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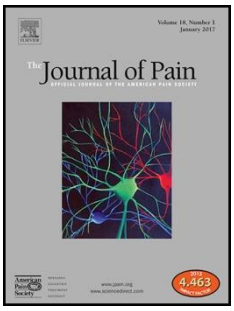

Title: Individual Variation in Pain Sensitivity and Conditioned Pain Modulation in Acute Low Back Pain: Impact of Stimulus Type, Sleep, Psychological and Lifestyle Factors.

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Title: Individual variation in pain sensitivity and conditioned pain modulation in acute low back pain: impact of stimulus type, sleep, psychological and lifestyle factors.

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Highlights

- Enhanced sensitivity consistent with generalized hyperalgesia was observed
- Acute back pain includes four subgroups with sensitivity and modulation profiles
- Various factors including sleep and alcohol explain some variation in presentation

Abstract

Generalised hyperalgesia and impaired pain modulation are reported in chronic low back pain (LBP). Few studies have tested whether these features are present in the acute-phase. This study aimed to test for differences in pain presentation in early-acute LBP and evaluate the potential contribution of other factors to variation in sensitivity. Individuals within two weeks of onset of acute LBP (N=126) and pain-free controls (N=74) completed questionnaires related to their pain, disability, behaviour and psychological status before undergoing conditioned pain modulation (CPM) and pain threshold (heat, cold and pressure) testing at the back and forearm/thumb. LBP participants were more sensitive to heat and cold at both sites and pressure at the back than controls, without differences in CPM. Only those with high-pain (numerical rating scale, NRS≥4) were more sensitive to heat at the forearm and pressure at the back. Four subgroups with distinct features were identified: "high sensitivity", "low CPM efficacy", "high sensitivity/low CM efficacy", and "low sensitivity/high CPM efficacy". Various factors such as sleep and alcohol were associated with each pain measure. Results provide evidence for generalised hyperalgesia in many, but not all, individuals during acute LBP, with variation accounted for by several factors. Specific pain phenotypes provide candidate features to test in longitudinal studies of LBP outcome.

Perspective: Sensory changes indicative of increased/decreased central processing of pain and nociceptive input presented differently between individuals with acute low back pain and were related to factors such as sleep and alcohol. This may underlie variation in outcome and suggest potential for early identification of individuals with poor long-term outcome.

Keywords: Generalised hyperalgesia; localised hyperalgesia; conditioned pain modulation (CPM); central sensitisation; peripheral sensitisation; low back pain (LBP).

1. Introduction

Low back pain (LBP) is the leading cause of disability worldwide,[109] costing well over $100 billion a year in the USA alone.[5] Treatment effects remain small, which is generally explained by the multi-factorial nature of long-term pathophysiological changes, mediation by peripheral and/or central nervous system sensitisation, and interaction between biological and psychosocial features.[26] The mechanisms responsible for pain sensitisation,[32, 99, 116] and the relative contribution of peripheral and central changes to generation and/or persistence of LBP are major targets of research. Most work has investigated individuals with chronic pain.[7, 16, 30, 76, 85] It remains unclear how sensory changes present during an acute LBP episode.

Enhanced nociceptive sensitivity commonly follows injury through activation and sensitisation of peripheral nociceptive neurons by inflammatory mediators[21] that trigger a cascade of internal events, leading to depolarisation, delayed repolarisation and lowering of the threshold for action potential firing.[60] Sensitisation begins rapidly and is protective.[100] If noxious stimuli or inflammation persist, maladaptive physiological changes can occur (e.g. cytokine mediated up-regulation of ion channels and excitatory receptors) that contribute to the maintenance of nociceptor discharge.[43, 115] This "peripheral" sensitisation induces hyperalgesia at the injury site (primary hyperalgesia).[93, 116]

Sensitivity can also spread to undamaged tissues surrounding (secondary hyperalgesia) and remote (generalised hyperalgesia) to the injured site, even after the initial injury has healed. This sensitivity is mediated by changes in the central processing of nociceptive information rather than extension of the area of peripheral damage/inflammation.[51, 116] Secondary hyperalgesia is mediated at the spinal cord whereas generalised hyperalgesia is thought to be mediated further upstream.[13, 30, 65, 71] Both forms of hyperalgesia characterise many chronic pain states.

Localised (primary and/or secondary hyperalgesia) and generalised hyperalgesia are common in chronic LBP. Lower pain thresholds to cutaneous heat,[23, 57, 85] cold,[23, 38] and mechanical stimuli[16, 30, 75] at (or near) injured and non-injured sites have been reported. Brain imaging in chronic LBP reveals activation patterns similar to fibromyalgia, a condition characterised by generalised mechanical hypersensitivity.[30] Conditioned pain modulation (CPM) reflects the capacity of endogenous pain modulatory systems to enhance or diminish pain.[117] With normal CPM functioning, painful stimuli reduce pain from noxious stimuli in another body region.[64] Various chronic pain conditions[2, 41, 81, 108] including chronic LBP[17, 68] have been associated with lesser descending nociceptive inhibition or greater nociceptive facilitation, but it is not clear whether these changes are a precursor to chronicity or develop over time.[59] Hyperalgesia and deficient CPM have also been linked to various demographic, sleep-related[34, 96] and psychological[27, 28, 69] factors, many of which are common in chronic LBP.[38]

Our overall objective was to test for evidence of localised and generalised hyperalgesia during an acute LBP episode. This study aimed to: (i) compare a suite of pain measures (at the back [pain site] and forearm/thumb [remote site]) between pain-free controls and people within two weeks of onset of an acute LBP episode; (ii) compare pain measures between participants with low- and high-level pain, iii) identify potential subgroups with

similar features, and (iv) evaluate the potential contribution of demographic, behavioural and psychological factors to variation in pain measures.

