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Positive affect and distraction enhance while negative affect impairs pain modulation in recurrent low back pain patients and matched controls

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Abstract

Pathophysiological causes of low back pain (LBP) remain generally unclear, so focus has shifted to psychosocial features and central pain processing. Effects of attentional and affective manipulation on conditioned pain modulation (CPM) and tonic pain perception were examined in thirty recurrent LBP patients in two sessions, one with and one without

clinical pain, and compared to healthy participants. Phasic cuff pressure on one leg, scored on a numerical rating scale (NRS), was used for test-stimuli (TS) and contralateral tonic cuff pain rated on an electronic visual analogue scale (eVAS) was the conditioning-stimulus (CS). TS were assessed before and during: 1) control with no manipulation/CS, 2) three attentional manipulations (Flanker with/without CS or CS-Only), and 3) three affective manipulations (positive, neutral, negative pictures) with CS. Greater inhibition of TS-NRS scores was observed in CS-only (P=0.028), combined CS&attention (P=0.026), and CS&Positive (P=0.006) than Control paradigms, and greater in CS&Positive (P=0.019) than CS&Negative paradigms. eVAS scores of CS pain increased throughout all paradigms with CS (P<0.05), except the CS&Positive paradigm, and greater facilitation was observed in the CS-Only paradigm than all others (P<0.02) and lower facilitation was additionally observed in the CS&Positive paradigm compared to CS&Attention and CS&Negative paradigms (P<0.01). Flanker effects and interruptive effects of CS pain on attention were observed consistent with prior findings, and affective manipulation produced less shift in valence among people with RLBP than controls (P<0.05). Attention and positive affect with CS pain evoked CPM, and all attentional/affective tasks, especially positive affect, reduced facilitation of CS pain.

Keywords: low back pain; Conditioned pain modulation; tonic pain facilitation; affective manipulation; attention task performance

INTRODUCTION

Low back pain (LBP) is the leading cause of global years lived with disability[19]. However, the pathophysiological cause of LBP is often unclear, hence increasing focus has been on psychosocial factors and alterations in central nervous system sensory processing as possible

contributors to pain persistence[16,50]. While such factors have been investigated independently in various formats, the interaction between attentional or affective manipulations and pain processing is unclear. Moreover, the competing influence of current clinical pain on these interactions remains largely unknown.

It is well established that shifting attentional demands and changing affective states can alter pain perception in experimental contexts[59]. Typically, attentional tasks requiring sufficient cognitive engagement to distract an individual from pain will reduce perceived stimulus intensity, whereas focus toward the stimulus will increase the pain perceived[40]. With regard to affect, tasks eliciting positive affect will result in reduced pain perception, whereas negative affect may enhance pain perception[35]. In the past two decades, research has primarily focussed on attentional and affective effects on static pain perception of either brief stimuli or pain threshold measures. However, more interesting is the effect that attention and affect may have on dynamic pain inhibitory and facilitatory pain mechanisms.

Recent work has shown that simply directing attention preferentially toward the test or conditioning stimulus can result in differing magnitudes of descending inhibitory control, as assessed by conditioned pain modulation (CPM)[27]. Similarly, distracting participants by directing attention toward a simple cognitive task has shown to provide an additional inhibitory effect to CPM paradigms alone[39]. Regarding affective manipulation, these interactions remain largely unexplored, however, there are clear influences of negative or positive affect induction on pain thresholds, perception and cortical regions associated with pain modulation[7,31,45]. Naturally, such interaction is likely bidirectional, and both experimental and clinical pain states may impact attentional performance and success of affect induction. In line, cross-sectional differences have been observed with regard to attentional task performance[4] and affect[5] between chronic pain populations and pain-free

individuals. It is however unclear how the presence of clinical pain will influence the interaction between attention/affect and pain mechanisms.

This experiment aimed to examine the impact of attentional and affective manipulation on pain ratings of pressure stimuli among recurrent LBP (RLBP) patients with and without a current clinical episode, as well as in age and sex-matched pain-free individuals. It was hypothesised that conditions involving positive affect or distraction from pain would be beneficial to inhibitory function during CPM, hence reducing conditioning and post-conditioning test stimulus ratings during these tasks, whereas negative affect would have a detrimental impact and increase conditioning and post-conditioning test stimulus pain ratings. LBP patients were expected to show increased pain ratings during all tasks, and it was hypothesised that they would confer less benefit (impaired inhibition) from positive affect and distraction compared to healthy individuals. In supplementary analysis, it was expected that both experimental and clinical pain would impair attentional performance (reduce accuracy and increase reaction time) and clinical pain would reduce the efficacy of affective manipulations (less deviation in valence from neutral).

