60.3 (12.4) |
| >65 years (n [%]) | 33 (49.3%) |
| ≤65 years (n [%]) | 34 (50.7%) |
| Sex |  |
| Males (n [%]) | 23 (34%) |
| Females (n [%]) | 44 (66%) |
| BMI (kg/m²) | 30.4 (9.7) |
| **Pain measures** |  |
| Duration of pain (y) | 10.8 (12.3); median: 7 (2 to 15) |
| No. of painful joints | 5.3 (3.1) |
| Chronic widespread pain (n [%]) |  |
| No | 35 (52%) |
| Yes | 32 (48%) |
| Most painful joint/region (n [%]) |  |
| Low back | 24 (36%) |
| Hip | 12 (18%) |
| Knee | 15 (22%) |
| Neck | 6 (9%) |
| Shoulder | 10 (14%) |
| Brief pain inventory scores (most painful joint/region) |  |
| Pain severity subscore | 4.2 (2.0) |
| Pain interference subscore | 4.4 (1.8) |
| **Pain severity** |  |
| Worst pain in the past 24 hours | 6.3 (2.2) |
| Worst pain in the past 4 weeks | 7.0 (2.0) |
| Least pain in the past 24 hours | 2.6 (2.2) |
| Least pain in the past 4 weeks | 2.8 (2.5) |
| Average pain in the past 24 hours | 4.8 (2.2) |
| Average pain in the past 4 weeks | 5.0 (2.2) |
| Current pain (at the time of testing) | 3.3 (2.9) |
| PainDETECT total score | 13.5 (6.9) |
| Nociceptive pain (n [%]) | 32 (47.8%) |
| Mixed type (n [%]) | 18 (26.9) |
| Neuropathic pain (n [%]) | 17 (25.4%) |
| Pain medication before session (n [%]) |  |
| No | 32 (48%) |
| Yes | 35 (52%) |
| **Psychological and other variables** |  |
| PCS—total score | 14.5 (11.7) |
| PCS—rumination score | 4.9 (4.3) |
| PCS—magnification score | 3.0 (3.0) |
| PCS—helplessness score | 6.6 (5.3) |
| PVAQ score | 39.3 (13.1) |
| DASS—total score | 28.9 (9.6) |
| Depression score | 8.3 (7.5) |
| Anxiety score | 7.1 (6.6) |
| Stress score | 13.6 (7.9) |
| Pain self-efficacy score | 9.0 (2.3) |
| CSI total scores | 59.7 (17.9) |
| >40 score | 60 (89.6%) |
| <40 score | 7 (10.4%) |
| Sleep quality (n [%]) |  |
| Good | 30 (45%) |
| Bad | 37 (55%) |
| **Physical activity and sedentary behaviour variables (primary predictor variables)** |  |
| Total days of activity (d/wk) | 4.7 (2.5) |
| Total activity (min/wk) | 105.1 (107.1); median: 85 (40 to 120) |
| MET-min/wk—vigorous | 642.4 (1684.9); median: 0.0 (0.0 to 480) |
| MET-min/wk—moderate | 697.3 (878.9); median: 300.0 (160 to 960) |
| MET-min/wk—walking | 340.1 (486.7); median: 146.5 (0.0 to 594) |
| MET-min/wk—total | 1679.8 (2428.8); median: 960.0 (292 to 1950) |
| Physical activity categories (n [%]) |  |
| Low | 34 (50.7%) |
| Moderate | 19 (28.4%) |
| High | 14 (20.9%) |
| Sedentary behaviour—daily estimates (h/d) | 8.2 (3.0) |
Seven participants did not undergo CPM assessment due to safety reasons.

**Table 3**

| Table 3 (continued) | **Summary of demographics, pain, psychological, and predictor and outcome variables.** |
|---------------------|-----------------------------------------------------------------------------------|
| **Domains and variables** | **Descriptive scores (mean (SD) or n [%]) and/or median (percentiles)** |
| **Outcome variables** | **MTS-S NPRS change scores (N = 67)** |
| MTS-R NPRS change scores (N = 67) | 1.9 (1.8); (median: 1.7; 0.7 to 2.7) |
| *CPM30sec % change scores (N = 60) (PPT-P4 at 30 seconds — PPT-P4 preconditioning score) | 1.4 (1.5); (median: 1.0; 0.3 to 2) |
| *CPM60sec % change scores (N = 60) (PPT-P4 at 60 seconds — PPT-P4 preconditioning score) | 17.4 (28.9%); (median: 12.0; −2.2 to 32.8%) |
| *CPM90sec % change scores (N = 60) (PPT-P4 at 90sec — PPT-P4 preconditioning score) | 20.7 (37.0%); (median: 14.8; −6.5 to 38.4%) |

