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Recurrent low back pain patients demonstrate facilitated pro-nociceptive mechanisms when in pain, and impaired anti-nociceptive mechanisms with and without pain

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Abstract

Low back pain (LBP) has been inconsistently associated with enhanced pro-nociceptive and impaired anti-nociceptive mechanisms. It remains unknown whether alterations are causal, consequential or coincidental to pain presence. This study investigated pro-nociceptive and anti-nociceptive mechanisms in recurrent LBP (RLBP) patients across painful and pain-free periods, compared to age/gender-matched asymptomatic controls. During a painful episode (Day0) and when pain-free (Day28) thirty RLBP patients were assessed and compared to thirty controls over the same timeframe. Pressure pain thresholds (PPTs) were recorded bilaterally on the arm, back, and leg. Cuff-algometry was used to assess pressure-pain detection (cPDT) and tolerance (cPTT) thresholds on the lower legs, as well as temporal summation of pain (TSP: 10 repeated painful cuff test-stimuli on the dominant leg scored on a visual analogue scale, VAS) and conditioned pain modulation (CPM: cuff pain detection/tolerance threshold on dominant leg, prior versus during painful cuff conditioning on the contralateral leg). RLBP patients displayed reduced PPTs at the arm and back on Day0 compared to Day28 ($P<0.047$) and to controls on Day0 ($P<0.049$). cPDT was reduced and ratings of suprathreshold test-stimuli were increased in RLBP patients on Day0 compared to Day28 ($P<0.02$). TSP-magnitude (increase in VAS scores) was enhanced in RLBP participants on Day0 compared to Day28 ($P=0.027$) and to controls on Day0 ($P=0.039$). CPM-magnitude (increased threshold during conditioning) was lower overall in RLBP participants than controls ($P=0.021$). Enhanced pro-nociceptive mechanisms were observed in RLBP patients. When pain-free, measures returned to similar levels as controls, except for CPM which remained impaired.

Keywords: conditioned pain modulation; temporal summation of pain; pain mechanisms; recurrent low back pain; pressure pain thresholds; longitudinal case-control study

INTRODUCTION

In painful conditions, the assessment of pain mechanisms has received increasing attention as a way to probe the role of pain-related neuroplasticity [4]. As such, many cross-sectional studies have examined differences between pain patients and pain-free individuals, generally showing patients to have pain mechanisms with a

more pro-nociceptive profile [4,28,32,45]. However, in low back pain (LBP) specifically, findings are highly variable [28]. From such cross-sectional studies, there are common reports of local and/or widespread hyperalgesia [9,11,20,48] and other enhanced pro-nociceptive mechanisms (e.g. temporal summation of pain) [8,9,17,61], but conflicting results for anti-nociceptive mechanisms (e.g. conditioned pain modulation) [11,31,39,60].

One possibility is that observed alterations in pro-nociceptive and anti-nociceptive measures are consequential to the presence of ongoing pain and disability, and thus fluctuate with the pain experience, potentially explaining conflicting results. In line, there are varying degrees of evidence to suggest that provoking nociceptive activity and thus experimental pain can impair or facilitate these phenomena (Hoeger Bement, et al. unpublished data) [5] and successfully treating clinical pain by removing effects of peripheral sensitization [21,25] can enhance or restore pro-nociceptive and anti-nociceptive measures. The alternative explanation is that differences in pain mechanisms precede the onset of a pain condition and thus could be used to predict persistent pain development. Consistent with this, there is preliminary evidence to suggest that early changes in pain sensitivity may be associated with persistence of spinal pain [37,51], and that pre-operative [47,64] or pre-injury [7,38] pain sensitivity testing can partly explain variability in post-operative or post-injury pain severity. However, despite these existing indications on the nature of the relationship between pain sensitivity and pain development, confounding factors (i.e. pain presence during assessments, extrinsic provocation of pain, or lack of control comparators) make it difficult to draw firm conclusions on the possibility of pre-existing sensitisation.

For LBP, pain sensitivity measures of most relevance are those assessing deeper musculoskeletal structures implicated in the clinical pain, with pressure modalities suggested to have high discriminative ability [42]. Handheld and cuff pressure algometry are reliable tools used to assess sensitivity to superficial and deep pressure, respectively [6,24,62]. Further, cuff algometry has been shown to be a reliable user-independent method of assessing nociceptive facilitation and inhibition from deep-tissues [10,23,24,29], via temporal summation of pain (TSP) and conditioned pain modulation (CPM) paradigms, respectively.

To explore whether alterations in pain sensitivity may be a consequence of pain presence, this study intended to assess a group of participants with subclinical recurrent low back pain (RLBP) during a painful

episode and when pain-free again one-month later. Further, to assess the magnitude of alteration in pain sensitivity, participants were compared to age and gender matched pain-free individuals. It was hypothesised that participants with RLBP would show hyperalgesia, enhanced TSP and reduced CPM during the painful period compared to the pain-free participants, with maintenance of these alterations during the pain-free period expected.