2. Methods

2.1 Participants

One hundred and twenty-six people in an acute episode of LBP (62 M, 64 F) aged 29±8 (mean±SD) years and 74 pain-free controls (29 M, 45 F) aged 27±7 years participated in the study. Participants were recruited through advertisements around the university and local community, social media, and via a participant recruitment agency. Ethical clearance was obtained from the Institutional Medical Research Ethics Committee. All participants provided informed consent and procedures were conducted in accordance with the Declaration of Helsinki.

LBP participants were recruited and assessed within two weeks of onset of an acute episode of LBP that was preceded by at least one month without pain. A LBP episode was defined as pain that had lasted longer than 24 hours, caused functional limitation, and caused them to seek or seriously consider medical or allied health intervention. They were included if they continued to experience pain and disability in the week prior to assessment (see below). Participants were excluded from either group if they had known or suspected serious spinal pathology (e.g. fracture, inflammatory/infective spinal disease, cauda equine syndrome, metastasis and neurological disorders). Participants were also excluded if they were less than 18 or more than 50 years old, had major pain or injury to other body regions in the previous 12 months, or had other major diseases or disorders (e.g. chronic renal/endocrine disorders).

On arrival at the assessment session participants were asked to rate their "average" level of LBP over the last week using a numerical rating scale (NRS) anchored with "no

pain" at 0 and "worst pain imaginable" at 10. Pain-related disability was assessed using the Roland Morris Disability Questionnaire (RMDQ),[91] which is a self-administered questionnaire consisting of 24 items associated with physical functions likely to be affected by LBP. An item receives a score of 1 if it is applicable to the respondent or a score of 0 if it is not, with a total score range of 0 (no disability) to 24 (severe disability). Potential control participants who reported a score >0 on the NRS and/or RMDQ were excluded from the study. Potential LBP participants who reported pain of <1 on the NRS and/or a score of <1 on the RMDQ in the past week were excluded from the study.

2.2 Categorisation of participants

Participants were categorised in two ways: 1) those with (LBP) and without LBP (controls), and 2) those with moderate-to-severe LBP (NRS ≥4, "high-pain"), those with mild LBP (NRS <4 but >1, "low-pain"), and controls. Six LBP participants could not be categorised further (high- or low-pain) because their pain level was unclear. The NRS cut-off used to distinguish between moderate-to-severe and mild LBP is based on those reported by Boonstra et al.[10]

2.3 Procedures

Participants completed a series of online questionnaires related to their general health, demographics, psychological status and sleep behaviours within 24 hours of their laboratory assessment. Pain thresholds in response to pressure (pressure pain threshold: PPT), heat (heat pain threshold: HPT) and cold (cold pain threshold: CPT) were measured in sequence before assessing CPM.

2.3.1 Questionnaires

General health and demographic variables: Age, sex, co-morbidities, and self-reported body mass index (BMI: weight [kg] divided by the squared height) were collected.

Participants reported smoking history (current/previous smoker), alcohol habits (frequency and amount consumed), and whether they had experienced previous LBP (yes/no).

Psychological variables: Psychological measures were selected based on three domains of relevance in LBP: cognitive (expectations, beliefs and perceptions' concerning pain),[9, 37, 61, 63] emotional (distress, anxiety and depression),[82] and behavioural (coping, pain behavior and activity/activity avoidance).[37, 61, 63]

The 20-item Centre for Epidemiological Studies of Depression Scale (CES-D)[87] was used to assess depressive symptoms in the past week. Both total CES-D score (range 0–60) and whether they are experiencing clinical depressive symptoms, defined as a total score greater than 15,[58] were considered in the analysis. Thoughts and feelings related to pain suggestive of catastrophic cognitions were measured with the valid and reliable 13-item Pain Catastrophizing Scale (PCS).[79] The PCS yields a total score of 0–52, as well as three subscale scores of magnification ("I become afraid that the pain will get worse"), rumination ("I worry all the time whether the pain will end") and helplessness ("I feel I can't go on"). Individual component and total PCS scores were used for analyses. The Fear Avoidance Beliefs Questionnaire (FABQ) was used to assess fearful and avoidant behaviours related to physical activity (FABQ-PA: 5 items, range 0–66) and work (FABQ-W: 11 items, range 0–66) owing to the participants' LBP, with higher scores indicating higher levels of fear-avoidance beliefs.[111] Unemployed participants were removed from the final FABQ-W dataset. The 10-item Pain Self-Efficacy Questionnaire (PSEQ) was used to quantify the confidence LBP participants had in performing activities while in pain[70] with higher scores reflecting stronger pain-specific self-efficacy beliefs.