CPM, conditioned pain modulation; CSI, central sensitization inventory; DASS, depression, anxiety, and stress Scale; MTS-S, mechanical temporal summation—symptomatic joint; MTS-R, mechanical temporal summation—remote site; NPRS, numeric pain rating scale; PVAQ, pain vigilance and awareness questionnaire; PCS, pain catastrophizing scale; y, years.

* Seven participants did not undergo CPM assessment due to safety reasons.

### 3.2. Conditioned pain modulation

Of 67 participants, 7 participants did not undergo CPM procedure due to safety concerns. Except for 2 participants, all participants completed 2-minute exposure to conditioning (cold) stimulus. There was a significant overall change ($\chi^2$: 18.5; $P \leq 0.001$) between preconditioning and postconditioning PPT-P4 raw scores. Pairwise comparisons found significantly higher postconditioning PPT-P4 scores at 30, 60, and 90 seconds (at all time points) when compared with preconditioning PPT-P4 average score (Table 5). Small to moderate (range 0.35–0.45) effect sizes were observed for all pairwise comparisons.

None of the demographic factors demonstrates significant associations with CPM response. Pain severity and interference scores were significantly positively associated with CPM60sec effect only (Table 2). None of the psychological and pain-related measures were significantly associated with CPM30sec, except sleep quality (bad vs good), which revealed a weak negative association with CPM30sec (Table 2). Pain severity and interference scores, pain medication intake before the test session, and PCS (helplessness subscore) demonstrated weak positive associations with CPM60sec, whereas PSE was negatively (weak) associated with CPM60sec. A range of psychological factors (PCS, PVAQ, DASS, and PSE scores) demonstrated significant positive associations with CPM90sec percentage change scores. The variable “pain medication intake before the test session” showed a significant weak-negative association with CPM90sec response (Table 2).

### 3.3. Association of physical activity and sedentary behaviour with conditioned pain modulation responses

All PA measures (except vigorous PA MET-min/wk) demonstrated significant weak negative correlations with CPM30sec and CPM60sec (Table 3). Sedentary behaviour showed significant weak positive associations with CPM30sec and CPM60sec (Table 3). No significant relationships were demonstrated between PA/SB measures and CPM90sec (Table 3). Table 4 presents the results of multiple linear regression analysis for CPM30sec and CPM60sec.

#### 3.3.1. CPM30sec

After adjusting for the confounder variables (SQ and PA levels), the final multivariate model (model 1) demonstrated a significant positive association of the daily durations of SB with the CPM30sec. However, the backward multiple regression model showed significant positive associations of SB with CPM30sec response (model 4). Independent models (models 2 and 3) were constructed for SB and PA. After controlling for sleep quality, SB measure demonstrated a significant positive association with CPM30sec response, but not the PA variable (Table 4).

#### 3.3.2. CPM60sec

After controlling for variables (pain severity, pain medication intake before the test session, and PCS—helplessness), neither PA nor SB measures demonstrated associations with CPM60sec response (model 5). Independent models (6 and 7) were constructed for SB and PA against CPM60sec response. In the model 6, after controlling for variables, SB measure demonstrated a significant positive association with CPM60sec response (model 6). However, in model 7, after controlling for variables, PA was not associated with CPM60sec. However, in the backward multivariate model (model 8), SB and pain medication intake before the test session remained in the model, and both demonstrated significant positive associations with CPM60sec response. Pain interference and PSE were not included in the model to avoid multicollinearity with pain severity and PA variables (Table 4).

#### 3.3.3. CPM90sec

Multiple linear regression analysis was not conducted for CPM90sec due to nonsignificant relationships between PA/SB variables and CPM90sec percentage change scores (Table 3).