METHODS

Participants

Participants with recurrent low back pain (RLBP) and healthy age- and gender-matched controls, fluent in English, were recruited from the university setting and wider community, via social media and advertisements in recreational facilities, fitness centres, clinics, and on local notice boards. All participants underwent a verbal information meeting prior to inclusion, and those with current acute lower limb pain, chronic pain, neurological, musculoskeletal, cardiorespiratory, or mental disorders were excluded. Additionally, participants with RLBP underwent a thorough patient history to ensure that they met the recommended criteria [55] with pain between the lower costal margin and gluteal folds for more than 24 hours at the time of recruitment and with more than one LBP episode in the preceding 12-months. Due to the premise of the study, RLBP participants also needed to have current LBP during the first experimental session and be expected to recover to pain-free within 4 weeks, based on individual experience with prior LBP episodes. Healthy pain-free participants must not have had a history of significant LBP (i.e. LBP lasting more than 24 hours, not due to unaccustomed exercise), could not be experiencing pain of any origin during either experimental session, and had to match a RLBP participant in both age (+/-1 year) and gender.

Using G*Power 3.1.9.2 (Kiel University, Germany) a-priori sample size calculations were performed based on prior cuff algometry reliability data. For the main analysis of variance with 2 groups and 2 time-points at an alpha level of 0.05 and 80% power, a minimum of 22 participants per group would be required to show significant within-between interactions of moderate effect size ($f > 0.25$). Due to the risk of drop-outs and non-resolution of pain over the study timeframe, the aim was to recruit and include 30 participants per group.

Prior to participation, all participants were given written and verbal information, and all provided written informed consent. The protocol was approved by the local ethical committee (Den Videnskabsetiske Komité for Region Nordjylland, N-20170034), was pre-registered on ClinicalTrials.gov (NCT03463759) and was conducted in accordance with the Declaration of Helsinki.

Experimental Protocol

Two 2-hour sessions were conducted with each participant, at the same time of day, with an approximate 4-week interval (Fig. 1). If the LBP episode had not resolved by 4-weeks, the second session was rescheduled for 1-week later, to a maximum interval of 6-weeks (pain-free participants' inter-session intervals were matched where possible). At the beginning of each session demographic information was recorded, and participants completed a series of questionnaires on pain history, sleep, mood, menstruation, physical activity and pain-related distress. Participants with RLBP completed additional questionnaires to characterise their LBP intensity, quality and distribution, pain-related disability, and presence of neuropathic features. A short clinical examination was then conducted, including a brief patient history for those with RLBP, and physical examination to ensure painful/pain-free spinal movement as appropriate to group assignment. In each session, pressure-pain thresholds (PPTs) were then recorded three-times bilaterally over the extensor carpi radialis (ECR), upper trapezius (UT), first (L1) and fifth (L5) segments of lumbar erector spinae, and gastrocnemius (GAS) muscles. Finally, cuff algometry was used over the lower legs to record cuff pressure-pain detection (PDT) and tolerance thresholds (PTTs), and assess both TSP and CPM.

----------*Insert Figure 1 approximately here*----------

Demographics, History and Questionnaires

Demographic information collected included age, gender, body-mass index (BMI), and hand and leg dominance. Participants then estimated their sleep duration for the preceding night, and female participants answered questions regarding menstrual regularity and current day of cycle. All participants then completed the International Physical Activity Questionnaire (IPAQ), which estimates weekly energy expenditure based on self-reported daily hours of activity [26]; the Pain Catastrophizing Scale (PCS), which characterises

distressing thoughts related to painful experiences [58]; and rated their current mood on the Faces Scale (1-20, 1 = most positive) [33].

In the first session participants with RLBP answered questions about their usual frequency and duration of painful episodes and pain-free periods, the number of years since their first ever LBP episode, and clinical features of the pain. LBP intensity and unpleasantness was then rated on Visual Analogue Scales (VAS; 0 = no pain/unpleasantness, 10 = worst pain/most unpleasantness sensation imaginable), for current pain (sitting) and maximum pain (since pain onset). Pain area was then drawn on an electronic body chart (Navigate Pain, Aalborg University) for two different conditions: First when the participant imagined sitting comfortably, then when imagining bending/moving/lifting; and the size of pain areas (in pixels) were extracted. Additional questionnaires were also completed including: The Roland-Morris Disability Questionnaire (RMDQ), which scores daily function impacted by the back pain (maximum score = 24, highest disability) [49]; and the Pain-DETECT Questionnaire (PDQ), which characterises the presence of neuropathic pain-like symptoms [15]. Participants were also asked to keep a pain diary (morning and evening VAS LBP intensity rating) for the 4-weeks of the study period, and estimate total episode length at the second session.

Physical Examination

Lumbar flexion and extension range-of-motion (ROM) were measured as the change in distance between the T12 and sacrum, from upright stance to end of range, using a manually anchored tape-measure. The presence of pain on movement and the most aggravating movement direction was recorded. A passive straight leg raise (P-SLR) was performed on each leg to first onset of stretch/pain, with dorsiflexion added as a provocative manoeuvre, and provocation of usual back pain recorded as a positive test.

Pressure-Pain Thresholds

Pressure-pain thresholds (PPTs) were assessed using a rubber-tipped handheld pressure algometer (Somedic, Sweden) with 1 cm^2 contact area. Pressure was increased at a rate of 30 kPa/s until the participant indicated that the pressure became painful by pressing a button, at which point the pressure was recorded. PPTs were

assessed bilaterally over the: ECR (3 cm distal to the lateral epicondyle along a line toward the radial condyle), UT (midway between the C7 spinous process and the acromion), L1 and L5 (3.5 cm lateral to the L1 and L5 spinous processes, over the erector spinae muscle/fascial bulk), and GAS (midway between the popliteal line and calcaneal tuberosity) muscles. Assessments were randomized to start on the right or left side first, three repetitions were performed at each site and averaged across repetitions and sides for analysis, with >2 minutes interval between reassessment of the same site.