METHODS

Participants

Participants were recruited from the university and wider community via social media, flyers on local notice boards, at recreational facilities, and through physiotherapy and acupuncture clinics for a prior study throughout 2018 [32]. People with current acute lower limb pain, chronic pain conditions, and neurological, musculoskeletal, cardiorespiratory, or mental disorders were excluded. Participants then had to meet one of the following conditions: 1) currently experiencing an episode of recurrent low back pain lasting greater than 24 hours,

with expectation of resolution in less than 1-month and more than one prior episode in the preceding 12-months, or 2) no significant history of low back pain, and no current acute or recurrent pain conditions. Sample size was based on previous cuff algometry reliability data and a priori calculations were performed using G*Power 3.1.9.2 (Kiel University, Germany), for the main analysis of variance (ANOVA) with 2 groups and 2 repetitions at an alpha level of 0.05 and 80% power, giving a minimum of 22 participants per group to show significant within-between interactions of moderate effect size (f=0.25). Prior to participation, all participants were given written and verbal explanation of the study, and all provided written informed consent. The protocol was approved by the local ethical committee (N-20170034), was pre-registered on ClinicalTrials.gov (NCT03463759) and was conducted in accordance with the Declaration of Helsinki II.

Experimental Protocol

The experiment consisted of two 2-hour sessions with each participant, conducted at the same time of day, and separated by approximately 28-days (extended by up to 14 days if pain had not resolved). This was in an attempt to test participants with RLBP during an episode of back pain, and then once they were pain-free again.

In each session, all participants answered questions pertaining to demographics, pain, sleep and menstruation, then filled out the State and Trait Anxiety Inventory [55] (STAI, Chronbach's alpha: State = 0.89, Trait = 0.92), and Positive and Negative Affective Schedule [60] (PANAS, Chronbach's alpha: Positive = 0.91, Negative = 0.82). LBP participants further rated their average pain intensity and unpleasantness during this episode on a Visual Analogue Scale (VAS; 0 cm = no pain at all/not unpleasant at all, to 10 cm = worst pain imaginable /most unpleasant sensation imaginable), described their current pain using the McGill 72-word table [36], and completed the STarT Back Screening Questionnaire [18]

(SBQ, Cronbach's alpha: 0.71). Participants then underwent a physical examination and other sensory assessments (e.g. pressure pain thresholds and temporal summation of pain) for which data can be seen elsewhere[32]. Participants were positioned in a comfortable reclined sitting position, with a computer screen, keypad and electronic VAS (eVAS) placed on a height adjustable table over their hips (Fig. 1). Cuff pressure pain thresholds were assessed over the lower legs, to set the test and conditioning stimulus intensities. Three different attentional modulation conditions were then applied in a randomized order, followed by three different affective manipulations in randomized order. Before and following all conditions, a series of test stimuli were applied alone to assess for sensitisation across the session.

Cuff Algometry

A computerized cuff-algometry system (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 apply pressure stimuli. The cuffs were placed over the most prominent portion of the calf, with the top border sitting approximately 5-cm distal to the tibial tuberosity. Cuff pain tolerance (cPTT) thresholds were initially assessed on the non-dominant, then dominant leg, via a ramped 1 kPa/s inflation to a maximum of 100 kPa (safety limit). Participants rated continuously on the eVAS as pressure-pain increased, with cPTT defined as the point at which the pressure-pain became intolerable, indicated by the participant pressing the 'stop' button. Previous repetitions of this assessment were completed for another study[32], hence participants were familiarised with the procedure such that only one trial was required.

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

Test Stimuli

Three 1-s cuff stimuli (inflated at 100 kPa/s), separated by 10-s, were applied to the dominant leg at cPTT pressure intensity as the test stimuli, 30-s prior to and 80-s into each task (Fig. 1). Two verbal numeric rating scales were used to assess the pain intensity (NRS-I; 0: no pain at all, to 100: worst pain imaginable) and pain unpleasantness (NRS-U; 0: not unpleasant at all, to 100: most unpleasant sensation imaginable) of each test stimulus. The distinction between intensity and unpleasantness was thoroughly explained with use of the volume/response sound analogy[46], and understanding confirmed. The three stimuli ratings were then averaged to give a 'pre' and 'post' pain intensity and pain unpleasantness score, to be compared for each task in order to demonstrate an inhibitory or CPM-effect (i.e. NRS-pre minus NRS-post). Test stimuli were also applied prior to (Control, two sets of test stimuli with no task or conditioning in-between) and following all paradigms to assess for changes in basal pain sensitivity across the entire experimental session.