Sleep variables: Sleep duration and quality were assessed with the Pittsburgh Sleep Quality Index (PSQI). The 19-item questionnaire evaluates global sleep complaints along seven dimensions, including subjective sleep quality, sleep duration and latency (time taken

to fall asleep), and the frequency and severity of specific sleep-related complaints in the previous month.[12] Scores from each dimension (range: 0–3) are individually reported as component scores and summed to derive a sleep quality maximum score of 21; higher scores reflect greater sleep complaints. A PSQI score of 5 or higher is considered to indicate poor sleep.[12] The PSQI and its psychometric properties have been validated in various populations including those with insomnia.[4, 12, 14] For analyses we used self-reported hours of actual sleep, five individual component (sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, and use of sleep medication) and global PSQI scores, and whether they are experiencing poor sleep quality (PSQI>5).

2.3.2 Pain thresholds

Pain thresholds were assessed at two anatomical locations: (1) lower back (local) – site of "most" pain on palpation in LBP participants or at a fixed site approximately 5 cm rostral (towards the head) and lateral to the centre of the lumbo-sacral junction divided randomly between the left and right side of the body in control participants, and (2) thumb/forearm (remote) – thumbnail (PPT) and proximal volar aspect of the forearm (HPT and CPT) on the opposite side of the body to that used to assess pain thresholds at the lower back.

To assess PPT, a pressure algometer (Somedic A/B, Stockholm, Sweden) with a 1-cm disc-shaped probe head was applied three times at each location. Pressure was increased at a rate of ~40 kPa/s. Participants indicated when the stimulus changed from one of pressure to one of pain[103] and a mean score in kPa was calculated. Thermal pain thresholds were assessed using a Thermal Sensory Analyzer (TSA 2001, Medoc, Israel) system with a 30 x 30 mm Peltier contact probe. Participants received a continuously ascending or descending stimulus which started at 30°C and either increased (cut-off 52°C) or decreased (cut-off 0°C) at a rate of 0.7°C/s. Participants indicated with a button press when the sensation of heat/cold became

one of pain[103] and the stimulus returned to baseline (30°C) at a rate of 10°C/s. Five trials were performed at each site (back and forearm) for each test (HPT and CPT), separated by an inter-stimulus interval of 10 s. The mean temperature was calculated from the final three trials.[84]

2.3.3 Conditioned pain modulation

The CPM paradigm was based on our previous work validating the use of PPT as a test stimulus (TS) and the lower back as an application site for either the TS or conditioning stimulus (CS: noxious contact heat).[47] Four body regions were selected for testing to explore variation in CPM magnitude at different body sites[84] and whether application of the TS/CS to the painful region in LBP participants affects the CPM response: (1) lower back (site of pain or a standardised site for controls [see above]), (2) forearm (TS - proximal region of the muscle belly of extensor carpi radialis longus; CS - proximal volar aspect), and (3) thumbnail. Trials were conducted in three test blocks of different TS and CS arrangements in random order:

(1) TS – lower back, CS – contralateral forearm

(2) CS – lower back, TS – contralateral forearm and thumb

(3) CS – forearm (ipsilateral to lower back site), TS – contralateral forearm and thumb

CPM was assessed approximately 20 min after assessment of pain thresholds. In each block, the TS was first applied alone and then reapplied concomitantly with the CS 30 s after onset. The CS was maintained until all TS measurements had been completed (~60 s). A 15-min rest was enforced between blocks to eliminate any unresolved CPM effects.[113]

PPT was performed in an identical way to that outlined above (section 2.3.2) for the TS. The CS was noxious contact heat, delivered by a computerised stimulation device (TSA 2001 system with a 30 x 30 mm Peltier contact probe). Unlike limb immersion techniques (e.g. hand immersion in painfully hot or cold water), contact heat enabled application of a CS

to the back. Target CS temperature was set at 1°C above the participant's HPT (as determined earlier) for each test site. During CPM testing, the CS was applied at an initial temperature of 30°C and rose by 0.7 °C/s to the predetermined temperature. Temperature was returned to baseline at 7°C/s after completion of TS measurements. At three time-points during exposure to the CS (0 s, 30 s, and just prior to cessation of the CS – after the last TS recording), participants reported the pain intensity caused by the CS on a 101 point numerical rating scale (101-NRS) anchored with "no pain" at 0 and "worst pain imaginable" at 100. Some participants were unable to tolerate the target CS during CPM trials, so the CS was reduced at 0.5°C increments until the reported pain scores were below "80" on the 101-NRS. If the reported pain in response to the CS was less than "45" on the 101-NRS before application of the TS (30 s after commencement of the CS), the temperature was increased until pain exceeded "45". This "revised" temperature was then used for all remaining CPM trials that involved the same CS test site unless further modifications were required (i.e. increase or decrease temperature). This procedure ensured the CS was safe and sufficiently intense to induce CPM over a short application time.