Cuff-Pressure Pain Sensitivity

Cuff-pressure pain sensitivity was assessed using a computer-controlled cuff algometry system (Nocitech, Aalborg University, Denmark), paired with two 10-cm wide tourniquet cuffs (VBM Medizintechnik GmbH, Sulz am Neckar, Germany) and an electronic-VAS (eVAS). The eVAS was anchored with "no pain" as 0-cm and "worst pain imaginable" as 10-cm. The cuffs were placed over the widest portion of each lower leg, approximately 5-cm below the tibial tuberosity. Pressure was increased slowly at a rate of 1 kPa/s to a maximum of 100 kPa (device safety limit) on each leg, and participants were instructed to begin moving the eVAS dial upward when the pressure became painful, to keep rating as the pressure-pain increased, then to press the 'stop' button when they could no longer tolerate further increases in pressure-pain. Cuff pain detection threshold (cPDT) was defined as the pressure when the eVAS passed 1-cm, cuff pain tolerance threshold (cPTT) was defined as the pressure immediately prior to pressing the stop button, and the eVAS rating immediately prior to pressing the stop button was extracted (eVAS@cPTT). cPDT, cPTT and eVAS@PTT were assessed on each leg prior to other cuff assessments and averaged across sides for analysis.

Supra-threshold Cuff Stimulation

Three single cuff-pressure stimuli set at cPTT intensity recorded in the same session were performed on the dominant leg. Each time the cuff was inflated at 100 kPa/s to reach cPTT pressure, remained at that pressure for 1-s, and then deflated as fast as possible, with a 10-s break between stimuli. For each stimulus, the

participant was instructed to rate the intensity of pain on the eVAS, then return the dial to zero each time. The maximum eVAS score for each stimulus was extracted and averaged for analysis.

Temporal Summation of Pain

A series of ten 1-s cPTT stimuli were applied, with 1-s in-between (0.5 Hz). Participants were instructed to rate the pain intensity of the first stimulus quickly on the eVAS, then adjust as necessary for subsequent stimuli, if the pain was increasing or decreasing, without returning to zero. eVAS ratings were extracted for each stimulus. Normalized epochs were created by subtracting the first stimulus eVAS rating and then averaging eVAS ratings of the 2^{nd}-4^{th} stimuli (I), 5^{th}-7^{th} stimuli (II), and 8^{th}-10^{th} stimuli (III) for analysis.

Conditioned Pain Modulation

CPM was assessed using cuff algometry, with ramped test-stimuli (as above to assess cPDT and cPTT) applied to the dominant leg, and a conditioning stimulus of tonic cuff pressure applied to the non-dominant leg. Four test stimuli were applied with 30 s rest in-between, with a fifth test stimulus applied approximately 5-minutes after conditioning. Simultaneously with the third stimulus, tonic cuff pressure at 70% cPTT (as assessed immediately prior) was applied and maintained until the end of the third stimulus. Initial pain intensity of the tonic conditioning stimulus was assessed using a verbal Numerical Rating Scale (NRS, 0 = no pain, 10 = worst pain imaginable). cPDT and cPTT values were extracted for each test stimulus. The change in cPDT and cPTT from the first ramp to the second, (2^{nd} minus 1^{st}, sequential unconditioned), third (3^{rd} minus 1^{st}, during conditioning), fourth (4^{th} minus 1^{st}, immediately post conditioning) and fifth (5^{th} minus 1^{st}, 5 min post conditioning) ramps were calculated for analysis (named CPM-effect).

Statistics

All data were analysed using SPSS (v24.0; IBM, Armonk, NY). 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. Normality was assessed within-groups by the Shapiro-Wilks test and parametric or non-parametric analysis was used as appropriate. Differences in questionnaire responses, clinical features and

methodological factors were compared using independent samples t-tests or Mann-Whitney U-tests (between-group: RLBP or control), paired t-tests or Wilcoxon signed ranks tests (between-session: Day0 or Day28), or two-way ANOVAs (Group: RLBP or control; and Session: Day0 or Day28) as appropriate.

For pain sensitivity outcomes (PPT, cPDT, cPTT and eVAS@cPTT, eVAS scores to supra-threshold pressure stimuli, TSP and CPM), a two-way mixed ANOVA (with additional repeated factors when multiple sites, thresholds or stimuli were assessed within a session) was performed, with the between-subjects factor *Group* (RLBP or Control), and within-subjects factors *Session* (Day0 or Day28) and *Site* (ECR, UT, L1, L5, GAS; or dominant/non-dominant), *Stimulus* (TSP: three normalised eVAS-epochs, CPM: one unconditioned and three conditioned stimuli normalized by subtraction to the first stimulus) and/or *Threshold* (cPDT or cPTT). For CPM, an additional analysis of non-normalized data (i.e. five raw cPDTs and cPTTs) was undertaken within-groups, with planned contrasts conducted following these analyses between the first threshold and each subsequent threshold, to confirm the presence of inhibition (supplementary material, available at http://links.lww.com/PAIN/A862). Intraclass correlation coefficients (ICC(3, k)) were also performed on repeated tests (PPT, cPDT, cPTT, eVAS@cPTT, and eVAS scores to supra-threshold pressure stimuli) within-session for each group, and repeated tests (PPT, cPDT, cPTT, eVAS@cPTT, eVAS scores to supra-threshold pressure stimuli, TSP and CPM) between-sessions for the control group, based on a two-way mixed model with consistency definition, and are included in the supplementary material (available at http://links.lww.com/PAIN/A862) . Exploratory Pearson's or Spearman's correlational analysis was undertaken to identify potential explanatory relationships between demographic (age, gender, BMI), questionnaire (mood, sleep, IPAQ, PCS, RMDQ, Pain-DETECT), or clinical (flexion, extension, pain intensity, unpleasantness, area, RLBP duration, current episode duration) data, and psychophysical testing (PPT, cPDT, cPTT, eVAS on suprathreshold stimuli, TSP and CPM of cPDT and cPTT) within each session. Post-hoc pairwise comparisons or planned contrasts were conducted as indicated with Bonferroni correction. Significance was accepted at $P<0.05$.