Conditioning Stimuli

The conditioning pressure pain stimulus was applied to the non-dominant leg via a cuff inflated to 70% of cPTT for approximately 105-s. An eVAS was used to record the intensity of pain experienced due to this tonic conditioning stimulus at four time points during each application. Raw conditioning stimulus eVAS ratings were averaged across each sequence/paradigm for analysis. Further, to quantify facilitation of pain perception due to the conditioning stimulus, the second to fourth eVAS ratings were normalised, by subtraction, to the first rating in each task for analysis.

Attentional Manipulations

A modified flanker task, programmed using E-Prime (Psychology Software Tools, USA) and presented on a 17" computer screen, approximately 50 cm in front of the participant at eye-level, was used as the attentional task. In this task, participants were asked to respond to the direction of the middle arrow, in a group of five arrows, by responding with either a '1' for left or a '3' for right with the dominant hand on a keypad. The four surrounding arrows could either point in the same direction (congruent) or the opposite direction (incongruent) to the middle arrow. Arrows were presented in one of four positions (offset to the right or left, above or below the centre of the screen) for 500 ms followed by a 800 ms fixation cross. The order of all directions, conditions and positions was randomized without replacement for each block. Participants were given 32 practice trials (two per position for each possible condition) with unlimited response time and feedback after each stimulus. Following this, another 1 minute of practice without feedback at the pace used during the experiment, to ensure adequate task acquisition and achieve near maximal performance.

Three paradigms were then performed: CS-only (where only the cuff conditioning stimulus was applied with no attention task), Attn-only (where only the attention task was performed with no conditioning stimulus), and CS&Attn (where the attention task and conditioning stimulus were applied simultaneously). During paradigms with the attentional task, 48 stimuli were presented in total, with a 'rate pain now' instruction given after every block of 12 stimuli (72.5 s total task duration). During the CS-only paradigm, a fixation cross was presented on the screen in-between the same timed cues to 'rate pain now'. Immediately following each attentional paradigm, the 'post' test stimuli were applied.

Affective Manipulations

The International Affective Picture System (IAPS) is a catalogue of over 1000 photographs, with normative valence (pleasantness), arousal and dominance rating data (as per the Self-Assessment Manikin, SAM), designed for use in affective research[29]. Images were selected from this catalogue, based on normative valence scores[29] (for which the combined mean (±SD) values are shown here), to form two sets of three distinct affective groups: positive (Set A SAM: 7.6±0.4, Set B: 7.6±0.4), negative (Set A: 2.2±0.6, Set B: 2.3±0.5), and neutral (Set A: 5.2±0.7, Set B: 5.1±0.6). Further, attempts were made to match images between valence groups based on content (i.e. child, animal, scene, etc.) and arousal, though generally negative images (5.8±0.8) had slightly higher normative arousal ratings than positive images (5.1±0.9), and both positive and negative slightly higher than neutral images (4.2±0.9). In an effort to reduce variation in affective responses, images rated differently (>1/9) between genders, or with large standard deviations (>2/9) in valence, were purposely not selected. Two matched sets per affective group were created, such that in each session different images of matched valence, arousal and content could be used, without compromising stimulus novelty. As using series' of contextually congruent images has previously been suggested to induce larger shifts in affective state[8,61], 8 blocks of 3 context-congruent images (total 24) were used for each set in each valence category (see Supplementary Table 1, available at http://links.lww.com/PAIN/B459). Prior reports suggest affective manipulation effects to last anywhere from 6-16 seconds[8,14] up to 1-2 minutes[26,53], with wash-out periods recommended to be 2-5 minutes[10,26]. Intervening tasks are also commonly used to improve return to neutrality[10,20,22], hence a 3-minute washout period with intervening task between paradigms was used here.

Three paradigms using these images were performed: CS&Positive (with positive image set A or B and simultaneous cuff conditioning), CS&Neutral (with neutral image set A

or B and simultaneous cuff conditioning), and CS&Negative (with negative image set A or B and simultaneous cuff conditioning).

Images were presented as a timed slideshow using E-Prime (Psychology Software Tools, USA), in the same manner as for attentional manipulations. Each image was presented for 2000 ms followed by a 500 ms fixation cross, and after every 6 images an instruction to 'rate pain now' was shown on the screen (72.5 s presentation total). During the last image (held for max. 25 s), the 'post' test stimuli were applied.

