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ALTERATIONS IN TEMPORAL SUMMATION OF PAIN AND CONDITIONED PAIN MODULATION ACROSS AN EPISODE OF EXPERIMENTAL EXERCISE-INDUCED LOW BACK PAIN

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Abstract:

Persistent pain conditions, including low back pain (LBP), are often accompanied by alterations in pro-nociceptive and anti-nociceptive mechanisms, as quantified by Temporal Summation of Pain (TSP) and Conditioned Pain Modulation (CPM). It remains unclear whether altered pain sensitivity, CPM and/or TSP are a consequence of pain presence, or determine the degree of pain development. Pressure pain sensitivity, TSP, and CPM were assessed across an episode of exercise-induced-LBP maintained for several days. Thirty healthy individuals participated in three experimental sessions: Before (Day-0), two-days after fatiguing back muscle exercise with exercise-induced-LBP present (Day-2), and after pain resolution (Day-7). Both handheld and cuff pressure-pain thresholds, along with TSP (10-cuff pain stimuli at 0.5Hz) and CPM (cuff pain detection threshold prior versus during painful-pressure conditioning) were assessed, alongside questionnaires pertaining to pain, disability, mood, sleep, menstruation, physical activity, and catastrophizing. The exercise-induced-LBP model produced mild pain and disability, and reductions in pressure pain thresholds over both the lumbar and distant testing sites ($P<0.007$). No pain-related changes were observed for TSP ($P>0.44$) or CPM ($P>0.17$). Baseline TSP was associated with the peak pain intensity of the exercise-induced-LBP ($P<0.003$).

Perspective:

Pressure pain sensitivity was impacted by the presence of exercise-induced LBP; whereas TSP appeared more stable and was instead associated with the intensity of pain developed. No significant pain-related changes nor associations were observed for CPM, suggesting this measure may have less utility in mild musculoskeletal-pain conditions.

Keywords: Conditioned pain modulation, temporal pain summation, cuff algometry, low back pain model, translational

INTRODUCTION

Low back pain (LBP) is the leading cause of disability worldwide[26], yet up to 90% of patients are diagnosed with non-specific LBP, meaning the pathoanatomical source is unclear[10]. Further, recurrence following an acute episode may be up to 80%[25], with little understanding as to why some patients develop ongoing symptoms[9]. There has recently been increasing focus on alterations in pro-nociceptive and anti-nociceptive mechanisms, purported to explain or contribute to pain exacerbation and persistence across a range of acute to chronic pain conditions[34,45,72]. However, it is not well understood when such alterations occur, and hence whether they really are a cause, or merely a consequence of ongoing pain.

Two measures are commonly used to quantify pro-nociceptive and anti-nociceptive mechanisms, known as Temporal Summation of Pain (TSP) and Conditioned Pain Modulation (CPM), respectively. TSP quantifies increasing pain perception to repeated brief noxious stimuli (e.g. electrical, thermal, mechanical) applied at a frequency >0.33 Hz, thought to reflect increasing dorsal horn excitability[71]. CPM is suggested to quantify the activation of descending inhibitory pathways from the midbrain, by assessing changes in sensitivity to noxious stimuli (e.g. thermal, mechanical) following application of a heterotopic painful conditioning stimulus; with reduced sensitivity or intensity reflecting appropriately functioning inhibition[73].

Many factors, such as gender, age, sleep quality, psychological factors, hormonal cycles, and physical activity levels, have been suggested to impact TSP[55] and/or CPM[23], and should be considered when using these measures. Further, different modalities are known to yield different TSP and CPM magnitudes with varying reliability[17,27,28], though pressure stimuli may be preferable for assessing musculoskeletal pain[62], as this modality can excite deep nociceptive afferents innervating musculoskeletal structures[16,39]. Similarly, consideration of methodology is especially important for CPM, with tests of inhibitory effects on both pain thresholds and pain ratings to supra-threshold stimuli commonly recommended[74].

In some cases, TSP and CPM may be predictive of subsequent pain, consistent with a possible role in pain development[57]. For instance, TSP and CPM, assessed pre-operatively in pain-free patients undergoing thoracotomy, demonstrated predictive value in determining post-operative pain intensity[70,75]. TSP and CPM magnitude in people with pain conditions can also relate to the intensity of pain experienced[5,49,65], suggesting fluctuations in TSP and CPM may be consequential to pain[2,15]. In line with this suggestion, clinical studies have demonstrated improvements in CPM and pain sensitivity following replacement of painful osteoarthritic joints[18,30], and experimental studies have shown impaired CPM following painful saline injection[2].

Experimental pain models can provide additional insight into dynamic changes in pain sensitivity measures in response to a standardised painful condition, as well as allowing for measurements prior to pain development, which is often not possible in clinical populations. Further, prolonged experimental pain models, such as delayed-onset muscle soreness (DOMS) following unaccustomed eccentric exercise, can induce soreness lasting for several days, mimicking the deep, movement-evoked pain and functional impairment seen in mild non-specific LBP patients[6]. Prior experimental work has demonstrated that DOMS increases TSP magnitude over painful muscles[22,47] and in nearby regions[5]. However, changes in TSP over distant testing sites outside the painful region (which may better indicate central pain processing changes) as is assessed and often altered in clinical populations[65,66], as well as changes in CPM, have not been investigated in this LBP-model.

This study therefore aimed to: 1) Investigate changes in pressure-pain sensitivity, pressure-induced TSP and CPM, before, during and following the experience of exercise-induced-LBP; and, 2) Examine associations between baseline pressure-pain sensitivity, TSP and CPM, and the peak intensity of exercise-induced-LBP developed. It was hypothesised that: 1) During exercise-induced-LBP, pressure pain sensitivity and TSP would be increased, and CPM efficiency would be reduced;

and, 2) Baseline pressure-pain sensitivity, TSP and CPM would be associated with peak exercise-induced-LBP intensity.

METHODS

Participants

Healthy pain-free participants aged between 18-60 years were recruited for the experiment from the university and wider community. Prospective participants underwent a verbal information meeting prior to recruitment, and those with current or previous diagnoses of LBP, acute lower limb pain, chronic or recurrent pain conditions, or neurological, musculoskeletal, cardiorespiratory, mental or other exercise-precluding disorders, were excluded. Further, prospective participants who frequently trained their trunk or lumbar musculature were also excluded. Participants were advised to avoid strenuous exercise (except for the experimental protocol), excessive stimulants and analgesics, and maintain normal sleeping patterns prior to and during the study period. Prior to the first session, participants were given both written and verbal information about the study, and all participants provided written informed consent. The protocol was approved by the local ethical committee (N-20170034) and was conducted in accordance with the Declaration of Helsinki.