RESULTS

Participant Characteristics

A total of 182 participants were screened to include 30 RLBP patients (27.3 ±5.4 years; 16 males) and 30 matched controls in the experiment, though 1 RLBP patient was excluded after the first session due to the development of an unrelated medical condition (Table 1; and Supplementary Fig. 1, available at http://links.lww.com/PAIN/A862). All RLBP patients reported pain in the lower back region during the first session. By the second session after 28 days, the majority of patients were completely pain-free (n = 22), with the remainder either reporting only discomfort (n = 3, both pain intensity and unpleasantness VAS<1/10) or no expectation of further recovery within 2 weeks (n = 3). As the aim of the study was to compare painful and pain-free states among RLBP patients and to healthy controls, participants still reporting pain in the second session were excluded from further analysis (n = 26 included). None of the control participants reported pain during either session (n = 30 included). Mood scores were generally positive and sleep durations were within recommendations [27], with no differences observed between sessions or groups. Pain catastrophizing was higher in RLBP patients on Day0 (when in pain) compared to Day28 ($F_{1,54}$=9.288, P<0.004, η^2=0.147; Post-hoc: P<0.001) but was not different between groups during either session (P>0.28, η^2<0.022). Participants generally had greater flexion ($F_{1,54}$=11.377, P<0.002, η^2=0.174) and extension ($F_{1,54}$=7.045, P<0.011, η^2=0.115) range in the second session, and RLBP participants had less flexion range than controls ($F_{1,54}$=7.206, P<0.010, η^2=0.118). Leg dominance (used for cuff measurements) was similar between groups (RLBP: 24 Right, 2 Left; Controls: 23 Right, 7 Left).

Recurrent Low Back Pain Features

Patients reported pain of mild intensity and moderate unpleasantness on Day0 (Table 2), primarily in the lower back and occasionally extending toward the thoracic region or lower limbs (Fig. 2). Pain areas (total pixels coloured) were notably larger when imagining moving than when sitting comfortably at rest on Day0 (t_{25}=-5.09, P<0.001, d=0.48, Table 2, Fig. 2). For the majority of patients, their pain was unlikely (n = 17) or uncertain (n = 9) to be neuropathic in origin, on the basis of PainDETECT scores. In this sample, repeated pain episodes of roughly 2 weeks had been present for a number of years, notably since adolescence (<20 years) in over half the sample. Patients commonly reported their pain to be aggravated by prolonged static

positioning and lumbar flexion or extension, they reported mild disability as a result, and near half had consulted a physiotherapist or chiropractor in the past for their pain.

----------*Insert Table 2 approximately here*----------

----------*Insert Figure 2 approximately here*----------

Pressure Pain Sensitivity

Three-way ANOVA revealed a significant *Group*Session*Site* interaction ($F_{3.0,160.5}$=4.87, P<0.003, η^2=0.083, Fig. 3). On post-hoc testing, PPTs were found to be higher on Day28 than Day0 at the ECR (P=0.047, η^2=0.071), UT (P=0.007, η^2=0.128), L1 (P=0.003, η^2=0.149) and L5 (P<0.001, η^2=0.293) sites, though not significantly at the GAS (P=0.054, η^2<0.068) site, in RLBP patients, but no differences were found between sessions for controls (all P>0.05, η^2<0.067). PPTs were also higher in Controls than RLBP patients at the ECR (P=0.024, η^2=0.091), UT (P=0.049, η^2=0.070), L1 (P=0.014, η^2=0.106) and L5 (P=0.033, η^2=0.082) sites on Day0, but no between-group differences were observed at Day28 (P>0.25, η^2<0.003).

----------*Insert Figure 3 approximately here*----------

Cuff Pain Sensitivity

Three-way ANOVA revealed a *Group*Session*Threshold* interaction ($F_{1,54}$=4.381, P<0.041, η^2=0.075, Table 3), revealing that cPDT was higher for the RLBP-group on Day28 than Day0 (P=0.020, η^2=0.096). No differences between-sessions were observed for cPDT or cPTT for the control group (P>0.35, η^2<0.017), nor between-groups in either session (P>0.39, η^2<0.015). Two-way ANOVA of eVAS@cPTT ratings revealed no main effects or interactions of sessions or groups (P>0.42, η^2<0.013).