Manipulation Checks

Several parameters were obtained to confirm that the attentional and affective paradigms produced the desired effect. These included: 1) Accuracy and reaction time from each application of the attentional task for congruent and incongruent trials; 2) Perceived attentional direction (i.e. to the task, external/sensory distractions, task-related thoughts, and mind-wandering thoughts) and effort throughout each attentional paradigm rated on 7-point Likert scales (1: never/no effort; 7: always/maximum effort); 3) Subjective comparison of attentional task difficulty between paradigms with and without pain; 4) Memory of cuff pain while performing the attentional task (yes/no); 5) Affective state achieved by manipulation (i.e. one-word free response to the open question, "What one word would you use to describe how you felt while you watched the last series of images?"); and 6) Valence and arousal ratings on SAM (1-9 picture scale with 1=most negative/calm, 5=neutral, 9=most positive/aroused) following each affective manipulation. Complete analysis of this data is included in the supplementary material (available at http://links.lww.com/PAIN/B459).

Statistical Analyses

Data were analysed using SPSS (v24.0; IBM, Armonk, NY) and are reported as mean (± standard deviation, SD) or median (25th-75th quartiles) in-text and tables, and as mean (+ standard error of the mean, SEM) in figures. Normality was assessed within-groups by Shapiro-Wilks and parametric or non-parametric analysis was used as appropriate. Demographic information was compared between groups using independent-samples t-tests or Mann-Whitney U tests dependent on normality. Baseline questionnaire scores were analysed between-sessions with Wilcoxon signed-rank tests and between-groups with Mann-Whitney U tests. All pain-related data (cPTT, test stimuli NRS ratings, CPM-effects, and conditioning stimulus VAS ratings) were analysed via analysis of variance (ANOVA) with *Group* (RLBP or control) as a between-subjects factor, and *Session* (1/painful or 2/pain-free), *Leg* (Dominant or non-dominant, for cPTT), *Paradigm* (3 attentional paradigms: CS-only, Attn-only, CS&Attn; and/or 3 affective paradigms: CS&Positive, CS&Neutral or CS&Negative), *Time* (Prior, end or 2^{nd}, 3^{rd} 4^{th} rating) as within-subjects factors when appropriate.

Performance measures and manipulation checks were similarly compared with ANOVAs with *Group* (RLBP or control) as a between-subjects factor, and *Session* (1/painful or 2/pain-free) and *Paradigm* (Control paradigm; 3 attentional paradigms: CS-only, Attn-only, CS&Attn; and/or 3 affective paradigms: CS&Positive, CS&Neutral or CS&Negative) as within-subject factors as appropriate (supplementary material, available at http://links.lww.com/PAIN/B459). Differences in the proportion of dichotomous question responses were analysed with Fisher's exact test. When necessary, violations of sphericity were Greenhouse-Geisser corrected. Omnibus tests related to the main hypotheses of the study (i.e. those related to test stimulus modulation and conditioning pain facilitation) and those pertaining to subjective attentional or affective rating were each corrected for false

discovery rate using the Benjamini-Hochberg procedure [6]. Omnibus tests remaining significant after correction were reported with effect size as partial η^2 and were followed by post-hoc pairwise comparisons with Sidak correction. Post-hoc corrected significance was accepted at $P<0.05$ and statistics for these comparisons are presented as mean difference (MD) with 95% confidence intervals [lower, upper] and effect size as Cohen's d.

RESULTS

Demographics and Questionnaires

Twenty-nine individuals with RLBP and thirty age- and gender-matched pain-free individuals (27.3±5.4 years; 16 males per group) participated in two sessions with a 31.4±6.2 day interval (1 patient dropped out). Sleep time, menstrual phase and STAI-Trait scores were not different between sessions or groups (Table 1; $P>0.15$). STAI-State scores were higher in the painful session than the pain-free session among RLBP patients ($z=-2.226$, $P=0.026$), and tended to be higher in RLBP patients' painful session than controls during session one ($z=-1.909$, $P=0.056$). PANAS-Positive scores were also higher in the painful session than the pain-free session in RLBP patients ($z=-2.915$, $P=0.004$), but not different to controls in either session ($P>0.29$). Participants with RLBP reported mild to moderate VAS pain intensity and unpleasantness scores on average since episode onset in the painful session, with the majority completely recovered or reporting only discomfort in the second pain-free session.

---------- Insert Table 1 approximately here ----------

Basal Pressure Pain Sensitivity

Three-way ANOVA of cPTT revealed a main effect of *Leg* ($F_{1,57}$=46.9, P<0.001, partial η^2=0.451, Fig. 2), with cPTT being higher on the dominant (56.3±19.7kPa) than the non-dominant leg (51.1±17.6kPa, MD=5.14[3.64,6.64], P<0.001, d=0.28), but no significant difference between *Sessions* (P=0.052) or *Groups* (P=0.63).