#### 3.4. Mechanical temporal summation

A significant TS ($\chi^2$: 18.5; $P \leq 0.001$) was observed both at the symptomatic (z = −6.4; $P \leq 0.001$) and remote sites (z = −6.2; $P \leq 0.001$), with a large effect size (Table 5). When compared with the remote site, there was a significant (z value: −3.4; $P < 0.001$) TS (greater change in the pain ratings) at the symptomatic site, with a moderate effect size. Older adults’ group (>65 years) had a higher TS at the symptomatic when compared with the other age group (<65 years).

Significant positive relationships were shown between MTS-S and pain severity and interference scores. Similarly, MTS-R scores were positively correlated with pain interference, but not with pain severity scores. Pain severity, interference scores, and psychological factors (PCS, PVAQ, depression, anxiety, CSI, and PSE scores) were positively associated with both MTS-S and
Hence, a multivariate analysis was not conducted.

MTS-R change scores. However, the number of painful joints, PVAQ, and stress subscale scores were related to MTS-R change scores only. SChCat demonstrated a negative association trend with MTS-S change scores, whereas PSE scores showed a negative association trend with both MTS-S MTS-R change scores (Tables 2 and 3).

3.5. Associations of physical activity and sedentary behaviour with mechanical temporal summation

No significant correlations were demonstrated between both MTS-S and MTS-R and any of the PA or SB measures (Table 3); hence, a multivariate analysis was not conducted.

4. Discussion

This study demonstrated that the individuals who spent a longer duration in a day engaging in SB had a greater CPM effect. Also, PA levels were negatively correlated with the CPM effect. We did not find evidence of a relationship between MTS of pain and SB/PA levels.

4.1. Conditioned pain modulation

Sedentary behaviour levels were associated with greater CPM effects, independent of total time spent in moderate or vigorous physical activities. Also, a significant positive CPM effect (moderate effect size) was demonstrated. These findings are in contrary to the previous studies measuring CPM effect, where greater CPM responses were seen in healthy individuals: who engaged in higher levels of PA and had lower levels of sedentary time; performed better in endurance activities. Also, a significant positive CPM effect (moderate effect size) was demonstrated. These findings are in contrary to the previous studies measuring CPM effect, where greater CPM responses were seen in healthy individuals: who engaged in higher levels of PA and had lower levels of sedentary time; performed better in endurance activities; and participated in vigorous activities. Generally, these studies included young and older healthy adults, used different QST paradigms, studied different domains of PA, and measured PA using self-report and objective methods.

Table 2

Bivariate Spearman correlations between outcome variables and the demographic, pain, psychological, and sleep measures.

| Variables | MTS-S | MTS-R | CPM30sec§ | CPM60sec§ | CPM90sec§ |
|-----------|-------|-------|-----------|-----------|-----------|
| Age       | 0.164 | 0.092 | 0.048     | 0.348     | 0.058     |
| BMI       | −0.053| 0.335 | −0.057    | 0.324     | 0.131     |
| Pain       | 0.258†| 0.018 | 0.181     | 0.071     | −0.012    |
| No of painful joints | 0.133 | 0.143 | 0.212†    | 0.044     | −0.028    |
| Widespread pain (remote vs region) | 0.117 | 0.172 | 0.141     | 0.127     | −0.069    |
| Duration of pain | −0.064| 0.307 | −0.145    | 0.125     | −0.013    |
| PainSE—7 days | 0.210†| 0.044 | 0.16      | 0.098     | 0.092     |
| PainSE—interference score | 0.302*| 0.007 | 0.202     | 0.051     | 0.079     |
| Worst pain—24 hours | 0.195 | 0.057 | 0.11      | 0.188     | 0.194     |
| Worst pain—4 weeks | 0.156 | 0.103 | 0.118     | 0.171     | −0.047    |
| Least pain—24 hours | 0.09  | 0.234 | 0.04      | 0.374     | −0.075    |
| Least pain—4 weeks | 0.039 | 0.377 | 0.11      | 0.188     | −0.083    |
| Average pain—24 hours | 0.230†| 0.031 | 0.082     | 0.255     | 0.142     |
| Average pain—4 weeks | 0.208†| 0.045 | 0.210†    | 0.044     | 0.067     |
| Current pain | 0.19  | 0.061 | 0.289*    | 0.009     | 0.049     |
| PainDETECT—total | 0.028 | 0.41  | 0.153     | 0.109     | −0.126    |
| PCS—R     | 0.233†| 0.029 | 0.363*    | 0.001     | −0.006    |
| PCS—M     | 0.351*| 0.002 | 0.415*    | 0.001     | −0.045    |
| PCS—H     | 0.219†| 0.037 | 0.290*    | 0.009     | 0.03      |
| PCS—total | 0.290*| 0.009 | 0.372*    | 0.001     | 0.019     |
| PVAQ      | 0.037 | 0.382 | 0.234‡    | 0.028     | 0.035     |
| DASS—depression score | 0.249†| 0.021 | 0.286*    | 0.009     | 0.107     |
| DASS—anxiety score | 0.214†| 0.041 | 0.285*    | 0.01      | 0.084     |
| DASS—stress score | 0.074 | 0.275 | 0.232‡    | 0.029     | 0.156     |
| DASS—total s score | 0.02| 0.053 | 0.309*    | 0.005     | 0.153     |
| Pain self-efficacy | −0.195| 0.057 | −0.204†   | 0.049     | −0.174    |
| CSI       | 0.203†| 0.049 | 0.289*    | 0.009     | 0.023     |
| Sleep (good vs bad) | −0.197| 0.055 | 0.017     | 0.447     | 0.223†    |
| Pain medications intake before the testing session (yes/no) | 0.007 | 0.477 | −0.150    | 0.123     | 0.193     |