Experimental procedure

Three experimental sessions were scheduled on Day-0, Day-2 and Day-7 (Fig. 1). All sessions were conducted by the same investigator (MEM), at approximately the same time of day for each participant. Prior to data collection, participants were familiarised with experimental devices. On Day-0 participants were asked about their pain history, sleep habits, menstrual cycle, mood, physical activity and pain-related distress. Following this, a short physical examination was conducted to ensure pain-free spinal movement. Pressure pain sensitivity was assessed by

pressure algometry over 10 sites and with cuff algometry on the lower legs. TSP, along with two CPM methods (ramped: pain threshold or, phasic: supra-threshold stimulus rating), were then also assessed with cuff algometry on the lower legs. After a short break (approx. 5-min), a series of eccentric trunk muscle exercise was completed until fatigue to induce experimental LBP. Both handheld and cuff pressure algometry was reassessed immediately after the exercise (results presented in Supplementary Material). On Day-2 and Day-7, questionnaires relating to sleep, mood and disability were collected, then pain intensity, unpleasantness, quality and distribution were assessed. Following this, the same physical examination, handheld and cuff pressure algometry assessments were conducted (Fig. 1).

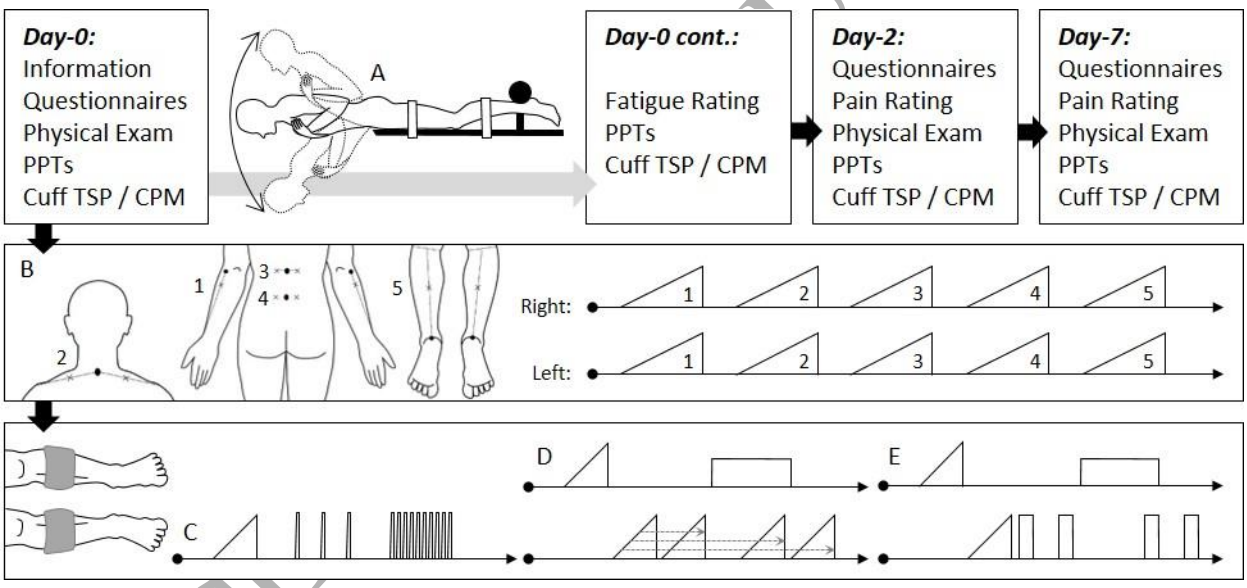

Figure 1: Experimental protocol showing session order and contents, including: (**A**) Eccentric exercise task, (**B**) Handheld pressure algometry sites (marked by 'x'), (**C**) Temporal Summation of Pain series, (**D**) Ramped CPM series, and (**E**) Phasic CPM series. Figures C-E indicate cuff pressure for the dominant (bottom) and non-dominant (top) legs. Dotted lines in figure D represent the change in pain detection threshold from the first stimulus to give sequential pain modulation (SPM, to 2nd ramp), CPM (to 3rd ramp) and Post-CPM (to 4th ramp).

Questionnaires

Mood was self-assessed by the participant using the Faces Scale[38] (20 faces coded into numerical rating, 1=most positive). Sleep duration (hours) for the preceding night was estimated by the participant, and for females, the day number in the menstrual cycle was collected. Physical activity was examined using the International Physical Activity Questionnaire[21] (IPAQ) with estimated activity expenditure (metabolic equivalent (MET)-minutes/week; higher scores indicate higher activity levels) extracted from participant's reported weekly vigorous, moderate, and mild activity time, as per the manual. The Pain Catastrophizing Scale (PCS) was used to assess general pain-related distress; higher PCS scores indicate a higher degree of pain-related catastrophic thinking [64]. On Day-2, the Roland-Morris Disability Questionnaire[56] (RMDQ; max score 24) was completed to characterise back-related disability induced by the LBP model.

Experimental low back pain

An eccentric trunk extension exercise, as developed previously[31,36], was used to induce muscle fatigue and subsequent DOMS in the low back (Fig. 1A). Participants were positioned on a purpose-built exercise bench, with a padded anchor over the posterior ankle, a firm belt over the posterior calves and hamstrings, and the torso unsupported. Participants were instructed to slowly lower their trunk (approx. 4 s per eccentric phase) from full extension to 45 degrees below horizontal and then return to full extension (approx. 1 s per concentric phase). Assistance was provided during the concentric phase, and short breaks were given after each 15 repetitions, to maximise the total number of eccentric contractions performed. The exercise was terminated when participants could no longer independently control the eccentric movement phase (i.e. unable to maintain extended position or eccentric phase >1 s). A modified Borg Perceived Exertion Scale[7] (BPE; 0: rest, to 10: maximal exertion) was used during each short break to quantify perceived effort throughout. A Likert scale (anchored at 0: not at all, to 4: extremely) was used

following the last repetition to quantify perceived muscle fatigue[31]. Total exercise time and number of repetitions were recorded.

Assessment of experimental low back pain

Intensity of experimental LBP was assessed both using a Visual Analogue Scale (VAS, anchored at 0 cm: no pain, and 10 cm: worst pain imaginable), and a 7-point Likert scale of back muscle soreness[36] (0: complete absence of soreness, 1/2: light/moderate muscle soreness felt only when touched, 3: light muscle soreness when lifting or carrying objects, 4/5: light/moderate muscle soreness, stiffness or weakness when flexing the back, 6: severe muscle soreness, stiffness or weakness that limits the ability to move). Pain unpleasantness was also assessed on a VAS (anchored at 0 cm: not unpleasant at all, and 10 cm: most unpleasant sensation imaginable). Pain quality was assessed using the word table from the McGill Pain Questionnaire[44] (MPQ). Subjects drew their pain distribution using an electronic body chart from the Navigate Pain application (Aalborg University, Denmark). In addition, participants were asked: "Do you currently have any pain or soreness due to the exercise session?" Participants who answered 'no', and participants who answered 'yes' but did not report any pain or soreness in the lower back region (as per the body chart) were excluded. A brief pain-diary was also given to participants for the duration of the experiment to record pain intensity (VAS) and location (paper body chart) diurnally for six days. Participants were advised to note deviations from the protocol, such as participation in exercise or seeking treatment, in this pain diary as well.