The CPM response was calculated as the difference between the TS scores obtained before and during the CS.[119] A higher TS score during the CS than baseline indicated pain inhibition (expressed as a positive value). A lower TS scores during the CS than baseline indicated pain facilitation (negative value).[117, 118]

2.4 Statistical analysis

Questionnaire data were compared between the control and LBP groups, and between the low-pain (NRS<4) and high-pain (NRS≥4) groups using chi-squared (categorical variables) or independent t-tests (continuous variables). Data that were not normally distributed (e.g. pain threshold and CPM measures were skewed [Kolmogorov-Smirnov test: $p<0.05$]) were log-transformed before further analysis. Because many CPT values were

allocated a zero score (pain threshold beyond the temperature cut-off limit), no suitable transformation method achieved a normal distribution, and nonparametric tests (i.e. Mann-Whitney U test, Kruskal-Wallis ANOVA and logistic regression) were used with raw CPT values. Pain thresholds and CPM values for each anatomical arrangement were compared between LBP and controls using independent t-tests (log-transformed PPT, HPT and CPM) or Mann-Whitney U tests (raw CPT values). Univariate ANOVAs/Kruskal-Wallis ANOVAs (group [3 levels] x PPT/HPT/CPT/CPM) were then used to explore differences between the high-pain, low-pain and control groups for PPT, HPT, CPT and CPM for each test site/stimuli arrangement separately. Bonferroni (PPT, HPT and CPM) and multiple comparisons of mean ranks (CPT) methods were used for post-hoc analysis.

For investigation of potential LBP subgroups, sensory data (PPT, HPT, CPT and CPM) were entered into a principal component analysis (PCA). PCA reduces the dimensionality of the original data set by generating new independent variables, called principal components (PC), to summarise the features of the data.[120] Most variation in the original data set is captured by the first PC, followed by the second PC, and so forth. PCs with eigenvalues >1 and/or above a break in the scree plot ("elbow" criterion: value at which added dimensions no longer explain the data substantially) were retained.[18, 40] V-fold cross-validation was used to validate the optimal number of PCs. Variables with considerable influence on each PC were defined as those with a factor loading $\geq \pm 0.5$.[35] Unbiased hierarchical clustering was then carried out on the retained PCs (individual participant t-scores) to determine the existence of subgroups in acute LBP based on the sensory testing results without using *a-priori* methods or other predefined assumptions. Clustering was performed using the publically available Morpheus webtool (https://software.broadinstitute.org/morpheus/) using the cosine similarity metric and average linkage method. The optimal number of clusters was determined by inspecting the

dendrogram/heatmap and limiting the minimum number of participants per cluster to 10. Sensory, demographic and basic clinical (pain and disability) data were then compared between clusters and controls with appropriate parametric and non-parametric techniques, as described above.

Stepwise linear regression with a strict variable entry/retention criterion of $p<0.05$ was used to identify the best combination of factors (health, demographic, psychological and sleep) to explain the variation in PPT, HPT and CPM. A stepwise approach was chosen because it could create the most parsimonious phenotypic model. In the same manner, we used stepwise logistic regression to assess which combination of factors was most predictive of a low-CPT (compared to a high-CPT) and facilitatory CPM (compared to inhibitory CPM). Low-CPTs and high-CPTs were defined as values in the bottom (high sensitivity) and top (low sensitivity) tertiles, respectively. Values that fell within the middle tertile were not considered for analysis. Facilitatory CPM represented a negative CPM value whereas inhibitory CPM represented a positive CPM value. The overall number of variables included in the regression analyses was limited to ensure a sufficient participant-to-variable ratio (for a complete list of variables refer to Table 1) for accurate estimation of regression coefficients, standard errors and confidence intervals.[3] Levels within categorical variables (e.g. sleep components: 0–3 levels) that had 10 or fewer participants were not included in the final model to avoid type 2 errors. Analyses were performed using Statistica v12 (StatSoft) and Stata v14 (Stata Corp). P-values <0.05 were considered statistically significant.

3. Results

3.1 Group characteristics

Participants with and without LBP were similar in terms of sex and current smoking status. Table 2 shows differences between groups in the following variables: age, BMI, previous/current smoker, previous LBP, sleep hours per night, sleep quality, poor sleeper, depressive symptoms, clinically significant depression, and pain catastrophizing (total and component scores). For the LBP group, those with low-pain (NRS<4) and high-pain (NRS≥4) shared similar characteristics except that average pain intensity (NRS) over the last week, disability (RMDQ) and feelings of pain-related helplessness (PCS) were higher in the high-pain group (Table 3).

3.2 Group comparison of pain thresholds and CPM

Pain thresholds and CPM magnitudes for each group are shown in Figures 1 and 2. LBP participants were more sensitive to heat and cold at both the back (t-test: $p<0.001$) and the forearm ($p<0.037$), and pressure at the back ($p=0.002$) but not the thumb ($p=0.313$), than controls. Three-way group comparisons showed that both high- and low-pain groups were more sensitive to heat at the back (main effect: group – $F [2, 192]=9.1$, $p<0.001$; post-hoc: $p<0.001$), but only high-pain sufferers were more sensitive to heat at the forearm (main effect: group – $F [2, 192]=4.3$, $p=0.015$; post-hoc: $p=0.014$) and pressure at the back (main effect: group – $F [2, 192]=4.4$, $p=0.014$; post-hoc: $p=0.017$), than controls. Although analysis of CPT values revealed no significant main effect for group (Kruskal-Wallis, $p>0.05$), post-hoc analyses suggested that high-pain participants tended to be more sensitive to cold (pain at a higher temperature) at the back than controls ($p<0.001$). Measures of CPT and PPT at the forearm/thumb were not different between the three groups and CPM was not different between groups for any stimuli combination.