Suprathreshold Pressure Pain Ratings

Two-way ANOVA of suprathreshold cuff pressure stimuli eVAS ratings revealed a *Group*Session* interaction ($F_{1,54}$=4.828, P<0.032, η^2=0.082, Table 3), with eVAS ratings being higher on Day0 than Day28

for RLBP patients (P=0.001, η^2=0.200), but no differences observed between-sessions for controls (P>0.47, η^2<0.011) nor between-groups in either session (P>0.19, η^2<0.032).

----------*Insert Table 3 approximately here*----------

Temporal Summation of Pain

Three-way ANOVA of normalised VAS-epochs revealed a main effect of *Epoch* ($F_{1.2,66.2}$=90.29, P<0.001, η^2=0.626, Fig. 4) and a *Group*Session* interaction ($F_{1,54}$=4.35, P=0.042, η^2=0.074). Post-hoc testing showed that each epoch was higher than the previous (I<II<III, P<0.001, η^2>0.652), demonstrating facilitation was observed during repeated stimulation. In addition, this facilitation was greater on Day0 than Day28 for RLBP patients (P=0.027, η^2=0.087) and greater than Controls on Day0 (P=0.039, η^2=0.077), but no differences were seen between-sessions in Controls (P>0.54, η^2<0.008) or between-groups on Day28 (P>0.67, η^2<0.004).

----------*Insert Figure 4 approximately here*----------

Conditioned Pain Modulation

Four-way ANOVA of CPM-effects (change from Ramp 1 to Ramps 2-5 in cPDT and cPTT, respectively) revealed a main effect of *Group* ($F_{1,54}$=5.62, P=0.021, η^2=0.094, Fig. 5), with Controls demonstrating higher CPM-effects overall than RLBP patients (P=0.021, η^2=0.094). In addition, a *Stimulus*Threshold* interaction ($F_{2.4,133.6}$=14.17, P<0.001, η^2=0.208) showed that immediately post conditioning (Stimulus 4) there was higher modulation of cPDT than cPTT (P=0.012, η^2=0.110), whereas at 5 min post conditioning (Stimulus 5) there was higher modulation of cPTT than cPDT (P=0.002, η^2=0.241). Moreover, for cPDT, modulation was higher during conditioning (3rd Ramp, P=0.039, d=0.59) and immediately post-conditioning (4th Ramp, P=0.002, d=0.83), and lower at 5 min post (5th Ramp, P=0.011, d=0.60), than on the second ramp, meaning that there was generally immediate inhibition of cPDT due to conditioning. Whereas for cPTT, CPM magnitude was higher during conditioning (3rd Ramp, P<0.001, d=1.46), immediately post-conditioning (4th Ramp, P=0.002, d=0.75) and at 5 min post (5th Ramp, P=0.001, d=0.90) than on the second ramp, suggesting

significant and prolonged inhibition of cPTT overall. No differences were seen between sessions (P>0.60, η^2<0.006).

----------*Insert Figure 5 approximately here*----------

Conditioning pressure during CPM was higher on Day28 (36.2±13.7 kPa) than Day0 (34.1±12.5 kPa; $F_{1,54}$=4.96, P=0.030, η^2=0.084), but not significantly different between groups (P>0.49, η^2<0.010). The NRS scores of conditioning pain were not different between groups or sessions (4.3±1.6 cm, $F_{1,54}$<1.34, P>0.25, η^2<0.024).

All data were normally distributed for the control group, but 4 outliers (>2SD from mean across measures) were noted in the RLBP group for some of the cPDT CPM effects. Removing them from the analysis increased the magnitude of overall group difference in CPM effect, suggesting that they were not driving the effects observed, hence to be conservative, these were retained in the analysis.

Exploratory Correlational Analyses

Consistent significant correlations were identified between male gender and PPTs outside of the lumbar region (R>0.348, P<0.01), cPDT (R>0.282, P<0.05) and cPTT (R>0.522, P<0.001) across both sessions. Pain area, both at rest and when moving, was also related to cPTT (R>0.636, P<0.001) among patients on Day0. All other correlations were insignificant and none of the measured demographic, questionnaire or clinical outcomes showed significant association to variation in TSP or CPM.

DISCUSSION

This is the first study to assess nociceptive facilitation and inhibition in RLBP patients over painful and non-painful periods. As hypothesised, patients in pain demonstrated reduced PPTs over both local and some distant sites, increased perceived painfulness of supra-threshold stimuli and enhanced TSP compared to controls. Contrary to the hypothesis, however, these alterations were not maintained when RLBP patients

were pain-free, with PPTs, supra-threshold ratings and TSP not different to controls on Day28. Overall, RLBP patients displayed weaker CPM-effects than controls across both sessions.

Participant Characteristics and Clinical Features

In this study, a subclinical RLBP population was investigated. No participants were actively seeking care, and all expected to recover within the study timeframe. This contrasts the inclusion criteria of many previous studies, where lower limits are often set for pain and disability scores [1,55], and patients are expected to be sufficiently impacted by their pain to contact a health practitioner. This subclinical sample was of particular interest to gain insight into alterations and fluctuations in pain mechanistic measures prior to individuals becoming "pain patients", as observed changes may be less influenced by comorbid ramifications, and more useful in identifying early intervention targets. Despite their subclinical status, the history and symptom presentation of these participants mirrored usual non-specific LBP complaints[13].