Handheld pressure algometry

A handheld pressure algometer (Somedic, Sweden) with a 1 cm^2 rubber-tipped probe was used to assess pressure pain thresholds (PPTs) at five different body sites, bilaterally. These sites were 1) extensor carpi radialis [ECR, approx. 3 cm distal to the lateral epicondyle], 2) upper trapezius [UT,

midway between the acromion tip and 7th cervical spinous process], 3) & 4) lumbar erector spinae [L1/L5, 3.5 cm lateral to the 1st and 5th lumbar spinous processes], and 5) gastrocnemius [GAS, midway between the popliteal line and calcaneus] muscles (Fig. 1B). Pressure was applied at a constant rate of 30 kPa/s over each site, until the participant indicated that the pressure had first become "uncomfortable or painful" by pressing a button. Each site was assessed three times, with approx. 2 minutes in-between, and the pooled average for both repetitions and sides was used for analysis.

Pressure pain sensitivity assessed by cuff algometry

A computer-controlled cuff algometer (NociTech, Denmark), paired with two 10 cm wide air-pressure cuffs (VBM, Germany) and an electronic VAS (eVAS, anchored at 0 cm: no pain, to 10 cm: worst pain imaginable), was used to assess cuff pressure pain sensitivity, TSP and CPM (Figure 1C-E). A cuff was fitted over the widest portion of each lower leg, approximately 5 cm below the tibial tuberosity. Ramped inflation of the cuff at 1 kPa/s, to a maximum of 100 kPa, was used to assess cuff pressure pain thresholds. During each ramp, participants were instructed to begin sliding the dial of the eVAS as soon as the pressure became painful, and to press the 'stop' button when they could no longer tolerate further increases in pressure-pain. The cuff pain detection threshold (cPDT) was defined as the pressure when the eVAS was at 1 cm and cuff pain tolerance threshold (cPTT) was defined as the pressure when the participant pressed the 'stop' button. In each session, cPDTs and cPTTs were recorded before each TSP and CPM assessment (Figure 1C-E), and each assessment was separated by at least 3-minutes.

Temporal summation of pain

Three individual peak inflations (1 s duration, 10 s interval) were applied to accustom participants to the type of stimulation and assess the perceived intensity of individual stimuli. This was

followed by a series of ten peak inflations (1 s duration, 1 s interval) to assess TSP. All stimuli were applied at the cPTT intensity recorded in that session to the dominant leg (Fig. 1C). For the first three peak-stimuli, participants rated their pain on the eVAS and returned it to zero in-between stimuli. Maximum eVAS-scores for the individual peaks were extracted and used for analysis. For the TSP series of 10-stimuli, participants were instructed to rate the intensity of the first stimulus on the eVAS and then adjust the dial as needed for each subsequent inflation without returning to zero in-between inflations. Electronic VAS-scores in each TSP series were normalized by subtraction of the eVAS-score from the first painful stimulus, then VAS-epochs (mean VAS rating of peaks I: 2-4, II: 5-7 and III: 8-10) were calculated for analysis, to reflect changes in pain perception across the series.

Conditioned pain modulation assessed by cuff algometry

A ramped CPM paradigm was assessed via a series of four ramped cuff stimulations (test stimuli) applied to the dominant leg with 30 s rest in-between. Simultaneously with the third stimulus, a tonic conditioning stimulus (constant, 70% cPTT) was applied to the non-dominant leg until end of the third stimulus (maximum 100 s, Fig. 1D). The initial perceived pain intensity of the conditioning stimulus was assessed via a Numerical Rating Scale (NRS) anchored identically to the VAS. The cPDT was extracted for each ramp, then the cPDT from Ramp-1 was subtracted from each of Ramps 2-4 to give the difference in cPDT, which was used to analyse sequential pain modulation (SPM: Ramp 2-1), CPM (Ramp 3-1) and post-CPM effects (Post-CPM: Ramp 4-1).

In order to investigate a CPM methodology more similar to that commonly used and recommended for thermal stimuli[74], for comparison, a phasic CPM protocol was also assessed where two supra-threshold test stimuli (5 s duration, 10 s interval) were applied to the dominant leg prior to and at the end (in the last 5 s and post) of 45 s of conditioning (at 70% cPTT) on the non-dominant leg (Fig. 1E). The pain intensity for each test stimulus was rated on the eVAS, with

re-zeroing in-between stimuli. The maximum VAS rating reached during each of the 5 s test stimuli was extracted and normalized by subtraction of the first stimulus rating for analysis. The sequence of CPM protocols (ramped or phasic) was randomized for each participant.

Statistical analysis

All data is reported as mean (± standard deviation, SD) or median (25^{th}-75^{th} quartiles) in-text and tables, and as mean (+ standard error of the mean, SEM) in figures. Statistical analyses were completed in SPSS Statistics (v24.0; IBM, Armonk, NY). Data normality was assessed by the Shapiro-Wilks test and relevant parametric or non-parametric analysis was used accordingly. Changes in mood, sleep and pain diary scores of the experimental LBP intensity, were compared using one-way repeated-measure analysis of variance (RM-ANOVA) or Friedman's test, with *Day* (Day-0, 2, 7 or Days 1-6 am/pm) as a factor.

Pressure pain sensitivity data was analysed using RM-ANOVA with factors *Day* (Day-0, 2, 7 or Pre/Post-exercise) and *Site* (PPTs) or *Assessment-number* (1-3 for cPDT and cPTT). Cuff-peak VAS scores, TSP and CPM data was analysed using RM-ANOVA or Friedman's test as appropriate with *Day* (Day-0, 2, 7 or Pre/Post-exercise) and *Stimulus* (VAS-epochs, Ramp or Stimulus-number) as factors. Greenhouse-Geisser corrections for violated sphericity were used when necessary, and all post-hoc comparisons were made using paired-samples T-tests or Mann-Whitney U-tests with Bonferroni correction.

A multiple linear regression analysis was conducted to determine if baseline parameters could explain the variance in peak pain intensity of the exercise-induced-LBP. Assumptions of linearity, independent residuals, homoscedasticity, no multi-collinearity, normality, and no outliers, were all assessed via appropriate statistical and visual inspection methods. The peak pain intensity (maximum VAS across days) was defined as the dependent variable, and independent variables considered were baseline PPT (averaged across low back sites), cPDT and cPTT (first

ramp, averaged across legs), TSP (normalized VAS-epoch-III), CPM, number of exercise repetitions performed, mood, sleep, PCS, IPAQ score, age and gender. The model was reduced by the backward elimination method, which sequentially eliminates the least predictive variable to achieve best fit (highest adjusted R^2). The significance level was set to $P<0.05$.