* indicates Spearman rank correlation coefficient or Spearman rho.
† Significant association, P < 0.01; one-tailed.
‡ Not corrected for multiple comparisons.
§ Percentage change in the PPT-P4 scores.
BIPI, Brief Pain Inventory; CSI, central sensitization inventory; DASS, depression, anxiety, and stress scale; MTS-S, mechanical temporal summation—symptomatic joint; MTS-R, mechanical temporal summation—remote site; NPRS, numeric pain rating scale; PCS, pain catastrophizing scale; PVAQ, pain vigilance and awareness questionnaire.
Another potential factor that might have contributed to the observed relationship was the participant’s PA pattern (un-measured variable) before the study period. Notably, individuals with chronic pain generally display behavioural patterns in engagement with PA, classically defined as “boom” and “bust” phases of the chronic pain experience cycle. Anecdotal evidence suggests that people in pain “flare-ups” after engagement in high levels of activity often reduce their activity levels or even engage in SB. It could be speculated that the participants’ SB might have induced transient better pain modulatory effects to protect against pain flare-ups, thus explaining the positive cross-sectional relationship between SB and CPM effect in this study.

Physical activity levels were negatively correlated with the CPM effect in this study. The contrasting observed relationship (vs healthy individuals) between PA and CPM effect may be moderated by psychological factors. This study revealed positive associations between a range of psychological factors (eg, catastrophizing, DASS scores, pain hypervigilance, and PSE) and later CPM responses (at 60 and 90 seconds). Similar positive associations were demonstrated in previous research, speculating a positive mediating role of general anxiety related or attentional bias associated catastrophizing thoughts on CPM efficiency. Contrastingly, previous studies report psychological status (self-reports and experimental induction of acute stress) negatively influence the CPM effect in healthy and symptomatic individuals. However, adjusting for the PCS-helplessness in this study did not significantly influence the variance of PA or SB on CPM effects. Since participants in this study had lower scores in PCS and other psychological attributes, the role of psychological confounding on the observed relationship cannot be entirely ruled out.

### 4.2. Mechanical temporal summation

Although significant negative associations were observed between MTS and PA/SB measures in the pain-free control population, this study failed to find such associations. Similar to this study, a recent study demonstrated no relationships between moderate or vigorous PA levels and heat-evoked TS of pain in a group of individuals with low back pain. Lack of null relationships between MTS and PA/SB measures in this study can be due to observations: lower and skewed MTS change score at the symptomatic site (mean [SD]: 1.9 [1.8]); skewed PA data; inter-regional TS differences (lower scores—neck/shoulder regions vs higher scores at low back/knee/hip regions); higher MTS-S scores in older adults group (vs <65 years); and higher MTS at the painful site (vs remote site). Besides, there is some evidence demonstrating hypesthesia in the painful region and no signs of CS, which may have influenced the TS responses in the symptomatic region. Other TS mechanisms such as local tissue responses and cognitive and affective responses (perceived threat) to the repeated sensory input can also explain the observed null relationships. This perceptual component is supported by our data showing significant positive correlations between MTS scores, PCS scores, and pain severity/interference. Thus, peripheral mechanisms of TS and perceptions might have confounded the relationship between PA/SB and MTS scores.