Hyperalgesia to Pressure

Participants with RLBP demonstrated hyperalgesia both locally at the lower back and at two distant sites both compared to themselves when pain-free, and to controls. Widespread hyperalgesia is purported to be a sign of facilitated central mechanisms[4] and has been demonstrated previously in patients with acute[30] and chronic[46] LBP. However, the present findings suggest that this may be a state rather than trait feature consequential to or maintained by ongoing nociception and/or pain, at least in patients with recurrent LBP, given it normalised by the second session. This is in line with studies showing normalisation of widespread hyperalgesia after temporary[57] or permanent[2,25] removal of peripheral nociceptive input, and with a previous study showing widespread hyperalgesia in the presence of experimental exercise-evoked LBP[38].

During the painful episode, participants with RLBP also demonstrated lower cuff pain detection thresholds than when pain-free. This provides further support to PPT findings, by showing similar pressure hyperalgesia during pain compared to when pain-free, with a user-independent method to minimise bias from lack of blinding. However, these thresholds did not differ from controls during either session. Cuff pain detection values in the present control group appear lower than those reported previously in larger pain-

free samples using the same methodology[24] though, suggesting the lack of group difference may be due to lower than normal control thresholds.

Temporal Summation of Pain

Temporal summation of pain was observed in each group and session across repeated stimuli, however the magnitude of this temporal increase in VAS scores was higher in participants with RLBP during their painful episode, than both themselves when pain-free and controls. In addition, it was clear that the RLBP group generally rated supra-threshold stimuli to be more painful in the first session than the second. Facilitated temporal summation is commonly observed in patients with current acute [56,61] and chronic [8,17,59] LBP, though previously effects in pain-free periods have not been well explored. A single pilot study[37] following acute LBP patients over 4 months did, however, show tendencies somewhat in line with the present work, whereby those who developed persistent back pain showed trends toward higher facilitation (wind-up ratio) at follow-up than those who had recovered. As well, it is well-known that experimentally provoked muscle pain can facilitate TSP locally over the affected muscle, compared to pain-free states[43,44].

Taken together, these findings are consistent with the original concept of wind-up [63], suggesting that, during a painful episode, ongoing peripheral nociceptive input drives enhanced spinal excitability, thus shifting the balance between inhibition and facilitation toward being more pro-nociceptive. However, other factors may also contribute, such as heightened vigilance toward painful sensations (supported by the higher PCS scores), such that all stimuli are generally perceived to be more salient and threatening when in clinical pain. This would fit with previous work in acute LBP, showing changes in pain-related fear and avoidance generally corresponding to exacerbation or reduction of pain[53]. Nonetheless, TSP is a relative measure, meaning heightened vigilance should have less influence here than on absolute or threshold measures.

Conditioned Pain Modulation

Larger overall CPM-effects were observed in controls than RLBP patients. Such findings of only weak overall effects are unsurprising in the context of the present literature, where reports of CPM efficacy in

LBP patients are highly variable[50]. Nevertheless, the small magnitude of difference here may be due to the relatively localised, low-intensity, low-disability pain that patients were experiencing. No relation between CPM and pain at the time of testing was observed here. However, prior studies have shown patients with more frequent, severe[22], and widespread[18] LBP to have greater CPM impairment. It is also important to note that this impairment in CPM-effect seemed to persist even in the absence of a painful episode. This could suggest that this mechanism may be impaired in these individuals even prior to the onset of pain. Alternatively, it could indicate a progressive degradation in CPM with continued or repeated painful experiences, which would be consistent with correlations between pain duration and CPM impairment demonstrated in other painful conditions[3].

In the additional analysis (supplementary material, available at http://links.lww.com/PAIN/A862), for controls, there was a clear effect of conditioning on test stimuli, with both cuff pain detection and tolerance thresholds increased during and following conditioning. On the contrary, RLBP participants demonstrated significant inhibition only for pain tolerance during conditioning, but not at any point for pain detection thresholds. This is in line with previous work in acute LBP[39] and migraine sufferers[40], where CPM-effects have been present, but for shorter periods than controls. As well, the contrast between inhibitory effects on tolerance, but not detection thresholds in RLBP patients is interesting. Pain detection may be more reflective of sensory factors and nociception, whereas pain tolerance has long been acknowledged to be more influenced by cognitive factors[16], and thus may be more amenable to inhibition via other supraspinal mechanisms.

Implications of Findings

Prior work has indicated that RLBP patients may show alterations in postural control[34] and muscle structure[12], even in periods of recovery. However, the present findings indicate, somewhat on the contrary, that once the pain episode subsides measures of pro-nociceptive pressure-pain sensitivity return to levels comparable with pain-free individuals. This may be due to the mild RLBP condition in the present sample, such that over longer durations with higher frequencies or intensities of pain episodes, participants may progress toward a more permanent state of sensitisation. Alternatively, the present work could raise

doubt over the significance of alterations in pro-nociceptive mechanisms observed in cross-sectional work, as these differences may be consequential to the presence of ongoing nociception and pain. In line, these findings could provide some explanation for variation among prior studies, given that the presence of 'pain flares' is not always considered in chronic LBP studies, despite recognition as a fluctuating condition[35,55].

Notably, CPM was one variable in which a normalisation between sessions was not demonstrable, and only overall differences from controls were observed. Although interpretation of this impairment is limited by the weak effects observed and high measure variability, this suggests impaired CPM may be an important contributor to LBP recurrence. Further, as CPM is known to be impaired by poor sleep[54], aberrant physical activity[14,41], and increased psychosocial stress[19]; factors also associated to LBP recurrence or persistence[30,52], it is conceivable that a constellation of symptoms on an already impaired pain inhibitory system may be enough to ignite a pain episode without obvious provocation. Causal relationships are, however, impossible to determine from the present work and thus this requires further investigation.