3.3 Subgrouping based on pain sensitivity in the LBP group

PCA derived two PCs (above the "elbow" point: Fig 3) accounting for 45.7% of the total variation in the sensory data (Table 4). These PCs can be summarised as representing

the dimensions pain threshold (PC1) and CPM (PC2). Hierarchical clustering based on these PCs revealed four subgroups with distinct sensory profiles (Fig 4), which were termed accordingly: "high sensitivity" (Cluster 1), " low CPM efficacy" (Cluster 2), "high sensitivity/low CPM efficacy" (Cluster 3), and "low sensitivity/high CPM efficacy" (Cluster 4). Five-way subgroup (clusters 1–4 and controls) comparisons confirmed a main effect for *subgroup* on all pain measures (ANOVA/Kruskal-wallis: all $p<0.029$, Table 5). When compared with controls, the high sensitivity subgroup (Cluster 1) was more sensitive to all stimulus types (pressure, heat and cold pain) at both the forearm/thumb and back (post-hoc: all $p<0.004$) and the low CPM efficacy subgroup (Cluster 2) showed lower CPM responses for two stimulus arrangements (TS-thumb/CS-forearm, post-hoc: $p<0.001$; TS-thumb/CS-back, post-hoc: $p=0.002$). The high sensitivity/low CPM efficacy subgroup (Cluster 3) was more sensitive to all stimulus types at all anatomical locations and displayed lower CPM responses for most stimulus arrangements (TS-thumb/CS-back, post-hoc: $p=0.021$; TS-back/CS-forearm, post-hoc: $p=0.002$; TS-forearm/CS-forearm, post-hoc: $p=0.056$) than controls. No sensory differences were found between the low sensitivity/high CPM efficacy (Cluster 4) subgroup and controls. Average pain intensity (NRS) over the past week and LBP-related disability (RMDQ) were greater in all four LBP clusters than controls but not between clusters. Other than age, which was higher in the low CPM efficacy subgroup than controls, demographic features were not different between the five groups.

3.4 PPT: Relationship with pain intensity, general health, demographics, psychological status and sleep

Factors predictive of pressure sensitivity differed between anatomical test sites (see Table 6 for statistical outcomes), except that being male was associated with higher PPTs (i.e. less sensitive) at both the back and forearm. Greater pain intensity (average over the past week) and depressive symptoms were associated with greater pressure sensitivity at the back

whereas a lower frequency use of sleep medication (<1 times a week) was associated with lower pressure sensitivity at the back. Consumption of five or more alcoholic drinks no more than monthly was associated with lower pressure sensitivity at the forearm.

3.5 HPT: Relationship with pain intensity, general health, demographics, psychological status and sleep

Combined factors related to heat sensitivity are summarised in Table 6. Greater average pain intensity over the past week was associated with greater heat sensitivity at both anatomical sites. Greater heat sensitivity at the back was also associated with higher pain catastrophizing (PCS) whereas lower heat sensitivity was associated with consumption of five or more alcoholic drinks in a single drinking session no more than monthly. With respect to sleep, findings were complex; a low frequency of sleep disturbance (<1 times a week) but frequent daytime dysfunction (1–2 times a week) due to poor sleep and poor sleep efficiency (65–75% of "actual" time spent sleeping while in bed) were associated with lower heat sensitivity at the back. Other than average pain intensity over the past week, only age was associated (positively: i.e. less sensitive) with forearm heat sensitivity.

3.6 CPT: Relationship with pain intensity, general health, demographics, psychological status and sleep

Combined factors predictive of a low pain threshold (i.e. more sensitive) to cold are presented in Table 7. In general, alcohol consumption more frequently and in greater volumes were predictive of a low-CPT at both anatomical locations. Further, participants who were younger and reported a higher pain intensity over the past week were more likely to report a low-CPT when the stimulus was applied to the back than participants who were older and reported a lower pain intensity. Although several sleep-related features were predictive of cold sensitivity, their relationships were mixed.

3.7 CPM: Relationship with pain intensity, health, demographics, psychological status and sleep

Most predictors of facilitatory CPM in which the TS (PPT) was lower (more sensitive) during the CS were related to sleep and alcohol behaviours (Table 8). Facilitatory CPM was associated with frequent sleep disturbance (≥1 episode a week) for all TS/CS configurations and high sleep latency (time taken to fall asleep: >60 min) for the TS-back/CS-forearm configuration. Interestingly, daytime dysfunction (≥1 episode a week) due to poor sleep (TS-thumb, CS-back) was negatively associated with facilitatory CPM for the TS-thumb/CS-back configuration. With respect to alcohol, consumption of five or more alcoholic drinks on average when drinking was positively associated with facilitatory CPM for some TS/CS configurations (TS-forearm, CS-forearm; TS-forearm, CS-back; TS-back, CS-forearm), but negatively associated with other configurations (TS-thumb, CS-forearm; TS-thumb, CS-back). Frequency of alcohol consumption was also associated with facilitatory CPM when stimuli were applied to the upper limbs. Other positive predictors of facilitatory CPM included being male, being a past/present smoker, and having greater LBP related disability.

4. Discussion

These results point towards enhanced sensitivity to noxious input in many, but not all, individuals with acute LBP. Although there was considerable variation in presentation, four subgroups could be distinguished. Factors including sleep and alcohol consumption explained some variation in sensitivity.