Despite specific explanation and distinction of construct differences, pain unpleasantness ratings often needed prompting. These ratings also paralleled pain intensity ratings of test stimuli throughout the session (Attentional manipulations, R=0.80, P<0.001; affective manipulations, R=0.83, P<0.001), hence only pain intensity ratings are presented here, but analysis of pain unpleasantness can be seen in the Supplementary Material (available at http://links.lww.com/PAIN/B459). Three-way ANOVA of test stimuli NRS pain intensity ratings for the control stimuli applied at the very beginning and end of each session revealed a main effect of *Session* ($F_{1,57}$=13.8, P<0.001, partial η^2=0.195, Fig. 2), with higher ratings in Session 1 (54.1±15.0) than Session 2 (46.7±16.0, MD=7.46[3.44,11.48], P<0.001, d=0.48), but no significant differences were evident between *Groups* (P>0.40) or over *Time* (P>0.17).

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Attentional and Affective Effects on CPM-effect as the Change in Test Stimuli Ratings Pre-to-Post Manipulation

Three-way ANOVA of the change in pain intensity NRS ratings for test stimuli pre-to-post for the seven paradigms (1 control, 3 attentional, and 3 affective) revealed a significant Main Effect of *Paradigm* ($F_{6,342}$=5.85, P<0.001, partial η^2=0.093, Fig. 3) with no *Session* or *Group* effects (P>0.31).

On post-hoc pairwise comparison, greater inhibition was observed in the CS&Attn (MD=4.03[0.26, 7.79], P=0.026, d=0.49), CS-Only (MD=3.75[0.22, 7.28], P=0.028, d=0.46), and CS&Positive (MD=4.81[0.86, 8.76], P=0.006, d=0.59) paradigms than the Control paradigm, and in the CS&Positive (MD=3.59[0.34, 6.85], P=0.019, d=0.47) paradigm than the CS&Negative paradigm.

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

Attentional and Affective Effects on Conditioning Stimulus Pain

Four-way ANOVA of normalized eVAS ratings throughout each paradigm revealed a *Paradigm*Time* interaction ($F_{8,456}$=6.148, P<0.0001, partial η^2=0.097, Fig. 4), with no *Session* or *Group* effects (P>0.86).

Post-hoc pairwise comparisons between paradigms within timepoints revealed that, at all 3 timepoints, greater facilitation was observed in the CS-Only than the CS&Attn (Rating 1: MD=0.29[0.04,0.53], P=0.011, d=0.41; Rating 2: MD=0.40[0.04,0.75], P=0.019, d=0.36; Rating 3: MD=0.56[0.10,1.01], P=0.008, d=0.40), CS&Positive (Rating 1: MD=0.52[0.29,0.74], P<0.001, d=0.82; Rating 2: MD=0.76[0.43,1.09], P<0.001, d=0.77; Rating 3: MD=0.98[0.56,1.39], P<0.001, d=0.77), CS&Neutral (Rating 1: MD=0.40[0.19,0.61], P<0.001, d=.60; Rating 2: MD=0.55[0.25,0.85], P<0.001, d=0.53; Rating 3: MD=0.77[0.43,1.10], P<0.001, d=0.60) and CS&Negative (Rating 1: MD=0.30[0.08,0.53], P=0.002, d=0.45; Rating 2: MD=0.42[0.11,0.73], P=0.002, d=0.41; Rating 3: MD=0.54[0.17,0.90], P=0.001, d=0.42) paradigms. In addition, lower facilitation was observed at all timepoints in the CS&Positive paradigm than CS&Attn (Rating 1: MD=-0.23[-0.42,-0.04], P=0.008, d=0.40; Rating 2: MD=-0.36[-0.66,-0.06], P=0.008, d=0.37;

Rating 3: MD=-0.42[-0.76,-0.08], P=0.008, d=0.34) and CS&Negative (Rating 1: MD=-0.21[-0.36,-0.07], P=0.001, d=0.40; Rating 2: MD=-0.34[-0.59,-0.08], P=0.003, d=0.38; Rating 3: MD=-0.44[-0.75,-0.13], P=0.001, d=0.39) paradigms.

While post-hoc comparisons between timepoints within paradigms revealed facilitation within the CS-Only (Rating 2>1: MD=0.30[0.13,0.48], P<0.001, d=.32; Rating 3>2: MD=0.30[0.17,0.43], P<0.001, d=.24), CS&Attn (Rating 2>1: MD=0.19[0.02,0.36], P=0.023, d=0.22; Rating 3>2: MD=0.14[0.003,0.27], P=0.044, d=0.11), CS&Neutral (Rating 2>1: MD=0.16[0.02,0.29], P=0.016, d=0.20; Rating 3>1: MD=0.24[0.04,0.43], P=0.012, d=0.26) and CS&Negative (Rating 2>1: MD=0.19[0.05,0.32], P=0.004, d=0.24; Rating 3>2: MD=0.18[0.08,0.28], P<0.001, d=0.18) paradigms, but not in the CS&Positive paradigm (all P>0.25).