Limitations

This study has several limitations requiring consideration. Firstly, the order of sessions could not be randomized due to the unpredictable nature of recurrent LBP combined with the decreasing reliability of psychophysical measures over longer intervals[36], however, a control group was used to mitigate the influence of time and order on observed effects. Secondly, the study was sufficiently powered to detect moderate effect sizes, though may have been less powered to detect small differences. The sample, albeit purposely recruited this way, were young and well-functioning despite pain, limiting generalisability to older and more severe populations. Finally, the assessor was not blinded to group, however, standardised instructions were given for all tests, care was taken to ensure consistent methodology, and several main outcomes were measured with user-independent equipment.

Conclusion

This study reports, for the first time, local and distant hyperalgesia to handheld and cuff-induced pressure, as well as facilitated pro-nociceptive mechanisms, in participants with mild RLBP currently experiencing a painful episode, both compared to themselves when pain-free and compared to age and gender-matched controls. CPM, as an anti-nociceptive mechanism, was generally lower in RLBP patients across sessions. Taken together, these findings indicate that enhanced pro-nociceptive measures in RLBP patients may be primarily consequential to the presence of pain, whereas impaired CPM may persist even in the absence of pain.

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Supplemental video content

A video abstract accompanying this article can be found at http://links.lww.com/PAIN/A863.

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Table & Figure Headings

Figure 1: *Illustration of study design showing procedure order, testing locations and parameters for psychophysical assessments. IPAQ = International Physical Activity Questionnaire, PCS = Pain Catastrophizing Scale, VAS = Visual Analogue Scale, RMDQ = Roland-Morris Disability Questionnaire, SLR = Straight Leg Raise, PPT = pressure pain threshold, ECR = extensor carpi radialis, UT = upper trapezius, L1/5 = 1st and 5th lumbar segments over lumbar erector spinae, GAS = gastrocnemius, STR = supra-threshold rating, TSP = temporal summation of pain, CPM = conditioned pain modulation, PDT = pain detection threshold, and PTT = pain tolerance threshold.*

Figure 2: *Pain distributions for male and female participants with low back pain when sitting (Rest) and when performing most provocative movement (Move) on Day0 and Day28 (includes those reporting discomfort VAS<1/10). The number of participants indicating pain areas are included (n).*

Figure 3: *Mean (+SEM) pressure pain thresholds for participants with RLBP (black) and control participants (grey), during each session (Day0, full colour, and Day28, striped), over the extensor carpi radialis (ECR), upper trapezius (UT), first (L1) and fifth (L5) segments of lumbar erector spinae, and gastrocnemius (GAS) muscles. Significant between-session differences within the RLBP group (*, P<0.047) and between-group differences within the first session (#, P<0.049) indicated.*

Figure 4: *Mean (+SEM) eVAS pain intensity ratings in normalised-epochs of stimulations 2-4 (I), 5-7 (II), and 8-10 (III), for assessment of temporal pain summation in participants with RLBP (black) and control participants (grey), in each session (Day0, full colour, and Day28, striped). Significant between-session difference within the RLBP group (*, P=0.027) and between-group difference within the first session (#, P=0.039) indicated.*

Figure 5: *Mean (+SEM) change in cuff pain detection (cPDT) and tolerance (cPTT) thresholds from 1st test stimulus to the 2nd unconditioned test stimulus (UC) and for conditioned test stimuli (3rd during, 4th immediately post, and 5th 5 min post ramps) in the CPM paradigm for participants with RLBP (black) and control participants (grey). Significant overall between-group difference (#, P=0.021) indicated, stimulus-threshold interaction effects not shown.*

Table 1: *Participant characteristics*

	Participants with RLBP (n = 26)		**Pain-Free Participants (n = 30)**		**P-value**	**Excluded (n = 3)**
	Painful Session (Day0)	***Pain-free Session (Day28)***	***Session 1 (Day0)***	***Session 2 (Day28)***		
Age (years)	26.4 ±5.0		27.3 ±5.5		>0.48	34.7 ±2.5
Gender (Male : Female)	14:13		16:14		-	2:1
Body Mass Index (kg/m^2)$^{\#}$	24.0 ±4.8		23.2 ±2.8		>0.87	27.8 ±5.6
Time between sessions (days)$^{\#}$	31.9 ±8.0		30.5 ±4.1		>0.55	34.7 ±7.6
Mood Now (/20)$^{\#}$	4 (3.75)	3.5 (3.75)	3 (2.75)	4 (4)	All >0.15	-
Mood Past Week (/20)$^{\#}$	3.5 (4.75)	3.5 (4.75)	4 (4)	3 (5)	All >0.30	-
Sleep (Hours)$^{\#}$	7.5 ±1.2	7.3 ±1.6	7.3 ±0.9	6.9 ±0.8	All >0.07	-
Activity (MET-mins/week)$^{\#}$	5996.1 ±5493.6	4097.6 ±5095.3	4147.6 ±3620.0	3901.5 ±3428.6	All >0.14	-
Daily sitting (mins)	360.2 ±207.3	405.4 ±224.5	459.0 ±182.6	451.7 ±159.9	All >0.24	-
PCS (/52)	15.5 ±9.0*	11.8 ±8.0	12.2 ±8.6	13.5 ±9.6	<0.001 RLBP Only	-
SLR – Passive (% Positive, R/L)	31% / 27%	0% / 0%	0% / 0%	0% / 0%	-	-
Flexion (cm)	12.3 ±0.7*¤	14.2 ±0.6¤	14.7 ±0.6*	15.8 ±0.5	P<0.010	-
Extension (cm)	6.7 ±0.4*	7.5 ±0.5	7.2 ±0.4*	7.8 ±0.4	P<0.011	-