4.1 Evidence of localised hyperalgesia

Group comparisons indicated a generally higher sensitivity to noxious input at the back to all stimuli in those with acute LBP than controls, and those with high- versus low-

pain. Related studies provide inconsistent findings. Although Starkweather et al.[102] reported greater sensitivity to pressure and cold, but not heat, at the painful region, the unusually low HPT for controls (HPT>44°C[85]) casts some doubt over the latter result. Other evidence of a no significant change in localised sensitivity to pressure in individuals with recent "trouble with their lower back"[74] is compromised by potential inclusion of individuals with sub-clinical LBP. LeResche et al.[57] observed localised hyperalgesia to cold but not heat in chronic LBP, but not in LBP of <6 weeks. Our detection of enhanced sensitivity to all stimuli might be explained by our larger sample size, strict criteria for symptom severity, and early analysis time point before resolution of early inflammatory changes that could mediate peripheral sensitisation.

Elevated pressure pain sensitivity only at the back in acute LBP concurs with previous work[102] that explained this difference as a consequence of sensitisation of local deep tissues. Hyperalgesia to pressure can depend on sensitisation of muscle/tendon nociceptors,[44, 48] as evidenced by the observation of hyperalgesia to blunt pressure induced by chemical stimulation of the erector spinae muscle but not overlying fascia and subcutis, despite greater tonic pain induced by chemical stimulation of the latter two tissues.[95] Although the edges of our testing instrument could excite cutaneous nociceptors, the role of cutaneous nociceptors in pain evoked by blunt pressure is minimal.[33, 106] Our finding that elevated pressure sensitivity was restricted to the area of LBP could be explained by peripheral sensitisation within deep somatic tissues and/or a central component (i.e. hyperalgesia of non-injured tissues impacted by the probe).

4.2 Evidence of generalised hyperalgesia

Sensitivity to heat and cold at both the affected and distant (forearm) body sites in acute LBP suggests a generalised state of enhanced sensitivity to thermal stimuli, indicative of central processes. Of two studies in acute LBP, one reported generalised hyperalgesia to

cold but not heat,[102] and the other reported a no difference.[38] Mixed findings from chronic LBP studies show generalised hyperalgesia to cold and heat,[23] cold only,[38] pressure[75] or none.[7] Inconsistency between results from small samples may be compounded by heterogeneity of participants within and between studies, with potential for different pain phenotypes.[30, 92] A recent study showed that chronic LBP patients presenting with non-mechanical pain (ill-defined, non-remitting, spontaneous) had lower wrist CPT than those with mechanical pain (anatomically defined, eases with specific postures/movements), who had similar profiles (CPT/PPT) to pain-free controls.[76] Others have also reported sensory features consistent with central sensitisation only within a subgroup of chronic LBP.[99] No studies have considered similar subgroups in acute LBP.

Our data revealed generalised sensitivity more commonly in individuals with high-pain. This has two possible interpretations. First, that greater central sensitisation is characterised by greater and more widespread sensitivity. Second, that the spread of sensitivity to remote uninjured areas depends on the severity of local symptoms. Although generalised hyperalgesia is thought to develop as a consequence of central changes (e.g. increased neuronal responsiveness[6, 114] and reorganisation of cortical structures and circuits[20, 25, 30]) secondary to continuous peripheral inputs,[114] few have studied its involvement in acute conditions.[104] Our data imply some changes present sooner than previously thought during acute LBP episodes for some individuals.

Absence of group differences in remote PPT implies differences in processing of different noxious stimuli. Electrophysiological studies have identified thalamic (site for modulation and relay of nociceptive signals to the cerebral cortex[1]) neurons that respond specifically to noxious heat, cold or pressure, and others to a combination of these stimuli.[11, 19, 55, 56] Further, different noxious stimuli can activate similar brain regions with different patterns of activation[15, 19] or different brain regions with similar patterns.[105] Our observation

of generalised hyperalgesia isolated to thermal stimuli could imply domain-specific effects of central processing, at least in the very early period.

Little is known of CPM in the acute context, though recent evidence suggests CPM is unaltered in LBP of <6 weeks.[110] We found no systematic difference in pain modulation between groups, but a marked reduction in some (Clusters 2 and 3) individuals. Although CPM efficacy is lower in some chronic pain populations,[59] evidence in chronic LBP is inconclusive.[17, 68, 86] Our data imply CPM is a feature of some subgroups of LBP or that CPM changes develop later. Whether altered CPM during acute LBP is a precursor to development of chronicity requires investigation.

4.3 Subgroups with different sensory profiles

Cluster analyses identified subgroups in acute LBP that were characterised by: high sensitivity (Cluster 1); low CPM efficacy (Cluster 2); high sensitivity/low CPM efficacy (Cluster 3); or low sensitivity/high CPM efficacy (cluster 4). This could imply different underlying pain mechanisms between individuals. Individuals that were more sensitive at the painful region were also more sensitive at remote regions to all stimuli. Similar features have been identified in chronic LBP patients with signs of central sensitisation.[76, 99] The addition of low CPM efficacy (or facilitatory CPM) in some individuals (Cluster 3) may indicate more extensive changes in pain processing within the CNS. A subset of individuals presented with low/facilitatory CPM but normal (comparable to controls) pain sensitivity. This may be because the pathophysiological processes involved in hyperalgesia and reduced descending inhibition are different[66, 80, 112] or that factors other than pain (e.g. expectation/distraction) influence CPM.[31, 72, 84] The subgroup with similar sensory profiles to controls may indicate resilience and greater potential for recovery.