RESULTS

Thirty participants (16 female) were recruited to attend three experimental sessions, though three participants rescheduled their last session one day before or after Day-7 (regarded as Day-7 for analysis). No protocol deviations were noted, suggesting participants refrained from strenuous exercise and seeking treatment. Six participants did not report low back pain at Day-2 and were excluded from between-sessions analysis (n = 24 included), but remain included in regression analysis (n = 30 included, all peak LBP VAS>0). All mood scores were positive (Median: 3, IQR: 2-6), and mean sleep time (7.0 ±1.2 hours) was within recommendations[24], with neither mood rating ($\chi^2_2 = 4.00$, $P>0.13$) nor sleep time ($F_{2,46} = 1.93$, $P>0.15$, $\eta^2 = 0.08$) varying over the study days. Participants reported moderate physical activity scores, normal PCS scores[63] (≤30/52), and females were evenly distributed across menstrual phases.

Excluded participants (n = 6, 3 females) were younger (22.0 ±2.3 years, $t_{17.1} = 2.37$, $P<0.031$, $d = 0.75$) than included participants, but were otherwise similar across both baseline characteristics (BMI: 23.7 ±3.0 kg/m^2, Mood: 3.5 (3-5.5), Sleep: 6.1 ±1.7 hours, IPAQ: 3277.6 ±3114.4 MET-min/week, Sitting Time: 315.0 ±86.6 min, PCS: 12.5 (9.25-16.5)) and exercise performance parameters (Likert Fatigue: 4 (3.25-4), Total Exercise Time: 553.7 ±166.1 s, Total Number Repetitions: 76.7 ±12.9).

Table 1: Mean (± SD) or median (1st-3rd quartiles) baseline characteristics at Day-0 including exercise performance parameters.

Baseline Characteristics	
Age (years)#	25.2 ±4.7
BMI (kg/m^2)	23.6 ±3.1
Mood (/20)#	3 (2-6)
Sleep (Hours)	7.0 ±1.2
Phase of menstrual cycle	n = 4 menstrual n = 5 luteal n = 4 follicular (n = 11 men)
Activity (MET-min/week)#	3984.6 ±3438.5
Daily sitting (min)	387.5 ±143.7
PCS (/52)#	10 (7-19.25)
Exercise Performance Parameters	
Mean BPE (/10)	8.3 ±0.8
Likert Muscle Fatigue (/4)#	4 (3-4)
Total Exercise Time (s)#	561.5 ±231.0
Total Number Repetitions	74.6 ±22.3
Baseline Pain Sensitivity	
PPT (kPa) – Elbow	237.6 ±102.5
Upper Trapezius	328.2 ±145.1
L1	520.6 ±189.1
L5	503.5 ±194.4
Gastrocnemius	376.3 ±137.1
Mean cPDT (kPa) - Dominant	25.1 ±12.4
Non-Dominant	25.5 ±14.2
Mean cPTT (kPa) – Dominant	59.7 ±19.0
Non-dominant	58.5 ±18.0
Ramped CPM (ΔPDT, kPa)	6.1 ±7.5
Phasic CPM (∆VAS, cm)	0.1 ±0.7
TSP (VAS-epoch-III, cm)	1.2 ±1.5

Note: PCS = Pain Catastrophizing Scale, BPE = Borg Perceived Exertion, PPT = Pressure Pain Threshold, cPDT = cuff Pain Detection Threshold, cPTT = cuff Pain Tolerance Threshold, CPM = Conditioned Pain Modulation, TSP = Temporal Summation of Pain.

Experimental low back pain

On Day-2, participants reported their VAS pain intensity as 2.9 ±1.8 cm, VAS pain unpleasantness as 2.8 ±2.4 cm, and rated their muscle soreness as 'light muscle soreness, stiffness or weakness when flexing the back' (median Likert score 4, IQR: 3-4). As rated on the VAS in the pain diary,

participants had pain for 3.3 ±1.2 days, peaking on average the morning after the exercise. The mean peak pain VAS score across days was 4.1 ±2.0 cm, and pain was rated higher in both morning and evening of Day-1 and Day-2 than Days 4-6 (RM-ANOVA: $F_{2.7,61.1} = 29.46$, $P<0.001$, $\eta^2 = 0.56$; post-hoc: $P<0.005$; pooled Day-1 and Day-2: 2.8 ±2.0 cm, pooled Days 4-6: 0.3 ±0.6 cm). Participants commonly described the LBP as 'annoying' (n = 13) and/or 'sore' (n = 11). All included participants developed pain in the 'low back region', i.e. between the inferior border of the lowest rib and the gluteal fold (Fig. 2). Participants showed only mild disability, with a mean RMDQ score of 2.3 ±3.0.

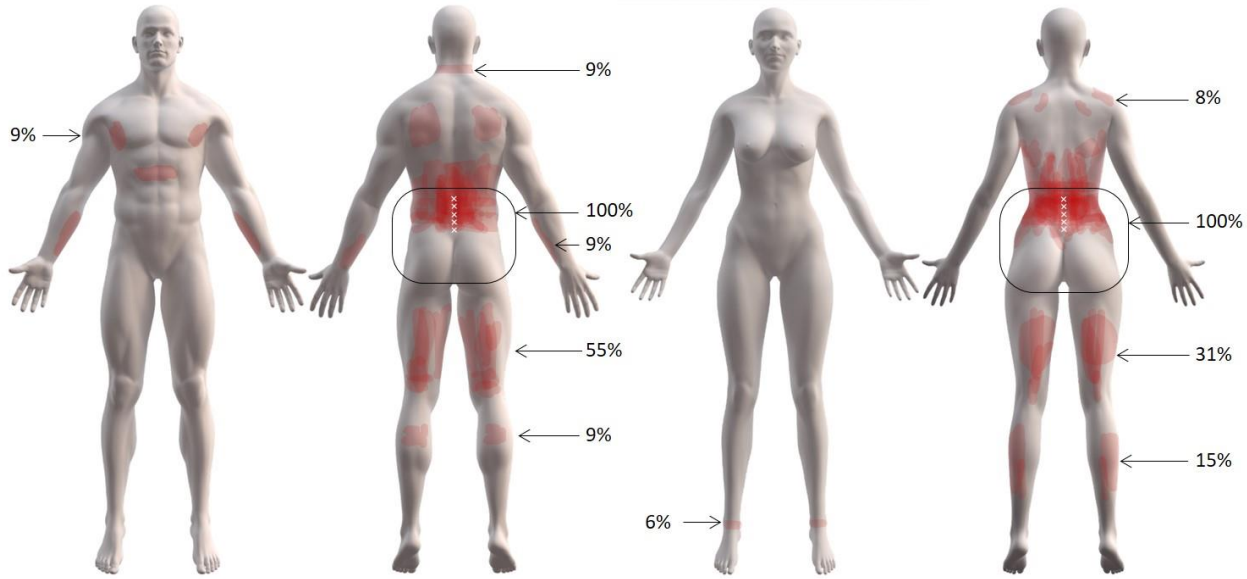

Figure 2: Overlay of individual pain distributions for males (n = 11, left) and females (n = 13, right), with frequency of participants marking each distinct area. The rounded square demarcates the region commonly defined as the 'low back'.