Percentage of participants, mean ± SD or median (IQR) values are indicated. Note: PCS = Pain Catastrophizing Scale, SLR = straight leg raise, R/L = right / left, $^{\#}$denotes non-parametric analysis. Significant between-session difference (*, P<0.006) and significant between-group difference ($^{¤}$, P<0.010).

Table 2: *Clinical characteristics of patients with recurrent low back pain*

	Painful Session (n = 26)	**Pain-free Session (n = 26)**
VAS Pain Intensity (cm)		
Current (during session)	2.7 ±1.5	0.1 ±0.2
Maximum (across present/most recent episode)	5.8 ±2.2	5.3 ±2.3
VAS Pain Unpleasantness (cm)		
Current (during session)	4.0 ±1.8	0.1 ±0.2
Maximum (across present/most recent episode)	6.6 ±2.0	5.4 ±2.3
Pain Area (pixels)		
Posterior view at rest	6034.2 ±5613.3	-
Posterior view when moving	10650.8 ±7986.4*	-
Pain Duration Characteristics		-
Age at initial LBP onset (years)	19.7 ±5.4	-
Frequency of episodes (%, <5/5-10/>10/year)	42 / 27 / 31	-
Approx. pain episode length (days)	Usual: 13.8 ±19.8	Current: 12.3 ±15.9
Approx. pain-free period duration (days)	Usual: 79.7 ±78.5	-
Aggravating / Easing Factors (most common)		
Aggravated by prolonged sitting (%(N))	73 (19)	-
Aggravated by prolonged standing (%(N))	50 (13)	-
Flexion most provocative mvmt (%(N))	23 (6)	-
Extension most provocative mvmt (%(N))	58 (15)	-
Eased by rest (%(N))	100 (26)	-
Eased by exercise (%(N))	46 (12)	-
Past Care-seeking / Trialled Treatments for Lower Back		
General Practitioner (%(N))	23 (6)	-
Imaging (%(N))	19 (5)	-
Surgery (%(N))	0 (0)	-
Physiotherapy / Chiropractor (%(N))	46 (12)	-
Massage (%(N))	12 (3)	-
Medication (%(N))	23 (6)	-
Roland-Morris Disability Questionnaire (/24)	3.5 (3.5)	0 (0-0)
Pain-DETECT (/31)	10.5 (9)	0 (0-0)
Uncertain neuropathic component (>12)	9	-
Likely neuropathic component (≥19)	2	-

Table 3: *Mean (±SD) cuff pain detection and tolerance thresholds, and tolerance and suprathreshold ratings*

	Participants with RLBP		**Pain-Free Participants**	
	Painful Session (Day0)	***Pain-free Session (Day28)***	***Session 1 (Day0)***	***Session 2 (Day28)***
cPDT (kPa)	21.3±10.5	25.5±12.1*	22.0±8.8	22.7±12.3
cPTT (kPa)	47.0±19.5	47.5±19.9	48.4±14.7	50.1±17.0
eVAS@cPTT (cm)	8.2±2.0	7.9±2.5	8.7±1.8	8.7±1.6
Supra-threshold Ratings (eVAS, cm)	5.5±1.5	4.1±1.7*	4.8±2.1	4.6±2.2

cPDT = cuff pain detection threshold, cPTT = cuff pain tolerance threshold, eVAS@cPTT = eVAS rating at cPTT, eVAS = electronic Visual Analogue Scale, RLBP = recurrent low back pain. Significant difference between-sessions within RLBP group (*, P<0.02) indicated.

Screening:
Appropriate for inclusion

Day-0:
Information, consent, demographics
Questionnaires: Pain history, sleep, menstruation, mood, IPAQ, PCS
Pain/Disability Questionnaires (patients only): VAS, body chart, RMDQ, Pain-DETECT
Physical Exam: Symptoms, movement, SLR
PPT: (A) 3 x 30kPa/s at ECR, UT, L1, L5, GAS
Cuff PDT/PTT: (B) 1kPa/s to max. 100kPa
Cuff STR/TSP: (C) 3 x 1:10, (D) 10 x 1:1 (@PTT)
Cuff CPM: (E) 5 ramps, 3rd conditioned (@70% PTT)

Day-28:
Collect pain diary, reconfirm consent
Questionnaires: Pain history, sleep, menstruation, mood, IPAQ, PCS
Pain/Disability Questionnaires (patients only): VAS, body chart, RMDQ, Pain-DETECT
Physical Exam: Symptoms, movement, SLR
PPT: (A) 3 x 30kPa/s at ECR, UT, L1, L5, GAS
Cuff PDT/PTT: (B) 1kPa/s to max. 100kPa
Cuff STR/TSP: (C) 3 x 1:10, (D) 10 x 1:1 (@PTT)
Cuff CPM: (E) 5 ramps, 3rd conditioned (@70% PTT)