### 4.3. Study strengths

This is the first study exploring the role of PA and SB on CPM effect and TS responses in a group of individuals with mixed persistent musculoskeletal pain. This study attempted to adjust known confounding factors in the analysis. Our study participants were free of cognitive impairments, thus minimizing the possibility of recall issues in reporting pain and PA levels. This study used the CPM protocol where the test stimulus was administered at the symptomatic joint against a standard research practice where the test stimulus was administered at the remote symptomatic region. Other TS mechanisms such as local tissue responses and cognitive and affective responses (perceived threat) to the repeated sensory input can also explain the observed null relationships. This perceptual component is supported by our data showing significant positive correlations between MTS scores, PCS scores, and pain severity/interference. Thus, peripheral mechanisms of TS and perceptions might have confounded the relationship between PA/SB and MTS scores.
contrary to a previous study, 51 positive CPM effect was observed, possibly explained by the mixed sample (older and middle-aged adults) of participants and suprathreshold pain (PPT-P4) used as a criterion for test stimulus in this study. Another potential limitation was towards the application of conditioning stimuli at the same segmental level (ie, cold bath immersion of the hand) in studies, the similar temperature was used in previous studies that have had induced significant conditioning response.25,37 In contrary to a previous study,51 positive CPM effect was observed, possibly explained by the mixed sample (older and middle-aged adults) of participants and suprathreshold pain (PPT-P4) used as a criterion for test stimulus in this study. 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participants with shoulders and neck pain (n = 16). Therefore, the role of segmental inhibition cannot be ruled out in the CPM response in this study. A percent change of suprathreshold (pain4) PPT scores was used in the statistical analysis to overcome the regional variability in PPT scores. However, the effect of the testing site (varied symptomatic regions) on the observed relationships cannot be entirely ruled out. A possibility of variance inflation due to multicollinearity between independent variables (PA and SB) was ruled out through meeting the statistical indices’ criteria (variance inflation factor and tolerance) of the multiple regression modelling.

Another limitation is not correcting P values for multiple correlations; however, using Bonferroni correction may inflate a type II error rate, possibly missing the real relationships. All previously published studies that investigated associations between PA and CPM/MTS in healthy as well as in symptomatic population did not correct for multiple comparisons, and they all found fair relationships. There could be potential group differences (middle-aged and older aged adults) in relationships of interest; however, age as a continuous measure was not associated with CPM/TS measures (P > 0.05). Therefore, it is reasonable to propose that potential group differences in relationships of interest do not exist.

4.4. Research recommendations
Prospective longitudinal research should use objective methods for measuring PA and SB patterns and their impact on pain modulatory mechanisms. Future research should explore the role of contexts, cognitive, affective factors (eg, fear of movement), and social factors in PA/SB engagement and their impact on pain modulatory systems. For example, structured PA, as opposed to leisure-based PA, may have differential effects on pain modulatory functions, mediated through cognitive, emotional, and social factors. Future research should consider measuring washout effects of a conditioning stimulus. Moved evoked pain paradigms such as "sensitivity to physical activity" or similar can be used in addition to experimental QST paradigms. Future studies could use a criterion (ie, at least > 2 points on an NPRS for defining a clinically meaningful summation of pain) to categorize the MTS data and assess the relationship. Future research should explore the role of central sensitization in humans: assessment and pharmacology. Handb Exp Pharmacol 2015;227:79–102.

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5. Conclusions
Sedentairness, independent of PA levels, is associated with greater CPM effect in people with chronic musculoskeletal pain. Both SB and PA levels were not related to mechanical TS. These findings collectively provide insights on mechanistic processes between PA behaviour and central nociceptive facilitation and inhibition in a symptomatic population. The study findings need to be interpreted with caution due to cross-sectional data and data sourced from a range of patients presenting with different regional pain presentations. Prospective longitudinal studies using objective measures of PA and SB are required to validate these observed relationships in a larger sample size, exploring relationships between PA characteristics, pain modulatory mechanisms, and clinical outcomes.

Disclosures
The authors have no conflict of interest to declare.

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