Handheld pressure algometry

Two-way RM-ANOVA of PPTs for Site (5) and Time (3) showed a Time*Site interaction (Fig. 3; $F_{4.0,91.2} = 8.24$, $P<0.001$, $\eta^2 = 0.26$). Post-hoc analysis revealed that PPTs were reduced on Day-2 at

L1 (P<0.002), L5 (P<0.003) and ECR (P<0.005), compared to Day-0 and Day-7. PPTs were also decreased on Day-2 at the UT muscle (P<0.007) and GAS muscle (P<0.001) compared to Day-7.

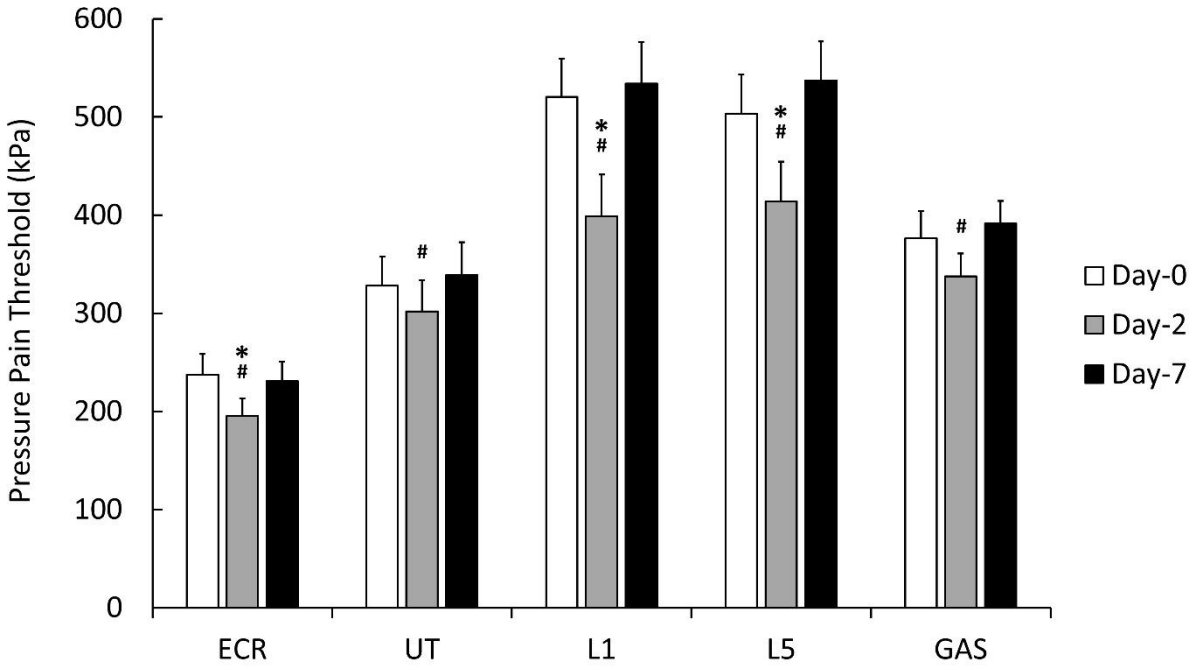

Figure 3: Mean (+SEM) PPTs at each site for Day-0, Day-2, and Day-7. Significant difference from Day-0 (*, P<0.005) and Day-7 (#, P<0.007) is indicated. ECR = extensor carpi radialis, UT = upper trapezius, L1/L5 = 1st and 5th lumbar segments, GAS = gastrocnemius muscle.

Cuff pressure pain sensitivity

For the dominant leg, RM-ANOVA of first cPDT in each cuff measurement series (Fig 1C-E) revealed an effect of Days ($F_{1.5,35.3}$ = 5.85, P<0.011, η^2 = 0.20, Table 2) and Assessment-number ($F_{1.4,32.6}$ = 9.39, P<0.002, η^2 = 0.29). The cPDT on the dominant leg was greater at Day-7 than Day-2 (P<0.001), and the second (P<0.001) and third (P<0.018) assessment were greater than first assessment. Similarly, the RM-ANOVA of the first cPTT on the dominant leg in each cuff measurement series demonstrated an effect of Days ($F_{1.5,34.3}$ = 8.17, P<0.002, η^2 = 0.26) and

Assessment-number ($F_{2,46}$ = 42.56, P<0.001, η^2 = 0.65); with cPTT greater at Day-7 than Day-0 (P<0.009) and Day-2 (P<0.001), and the second (P<0.001) and third (P<0.001) assessment greater than first.

For the non-dominant leg, RM-ANOVA of the first cPDT in each series revealed an interaction between Assessment-number and Days ($F_{2,46}$ = 3.44, P<0.040, η^2 = 0.13, Table 2), where the second cPDT was higher than the first cPDT at Day-2 (P<0.004) and Day-7 (P<0.034), but not at Day-0. The RM-ANOVA of the first cPTT in each series on the non-dominant leg, revealed an effect of Assessment-number ($F_{1,23}$ = 6.14, P<0.021, η^2 = 0.21), where the second cPTT was higher than the first (P<0.001).

Table 2: Mean (± SD) cuff pressure pain detection (cPDT) and tolerance (cPTT) thresholds for the first ramp in each measurement series for each leg on each day.

Leg and Parameter	Assessment Number	Day-0	Day-2	Day-7
Dominant cPDT (kPa)	**1**	22.9 ±10.5	22.3 ±9.8$^{\#}$	26.1 ±60.8
	2	26.4 ±12.0$^{¤}$	24.5 ±11.5$^{\#¤}$	32.3 ±17.1$^{¤}$
	3	26.1 ±14.5$^{¤}$	26.4 ±13.7$^{\#¤}$	31.5 ±17.3$^{¤}$
Dominant cPTT (kPa)	**1**	52.1 ±13.8$^{\#}$	53.4 ±16.9$^{\#}$	60.8 ±20.7
	2	60.4 ±19.1$^{\#¤}$	60.5 ±19.8$^{\#¤}$	68.5 ±21.7$^{¤}$
	3	63.0 ±19.2$^{\#¤}$	66.1 ±19.7$^{\#¤}$	71.0 ±22.3$^{¤}$
Non-Dominant cPDT (kPa)	**1**	25.7 ±13.4	22.1 ±11.0	24.8 ±11.9
	2	25.2 ±15.2	25.5 ±12.1*	28.7 ±14.8*
Non-Dominant cPTT (kPa)	**1**	57.1 ±17.1	53.8 ±19.1	53.8 ±17.6
	2	57.0 ±17.7$^{¤}$	59.5 ±18.2$^{¤}$	59.4 ±19.1$^{¤}$

Note: Significant difference from Day-7 ($^{\#}$, P<0.01, Main Effect), from assessment 1 ($^{¤}$, P<0.02, Main Effect), and between assessments within one day (*, P<0.04) indicated.