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

Effects of Pain on Attentional Performance and Affective Manipulation Efficacy

Complete analysis descriptions, along with statistics, graphic representations and tables of this data are included in the supplementary material (available at http://links.lww.com/PAIN/B459). Accuracy and reaction time showed a significant flanker effect (i.e. better performance during congruent than incongruent trials) across sessions and paradigms. Accuracy was higher in the second session than first, suggesting a possible learning effect, while reaction times were slower in the CS&Attn than the Attn-only paradigm.

Several differences were noted in perceived attentional direction between groups, sessions and/or paradigms, most interestingly showing: more attention toward the screen in the CS-Only condition among RLBP patients than controls; more attention directed to the

task in the Attn-only than CS&Attn paradigm across groups supporting the interruptive effect of tonic pain; more mind-wandering in the CS-Only paradigm than those with an attention task; less effort applied in the second session than the first, but more effort required when the CS was added to the attention task. No differences were noted in task difficulty between Attn-Only and CS&Attn paradigms, but RLBP patients indicated remembering feeling tonic cuff pain while performing the attentional task than controls.

Valence ratings and freely associated affective words generally reflected the intended affective state for each paradigm. As expected, arousal ratings were highest for negative images, then positive images, with both being more arousing than neutral images. Affective manipulation was, however, somewhat less effective in RLBP patients, where they showed less shift in positive and negative valence than healthy participants.

DISCUSSION

This study aimed to investigate the effect of attentional and affective manipulation on central pain processing mechanisms among RLBP patients with and without pain compared to pain-free matched controls. Contrary to the hypothesis, RLBP patients did not demonstrate enhanced pain sensitivity with no differences identified in pain tolerance thresholds nor pain ratings of test or conditioning stimuli compared to controls or between sessions. They further did not differ significantly from controls in any paradigm, though may have driven the overall difference in TS pain ratings noted between sessions. Generally, inhibition of test stimulus pain (CPM) was only present when the conditioning stimulus was presented alone, in combination with the attention task or positive affect, but not with neutral or negative affect, nor when the attentional task was used without conditioning. Conditioning pain ratings generally increased in all paradigms except positive affect induction, with the highest

facilitation seen when no other task was used. Conditioning pain impaired attentional performance, though clinical pain did not, but RLBP patients did show less susceptibility to affective manipulation.

Basal pain sensitivity

No clear differences in cuff pain tolerance thresholds were observed in RLBP patients, consistent with other data from this cohort[33]. Prior work has similarly demonstrated this in RLBP populations[15], though reductions have been observed with handheld and cuff pressure algometry in more severely affected chronic LBP patients[1,15,37]. It is unclear why pain tolerance remains unaffected, when pain detection thresholds are often reduced in LBP patients[12]. However, these thresholds are commonly reported to represent different constructs, with pain tolerance showing more consistent relation to cognitive-evaluative features like pain-related fear and expectations[44], personality traits[23] and other general health markers[2,52].

In relation to CPM, significant differences between controls and patients with RLBP were not observed. This is not consistent with CPM findings from the usual ramped cuff paradigm published previously in this cohort[33], nor with prior meta-analyses showing generally reduced efficacy of CPM in LBP[12,34]. However, the effect size on meta-analysis is small and depends on pain chronicity and severity, meaning high inter-individual variability in perceived painfulness of test stimuli or generally low levels of pain and dysfunction among the RLBP group could be responsible for this.

Attentional and affective effects on CPM

The addition of an attentional task to conditioning pain evoked significant inhibition. However, unlike prior studies demonstrating that distraction can have an enhancing effect on CPM[38], the magnitude of inhibition observed here did not significantly exceed that produced by the conditioning stimulus alone. Though the effects of distraction on experimental pain assessment in LBP populations have been mixed[21], in the present study, the attentional task alone also did not alter test stimulus ratings in either group. As observed previously, conditioning pain had interruptive effects on attentional performance[40,41], and when conditioning pain was present, the attention task was perceived to require more effort, suggesting major cognitive resources were needed. Nevertheless, it seems here that attentional tasks performed during or instead of conditioning, even when cognitively demanding [48,56] or where the task is novel[58], may not necessarily be able to reduce pain perception or have an additive effect on CPM.