Identification of subgroups raises important questions. First, what determines the development of different pain phenotypes following acute LBP? One potential factor is the

nature and/or severity of the pain/injury. Our findings of generalised hyperalgesia limited to high-pain participants but no difference in LBP intensity between subgroups (clusters 1–4) might suggest a non-linear relationship; a threshold input (intensity/duration) might be necessary to trigger central sensitisation. Non-linear relationships between generalised hyperalgesia and symptom severity have been reported in other chronic musculoskeletal conditions.[2, 46, 104] Other factors associated with sensitivity and CPM (see below) may predispose these responses. Second, do indicators of sensory function in acute LBP resolve or persist when the condition becomes chronic, or predispose outcome? Our findings and those in chronic LBP[23, 38, 74, 75] suggest signs of central sensitisation shortly after an episode of LBP might predict future pain. Whether this is more common in the subgroup with high sensitivity or low CPM efficacy requires longitudinal study.

4.4 Contribution of other factors to pain sensitivity and CPM

Variation in pain sensitivity and CPM was related to various factors. Poor sleep was associated with greater sensitivity to all stimuli and with facilitatory CPM. This concurs with the view that sleep and pain are reciprocally related – pain can lead to poor sleep which in turn can elevate pain, as occurs in chronic pain conditions[39, 42, 94] and sleep deprived controls.[22, 49, 78] Causality is most likely bidirectional. Sleep deprivation reduces pain thresholds[49, 78, 96] and pain inhibition,[101, 107] and sleep problems exacerbate existing pain and predict new-onset pain.[8, 77] The apparent opposing associations of some sleep components with sensitivity/CPM may be partly explained by the complex "u-shaped" relationship sleep has with pain and general health factors, e.g., either short or long sleep times are adversely associated with both.[45, 62, 97] Psychological factors can mediate the association between sleep and pain,[73, 78, 98] and conversely, sleep can mediate the relationship between pain and depression.[36, 67] Here, greater local sensitivity to pressure and heat at the back correlated with

depressive symptoms (CES-D) and pain catastrophizing (PCS), respectively. These data support a dynamic interrelationship between pain, sleep and psychological state.

Alcohol consumption may also interact in a bidirectional manner – greater pain may increase alcohol consumption, which may increase pain.[53, 121] In our data greater/more frequent alcohol consumption was generally associated with lower pain thresholds and facilitatory CPM. Although a causal link is biologically plausible,[121] most sensitivity studies focus on acute "dampening" rather than behavioural effects of alcohol, and the association between alcohol and LBP remains unclear.[54]

Relationships between age and pain measures were mixed. Older age was related to lower HPT (forearm) and higher CPT (back), but unrelated to PPT and CPM. Although this differs from observations of higher thermal pain threshold, lower PPT, and lower/facilitatory CPM with age,[29, 52, 89] our cohort's narrow age span limits confidence as the upper age was below the threshold for somatosensory changes.[50] With respect to sex, males were less sensitive to pressure (local/remote) and experienced facilitatory CPM more frequently. This concurs with observations of pressure sensitivity (although thermal sensitivity is also usually lower in males)[24, 90] but not CPM efficacy, which is often lower in females.[83] This might be explained by our lack of control for menstrual cycle (we prioritised assessment relative to pain onset), which impacts CPM.[88]

4.5 Methodological limitations

Many variables were analysed in this study, which raises the potential for spurious findings. Although several features were consistently related to all measures of sensitivity, we were concerned that some (e.g. alcohol consumption) related differently to CPM when different stimuli configurations were used. Larger and longitudinal studies are needed to fully understand the implications of these results. Further, CPM is known to be highly variable. By including multiple CPM measures we reduced the potential impact of spurious results. For

instance, the CPM measure that did not co-vary with the other four CPM measures, as determined in the PCA, was excluded from the final analysis. Finally, the use of stepwise regression has some inherent disadvantages that could have resulted in some variables (i.e. (health, demographic, psychological and sleep factors) not being included in the final stepwise solution despite being independently related to the outcome measure (i.e. sensory test). Our primary reason for using this approach was to identify the fewest variables to explain the greatest variability in the response to each sensory test.

4.6 Conclusion

This is the first study to demonstrate generalised hyperalgesia in early-acute LBP. As in chronic LBP, sensory profiles varied between individuals but subgroups with similar features were identified. The degree of sensitivity and CPM appears to be impacted by various factors such as sleep and alcohol consumption. Longitudinal examination is needed to assess the predictive value of specific pain phenotypes on outcome.

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Figure captions

Figure 1. Pain thresholds in response to heat, cold and pressure at the forearm/thumb and back between: i) low back pain and pain-free control participants, and ii) low back pain participants divided into those with high-pain (NRS≥4) and low-pain (NRS<4), and pain-free control participants. Box-plots represent median (*horizontal line*), 25th and 75th percentiles (*box*), and 10th and 90th percentiles (*lines outside the box*). *p<0.05; **p<0.01; ***p<0.001.

Figure 2. Conditioned pain modulation scores for different test stimulus (TS) and conditioning stimulus configurations between: i) low back pain and pain-free control participants, and ii) low back pain participants divided into those with high-pain (NRS≥4) and low-pain (NRS<4), and pain-free control participants. Descriptions of the box-plots are given in Fig 1. *p<0.05; **p<0.01; ***p<0.001.