Temporal summation of pain

Two-way RM-ANOVA of eVAS-scores of the three phasic stimulations demonstrated no significant main effects or interactions of Stimulus-number and Day ($F_{2.7,62.2}$ = 1.286, P>0.22, η^2 = 0.05, overall

mean eVAS rating: 5.5 ±2.2 cm). For TSP during the ten cuff stimulations, a two-way RM-ANOVA of normalized VAS-epochs revealed an effect of Epoch (Fig. 4; $F_{1.0,23.6} = 15.070$, $P<0.001$, $\eta^2 = 0.40$), showing an increase from epoch-1 to epoch-2 ($P<0.001$), epoch-1 to epoch-3 ($P<0.002$), and epoch-2 to epoch-3 ($P<0.023$), but no differences over days were observed ($F_{2,46} = 0.837$, $P>0.43$, $\eta^2 = 0.04$).

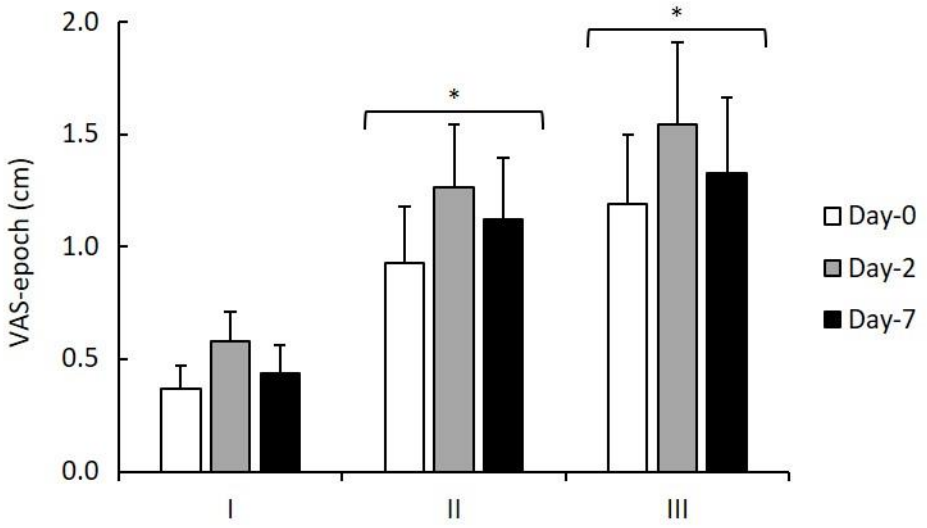

Figure 4: Mean (+SEM) VAS-epochs for temporal summation of pain at Day-0, Day-2 and Day-7. VAS-epochs are based on mean VAS rating of pressure stimulations 2-4 (I), 5-7 (II) and 8-10 (III), after normalisation to the VAS rating of the first stimulus. Significant increase compared to VAS-epoch-I is indicated (*, $P<0.004$).

Conditioned pain modulation

Conditioning pressure was not different over Days ($F_{2,46} = 0.743$, $P>0.48$, $\eta^2 = 0.03$). However, the NRS scores of the conditioning pain intensity (Day-0: 4.9 ±1.7 cm, Day-2: 4.6 ±1.5 cm, and Day-7: 4.3 ±1.7 cm) did show an effect of Day ($F_{1.6,36.1} = 3.58$, $P<0.048$, $\eta^2 = 0.14$), but post-hoc analysis was non-significant ($P>0.10$).

Compared with the first cPDT assessment, the difference to the second (SPM), third (CPM) and fourth (Post-CPM) cPDT values remained positive at each time point, indicating generally appropriate inhibitory responses during conditioning. One-way RM-ANOVA of the change in cPDT for each paradigm over Days (3) revealed a main effect on SPM ($F_{2,46}$ = 3.970, P<0.026, η^2 = 0.15), but no effects on CPM ($F_{2,46}$ = 1.801, P>0.17, η^2 = 0.07) or Post-CPM ($F_{2,46}$ = 0.998, P>0.37, η^2 = 0.04). Post-hoc analysis for SPM did not reveal any significant differences (Fig. 5, P>0.07).

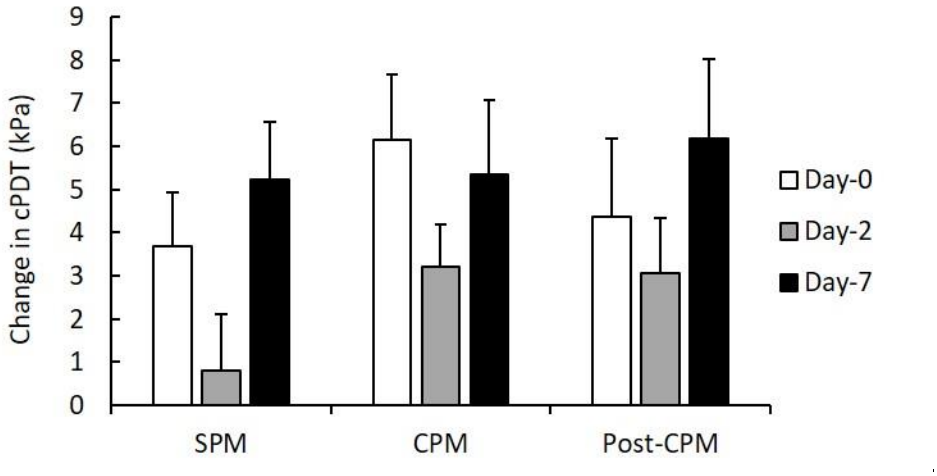

Figure 5: Mean (+SEM) change in cuff pressure pain detection (cPDT) thresholds from Ramp-1 to each subsequent ramp indicating sequential pain modulation (SPM, difference to Ramp-2), conditioning pain modulation (CPM, difference to Ramp-3) and post-CPM (Post-CPM, difference to Ramp-4) effects at Day-0, Day-2 and Day-7.

Phasic pain modulation

Two-way RM-ANOVA of normalized (to the first stimulus) eVAS-ratings for the Test Stimuli (3) at each Day (3) revealed no main effects or interactions ($F_{2.7,61.2}$ = 1.302, P>0.28, η^2 = 0.05), suggesting this paradigm was unable to provoke or quantify CPM-effects (data not presented).