Several prior studies have investigated effects of laboratory-induced affective states on pain perception[3,22,35,47,59], and often demonstrate valence specific modulation. The present findings extend this work, showing similar positive and negative effects of positive and negative affect, respectively, on CPM responses. Interestingly, in the present work, inhibition was not present during the negative manipulation, despite being present when the conditioning stimulus was used alone, suggesting negative affect actually impaired CPM. Higher arousal was observed in the negative than positive manipulation, which could contribute to this impaired analgesic effect[17], though the neutral condition also showed no significant inhibition despite having lower arousal ratings than both positive and negative manipulations, making this explanation unlikely. Among chronic LBP populations, negative affect has been associated with poorer response to analgesic medication and declining CPM with ongoing treatment[13]. Negative affect may therefore both acutely disrupt pain

inhibitory function and contribute to the development of hyperalgesia over time with ongoing pain, though this requires further investigation.

Attentional and affective effects on facilitation of conditioning pain

An overall reduction in facilitation of conditioning pain ratings was observed with the addition of the attention task or affective manipulations. Facilitation of pain perception over an ongoing noxious stimulus may be explained by wind-up mechanisms in the spinal dorsal horn[30], though it is not possible to differentiate spinal from supraspinal processing of pain. As such, prior work has shown distraction to reduce basal pain perception, but not alter summation of either pain perception or reflexes[51]. If the task and images were suitably distracting, it thus seems most probable that reduced tonic pain facilitation is a further reflection of descending inhibitory pathway engagement via cortical mechanisms[9].

Positive affect was particularly effective at attenuating facilitation of pain ratings, with lower facilitation than all but the neutral paradigm. As suggested previously, arousal may contribute to this, as higher arousal in the negative manipulation may heighten threat perception and interfere with inhibitory processes[57]. As well, enhanced pain during negative affective manipulation and reduced pain during positive affect manipulation would fit with the defensive and appetitive streams posited by the motivational priming hypothesis[28]. In this sense, it is perhaps surprising that positive manipulation still could not reduce conditioning pain perception, but only attenuate facilitatory effects.

One consideration is the potential interaction between conditioning pain perception and CPM effects. Prior studies have shown the perceived intensity of conditioning stimulation[54], though not objective stimulus intensity[11], to have a significant impact on CPM magnitude. It is thus conceivable that differences in facilitation of conditioning pain, and thus differences between paradigms in perceived conditioning pain intensity during the

reapplication of test stimuli, may have subsequently impacted CPM magnitude. So, by controlling for this, positive affect and distraction may have shown additive effects on CPM.

Effects of experimental and clinical pain on attention and affect

Experimental pain impaired reaction times during the attentional task across groups and sessions. This is consistent with prior experimental findings showing a general impairing effect of pain on time-based attentional performance measures[41].

Patients in pain and healthy participants with experimental pain have generally been shown to perform worse on cognitive tasks than pain-free individuals[41,43], especially when the tasks are complex[25]. Previous work examining people with and without menstrual pain[24] and headache[42], showed that clinical pain presence impaired task performance without producing specific cognitive or attentional deficits. Interestingly, the present work did not find such a difference in performance, once participants were accustomed to the task, suggesting that RLBP presence had little impact on task performance after acquisition. There are suggestions that mechanisms underlying effects of acute and chronic pain on attentional performance may differ[43], with experimental pain having detrimental effects on different types of attentional tasks to those impaired in chronic pain patients. Most of this prior work reports negative effects of clinical pain on divided attention or working memory tasks, hence the lacking effects here may relate to task selection.

Affective manipulation was not always equally effective in the RLBP patients, with less deviation from neutral shown in negative and positive paradigms than controls (supplementary material, available at http://links.lww.com/PAIN/B459). This warrants further investigation to understand if true impairments in affective processing exist, as observed in other pain populations[49].

Limitations

The unpredictable nature of LBP episodes made it necessary to recruit patients when in pain, meaning randomisation of painful/pain-free session order was not feasible. This should, however, be accounted for using matched controls over the same timeframe. RLBP patients had slightly lower levels of education than controls which may limit interpretations of attention task performance data. Due to the desired simultaneous assessment of pain and task performance, it was necessary to use a simple reaction time task. Affective manipulations were based on previous work and were designed to maximise efficacy, while minimising duration and carry-over effects. Despite this, it is possible that paradigms were not optimal and the decision to always conduct attentional then affective paradigms may have impacted CPM magnitude. Affective and attentional manipulation are also typically thought to alter pain unpleasantness and intensity preferentially, but this was not possible to see here potentially due to poor concept distinction. Finally, the IAPS, while attractive due to the availability of normative ratings, includes many dated images and has not been widely culturally adapted.