Baseline parameters associated with the degree of pain development

The regression analysis aimed to explain variance in peak VAS scores of the exercise-induced-LBP. The only significant explanatory variable was TSP (P<0.003), though averaged lumbar PPTs, mood, number of exercise repetitions and gender also contributed non-significantly to the final model. The model explained 40.9% of the variance in peak VAS scores, with an adjusted R^2 of 28.6% ($F_{5,24}$ = 3.319, P<0.020, Table 3), considered to be a moderate effect size by Cohen (1988).

Table 3: Summary of multiple linear regression analysis with Day-0 parameters to explain peak low back pain intensity (VAS)

Independent Variable	B	SE_B	β
Initial Model (All Variables)			
Average Lumbar PPT	-0.003	0.002	-0.316
Average First cPDT	-0.021	0.047	-0.122
Average First cPTT	0.002	0.036	0.018
TSP (Norm. VAS-epoch-III, cm)	**0.707**	**0.288**	**0.561***
CPM (ΔPDT, kPa)	0.029	0.050	0.129
Number of Exercise Repetitions	0.025	0.020	0.266
Mood (Faces Scale, /20)	-0.211	0.169	-0.271
Sleep (Hours)	0.002	0.347	0.001
PCS Score	-0.029	0.058	-0.122
IPAQ Total (MET-mins/week)	-0.000	0.000	-0.161
Age (years)	-0.053	0.112	-0.122
Gender	-0.800	0.932	-0.208
Final Reduced Model (Best Fit)			
Average Lumbar PPT	-0.003	0.002	-0.363
TSP (Norm. VAS-epoch-III, cm)	**0.685**	**0.208**	**0.544***
Number of Exercise Repetitions	0.020	0.016	0.214
Mood (Faces Scale, /20)	-0.244	0.137	-0.314
Gender	-0.818	0.673	-0.212

Note: PPT = Pressure Pain Threshold, cPDT = cuff Pain Detection Threshold, cPTT = cuff Pain Tolerance Threshold TSP = Temporal Summation of Pain, CPM = Conditioned Pain Modulation, PCS = Pain Catastrophizing Scale, IPAQ = International Physical Activity Questionnaire. B =

unstandardized regression coefficient, SE_B = standard error of the coefficient, β = standardized coefficient, *indicates significance at P<0.05.

DISCUSSION

This study aimed to investigate within-subject changes in, and the baseline explanatory value of, pressure-pain sensitivity, TSP, and CPM, over an episode of exercise-induced-LBP. Mild levels of pain and disability were produced, along with increased pressure-pain sensitivity over the involved muscles, as expected. No clear pain-related changes in TSP or CPM were observed, though a non-specific time-related change in SPM was indicated. Regression analysis identified baseline TSP as the only significant explanatory variable of peak exercise-induced-LBP intensity.

The exercise-induced-LBP model

The exercise-induced-LBP model produced pain intensities and disability levels consistent with, or even higher than, those reported in similar LBP models[6,31,36], with participants completing nearly twice as many repetitions as that reported previously[31]. Such pain and disability levels correspond to those observed in mild nociceptive LBP[60] or recurrent LBP conditions[43], but are generally lower than that seen in complex chronic pain populations[42,43,46]. Nevertheless, this data supports prior suggestions that DOMS is an appropriate experimental-LBP model, able to mimic a mild, brief LBP episode[6].

Changes in manual pressure pain sensitivity

Pressure-pain sensitivity was enhanced over the lumbar musculature during the painful session. As PPTs over lumbar musculature have previously shown excellent reliability for this time frame (ICCs>0.9)[3,29], and given the observed changes exceed minimum detectable thresholds[3,29], it is

highly likely that this reflects the sequelae of peripheral sensitization following exercise-induced micro-trauma[13].

PPTs were also reduced at the elbow compared to both pain-free sessions, as well as at the shoulder and lower leg compared to Day-7. However, the magnitude of reduction is below previously reported minimum detectable change values for the trapezius and lower leg[69]. These small changes may therefore reflect slight localised peripheral sensitization due to repeated testing, as has been reported previously[48,59,68], rather than a widespread effect of the exercise-induced-LBP. Other mechanisms may be involved though, as PPTs at these sites have previously shown excellent reliability even with short testing intervals of 1-5 days[48,69]. An alternative explanation may be that, due to the large number of muscles recruited as synergists and stabilisers in the chosen exercise, muscle micro-trauma and sensitization may have been produced at additional sites outside the lumbar region.

Changes in cuff pressure pain sensitivity

Cuff pressure-pain is thought to be distinct from handheld pressure-pain, as it stimulates a much larger area and higher proportion of deep-tissue afferents[39]. Consistent with prior work[52], cuff pain thresholds generally increased with each subsequent assessment within each session. This likely reflects a normal habituation process, well-described in the literature for thermal stimuli[4,32], whereby stimulus repetition reduces its salience[20] and hence perceived painfulness, through attentional and other central non-opioid-mediated mechanisms[14,54].

Habituation processes could similarly explain the between-session increases in cuff pain thresholds observed for the dominant leg from Day-0 and Day-2 to Day-7, though it is curious why between-session increases were not consistently observed between days and dominant versus non-dominant limbs. Although speculative, the lack of changes from Day-0 to Day-2 for the dominant leg may be due to competing sensitization and habituation processes[19]. Whereas, the

lack of between-session changes for the non-dominant leg may be because fewer ramped pressure stimuli were applied to this leg (two instead of six), hence salience and attention may have been better maintained.

Temporal summation during exercise-induced-LBP

Cuff pressure-induced TSP did not differ significantly between painful and pain-free sessions, suggesting that pain facilitation was unaffected by the presence of mild LBP. This result differs from prior observations in DOMS-LBP[5] and other muscle pain models[47]; though, this may relate to the modality used and the location of testing. With regard to test modality, previous studies have employed either thermal or pin-prick stimuli to evoke TSP[5,33]. However, these primarily test cutaneous afferents which were assumed to be less relevant to musculoskeletal pain. Deep-tissue afferent stimulation is assumed to evoke TSP through changes in dorsal horn excitability similarly to cutaneous afferents[17], though tissue-specific differences in afferent behaviour may contribute to differences between the present and previous findings[62].

This study intended to assess TSP outside the painful region to better quantify central pain mechanisms and avoid confounding influences from peripheral tissue damage and sensitization. Remote testing of TSP has previously been shown to be altered in acute LBP patients[61], and has been associated with higher pain intensity, increased disability and wider pain distribution in chronic LBP patients[11,49,66]. Hence, lack of facilitated TSP in the present study might suggest exercise-induced-LBP does not produce sufficient pain intensity, duration or distribution to provoke quantifiable sensitization of this mechanism. Alternatively, although the region of assessment (dominant lower leg) is innervated by nerves originating from the same spinal segments (L2-S3) as those innervating the likely sensitized lumbar musculoskeletal structures, lumbar sensitization may not have been accurately quantified by TSP at this remote site.

Pain modulation during exercise-induced-LBP

No specific changes in ramped-CPM effects were observed, suggesting that descending inhibitory function remained intact despite LBP presence. A reduction of CPM during pain was expected on the basis of commonly purported differences between patients with pain and pain-free individuals[34], normalization of CPM following pain-relieving procedures[18,30], and a prior acute experimental-pain study[2]. Further, it was thought that using larger muscle groups would produce more intense and widespread pain than prior experimental investigation[67], having greater potential to impact CPM[12]. However, the pain intensity produced here was clearly lower than chronic LBP populations[12,53], and hypertonic saline-induced pain[2], where impaired CPM has previously been observed. As well, DOMS predominantly produces movement-evoked pain, not pain at rest like that from hypertonic-saline[2]. Hence, the LBP-model used may not have been of sufficient intensity, either in the preceding days, or at the time of testing, to significantly alter CPM. Exercise-induced-LBP duration may also have been too short, though the relevance of pain duration to CPM impairment in LBP has been questioned[1]. Conversely, high variability of CPM responses[27,37,40] or differences in methodology (four test-stimuli instead of conventional two-stimulus paradigm[73]) may have precluded demonstration of a change, or it may be that impaired CPM precedes clinical pain development[58] and may not be as dependent on pain as anticipated.

For SPM, quantified by the change in pain detection threshold between sequential pressure stimuli, there was a main effect of Day, but no specific differences on post-hoc testing. Positive SPM values likely reflect normal habituation processes[4] as discussed above. This measure was of interest, as chronic LBP patients have shown reduced ability to habituate to repeated painful pressure stimuli compared to healthy individuals[50,51], and deficient habituation has been suggested as a possible predictor of chronic pain development[8,51]. The present study instead suggests that SPM may be a more dynamic 'state-like' measure, changing across days and

following fatiguing exercise (Supplementary Material), though future studies are needed to confirm the specific impact of pain presence.

It is unclear why no significant inhibition was produced when using phasic test-stimuli in the phasic-CPM paradigm. However, a recent study assessing CPM with thermal modalities similarly demonstrated reduced inhibitory responses with phasic versus tonic test-stimuli[35]. Here it was argued that phasic paradigms should use more than two test-stimuli, as pain ratings decreased from the first to third stimuli[35], and may decrease further with more stimulations. Therefore, inhibition may have been demonstrable in the phasic-CPM paradigm if more test-stimuli were applied.

Parameters associated to exercise-induced-LBP intensity

An interesting role of baseline TSP in explaining peak exercise-induced-LBP intensity was identified, which, along with the lack of time-related changes in TSP, could suggest a more trait-like role. Consistent with this, prior studies have shown TSP to have predictive value in determining post-operative pain intensity[70]. Still, such findings need more robust validation[57] as prospective studies with assessment prior to LBP development are lacking. So far associations between TSP and both LBP intensity[49] and disability[11] have been observed, and TSP showed a tendency toward facilitation in patients transitioning to persistent LBP[41], but has not yet shown independent prognostic value in this population[33]. Four other factors also contributed non-significantly to the model, indicating that participants with higher lumbar pressure-pain sensitivity, better mood, who performed more exercise repetitions, and were female, generally reported higher peak pain intensities.

Limitations

Although psychophysical measures are considered to show adequate reliability, responses can still vary considerably. For this reason, known influential factors[23] were measured, but it is possible that the selected self-report tools were not able to accurately capture these parameters. Further, it was chosen to avoid using a control group in this study on based on within-subject design and adequate test-retest reliability of the included parameters over this timeframe[3,17,28,48,69], along with the inclusion of two pain-free sessions for comparison, and the large between-subject variability in psychophysical measures challenging control group comparability. Finally, we used a stepwise backward elimination method of multiple regression, which risks overfitting the model to the present sample, hence this interesting relationship requires further validation in other low back pain conditions.

Conclusion

This study has, for the first time, assessed pressure-induced TSP and CPM within-subjects over an episode of experimental LBP. Main findings were that this endogenous experimental low back pain model was not able to significantly alter CPM or TSP, however, baseline TSP was associated with exercise-induced-LBP intensity. Future studies are required to examine the effect of pain presence, with greater intensity and duration, on pro-nociceptive and anti-nociceptive mechanisms.

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Figure Legends:

Figure 1: Experimental protocol showing session order and contents, including: (A) Eccentric exercise task, (B) Handheld pressure algometry sites (marked by 'x'), (C) Temporal Summation of Pain series, (D) Ramped CPM series, and (E) Phasic CPM series. Figures C-E indicate cuff pressure for the dominant (bottom) and non-dominant (top) legs. Dotted lines in figure D represent the change in pain detection threshold from the first stimulus to give sequential pain modulation (SPM, to 2nd ramp), CPM (to 3rd ramp) and Post-CPM (to 4th ramp).

Figure 2: Overlay of individual pain distributions for males (n = 11, left) and females (n = 13, right), with frequency of participants marking each distinct area. The rounded square demarcates the region commonly defined as the 'low back'.

Figure 3: Mean (+SEM) PPTs at each site for Day-0, Day-2, and Day-7. Significant difference from Day-0 (*, $P<0.005$) and Day-7 ($^{\#}$, $P<0.007$) is indicated. ECR = extensor carpi radialis, UT = upper trapezius, L1/L5 = 1st and 5th lumbar segments, GAS = gastrocnemius muscle.

Figure 4: Mean (+SEM) VAS-epochs for temporal summation of pain at Day-0, Day-2 and Day-7. VAS-epochs are based on mean VAS rating of pressure stimulations 2-4 (I), 5-7 (II) and 8-10 (III), after normalisation to the VAS rating of the first stimulus. Significant increase compared to VAS-epoch-I is indicated (*, $P<0.004$).

Figure 5: Mean (+SEM) change in cuff pressure pain detection (cPDT) thresholds from Ramp-1 to each subsequent ramp indicating sequential pain modulation (SPM, difference to Ramp-2), conditioning pain modulation (CPM, difference to Ramp-3) and post-CPM (Post-CPM, difference to Ramp-4) effects at Day-0, Day-2 and Day-7.

Table Legends:

Table 1: Mean (± SD) or median (1^{st}-3^{rd} quartiles) baseline characteristics at Day-0 including exercise performance parameters.

Table 2: Mean (± SD) cuff pressure pain detection (cPDT) and tolerance (cPTT) thresholds for the first ramp in each measurement series for each leg on each day.

Table 3: Summary of multiple linear regression analysis with Day-0 parameters to explain peak low back pain intensity (VAS)