Conclusion

Distraction and positive affective states allowed for CPM effects while negative affect impaired CPM across groups and sessions. Distraction and affective manipulation reduced facilitation of pain perception during conditioning, with positive affect completely attenuating this facilitation. Experimental pain demonstrated the well-established interruptive effect on attentional performance, while clinical pain presence did not, likely due to task selection. RLBP patients did, however, show less deviation in valence due to affective manipulation. Future work is encouraged to delineate mechanisms underlying these effects on CPM and the differential effects of experimental and clinical pain on attentional performance,

as well as to explore interactions between conditioning pain intensity and CPM magnitude and replicate impaired affective processing in RLBP patients.

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Supplemental video content

A video abstract associated with this article can be found at http://links.lww.com/PAIN/B460.

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Figure Captions:

Figure 1. Illustration of experimental setup and procedure. **A:** Baseline cuff algometry to assess cuff pain detection and tolerance thresholds. **B:** Attentional (attn) modulation series, blue box paradigms were performed in random order, blue arrows indicate assessment of mind-wandering scale. **C:** Affective modulation series, yellow box paradigms were

performed in random order, yellow arrows indicate assessment of valence, arousal and affective word association. **D:** Example of Flanker task timeline with one congruent followed by two incongruent trials separated by fixation crosses (all trials were delivered at random, 48 trials total per paradigm). **E:** Example of affective manipulation timeline with three contextually congruent images (International Affective Picture System, though stock photos shown here, 24 images total per paradigm).

Figure 2. Mean (+SEM) baseline cuff pain tolerance thresholds for each leg (non-dominant/dominant) of each group (RLBP = red, Control = black) in each session (Painful/Session 1 = solid, Pain-free/Session 2 = striped, Left), and mean (+SEM) test stimulus (TS) numerical rating scale (NRS) pain intensity for control set at the start (Prior) and end of each session for each group. Significant difference between legs or sessions indicated (*, $P<0.001$)

Figure 3: Mean (+SEM) change in pain intensity numerical rating scale (NRS) scores for test stimuli during each attentional paradigm (Control/CS&Attn/Attn-only/CS-only) in each session (Painful/Session 1 or Pain-free/Session 2) for each group (RLBP/Control), with grand means indicated by dashed bars. CS = conditioning stimulus, Attn = Attention task. Significant difference from Control paradigm (*, $P<0.03$) and from CS&Positive paradigm ($^{\#}$, $P<0.02$) are indicated.

Figure 4: Mean (+/- SEM) normalized eVAS ratings (at 2^{nd}, 3^{rd} and 4^{th} timepoints) across each paradigm divided by group (RLBP/Control) and session (Painful/session 1 or Pain-free/session 2, right), with grand means indicated by dashed bars. CS = conditioning

stimulus, Attn = Attentional task. Significant difference from 2nd (*, P<0.05) and 3rd (#, P<0.005) timepoints and significant differences between paradigms at all timepoints (§, P<0.008) are indicated.

Table 1: Participant characteristics and questionnaire responses

	Participants with RLBP		Pain-Free Participants	
	Painful Session (Session 1)	***Pain-free Session (Session 2)***	***Session 1***	***Session 2***
Height (cm)	175.6±11.2		170.9 ±9.9	
Weight (kg)	75.2±16.3		68.1±12.3	
Education (% S/UG/PG)	47 / 50 / 3		23 / 46 / 30	
STAI-State	35 (10)*	31 (9.5)	29.5 (10.75)	29.5 (12.25)
STAI-Trait	36 (12)	37 (13)	35 (11.5)	35.5 (11.25)
PANAS-Positive	31 (7.5)*	28 (12)	31 (9.25)	30.5 (9)
PANAS-Negative	13 (6)	12 (4)	11.5 (5)	12 (4)
Mean Pain Intensity current episode (VAS, cm)	4.4±2.1	-	-	-
Mean Pain Unpleasantness current episode (VAS, cm)	5.4±2.2	-	-	-
McGill Descriptors Total *Sensory* *Affective* *Evaluative*	21.7±11.0 14.3±6.4 1.9±2.8 1.6±1.3	2.7±8.0 2.0±6.0 0.3±1.1 0.1±0.4	-	-
STarTBack Screening	2 (2.25)	2 (2.25)	-	-

S/UG/PG = secondary/undergraduate/postgraduate qualification attained. STAI = State and Trait Anxiety Inventory. PANAS = Positive and Negative Affective Schedule. VAS = Visual Analogue Scale. Significant between-session difference in RLBP patients indicated (*, P<0.03)