Figure 3. Scree plot of the principal component extraction showing (dashed lines) the break ("elbow") in the curve, above which is considered to indicate the maximum number of principal components to extract. Two principal components were extracted – one less than the number at the "elbow" point.

Figure 4. Hierarchical clustering of low back pain individuals based on principal component analysis. Results are displayed as a heatmap and dendrogram in which the principal component (PC) scores are represented by shades of red (positive) and blue (negative). Each row is a PC, and each column is an individual low back pain participant. The dendrogram at the top shows group similarities, with four distinct clusters: Cluster 1 – "high sensitivity",

Cluster 2 – “low CPM efficacy”, Cluster 3 – “high sensitivity/low CPM efficacy”, and Cluster 4 – “low sensitivity/high CPM efficacy.

Table 1. Variables included in the regression analyses.

Variable	Variable type
Age (yrs)	Continuous
Sex (male, female)	Categorical
Body mass index (BMI)	Continuous
Current/previous smoker (yes, no)	Categorical
Previous LBP (yes, no)	Categorical
Pain intensity (numerical rating scale: NRS)	Continuous
Disability (Roland Morris Disability Questionnaire: RMDQ)	Continuous
Alcohol consumption (Alcohol Use Disorders Identification Test: AUDIT)	
Frequency (never, <monthly, 2-4 times/m, 2-3 times/w, >4 times/w)	Categorical
Quantity (drinks: 1-2, 3-4, 5-6, 7-9, >10)	Categorical
5+ drinks frequency (never, <monthly, monthly, weekly, daily or almost daily)	Categorical
Sleep quality (Pittsburgh Sleep Quality Index: PSQI)	
Total score	Continuous
Sleep hours per night (h)	Continuous
Sleep disturbance (not during the past month, <1 times/w, 1-2 times/w, 3-4 times/w)	Categorical
Sleep latency (<15 min, 16-30 min, 31-60 min, >60 min)	Categorical
Daytime dysfunction (not during past month, <1 times/w, 1-2 times/w, >3 times/w)	Categorical
Sleep efficiency (>85%, 75-84%, 65-74%, <65%)	Categorical
Use of sleep medication (not during past month, <1 times/w, 1-2 times/w, >3 times/w)	Categorical
Depressive symptoms (Centre for Epidemiological Studies Depression Scale: CES-D)	Continuous
Pain catastrophizing (Pain Catastrophizing Scale: PCS)	Continuous

Table 2. Low back pain (N = 126) and control (N = 74) participant characteristics.

	Control		LBP		
Characteristic	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**P-value**
Age (yrs)	27 (7)	18–47	29 (8)	18–50	**0.027**
Sex (male, %)	39.2	-	49.2	-	0.170
BMI (kg/m^2)	22.7 (4.4)	16.8–43.4	24.1 (3.8)	16.6–39.2	**0.021**
Current smoker (%)	2.7	-	7.6	-	0.159
Previous/current smoker (%)	20.5	-	40.7	-	**0.004**
Previous LBP (%)	4.2	-	92.3	-	**<0.001**
Sleep hours per night (h)	7.4 (1.2)	4–10	6.9 (1.3)	4–10	**0.006**
Sleep quality[a]	4.0 (2.3)	0–9	6.5 (3.2)	1–15	**<0.001**
Poor sleeper (%)[b]	27.1	-	57.8	-	**<0.001**
Depressive symptoms[c]	8.6 (6.5)	1–27	13.7 (9.0)	0–39	**<0.001**
Clinically sig. depression (%)[d]	15.3	-	34.5	-	**0.004**
Pain catastrophizing[e]:	7.5 (9.6)	0–41	13.5 (10.2)	0–49	**<0.001**
Rumination	3.0 (3.8)	0–13	4.7 (4.0)	0–16	**0.004**
Magnification	1.6 (2.1)	0–9	3.40 (2.7)	0–12	**<0.001**
Helplessness	2.9 (4.4)	0–23	5.4 (4.7)	0–21	**<0.001**

[a]Scored using the 19-item Pittsburgh Sleep Quality Index. Higher scores reflect poorer sleep.

[b]Interpreted from the Pittsburgh Sleep Quality Index. A global sum of "6" or greater indicates a "poor" sleeper

[c]Scored using the 20-item Epidemiological Studies of Depression Scale. Higher scores reflect greater depressive symptoms.

[d]Interpreted from the Epidemiological Studies of Depression Scale. A global sum of "16" or greater indicates clinically significant depressive symptoms.

[e]Scored using the 13-item Pain Catastrophizing Scale. Higher scores reflect greater pain-related catastrophizing. Components of the questionnaire include rumination, magnification and helplessness.

Significant values are in bold font.

Table 3. High- (N = 91) and low-pain (N = 29) participant characteristics.

	Low-Pain		High-Pain		
Characteristic	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**P-value**
Age (yrs)	31 (9)	18–49	29 (8)	18–50	0.290
Sex (male, %)	55.2	-	48.4	-	0.522
BMI (kg/m^2)	24.1 (3.6)	16.9–31.5	23.9 (3.9)	16.6–39.2	0.835
Current smoker (%)	6.9	-	8.0	-	0.853
Previous/current smoker (%)	41.4	-	39.8	-	0.878
Previous LBP (%)	96.4	-	90.9	-	0.342
Pain intensity[a]	2.5 (0.7)	1–3	5.8 (1.3)	4–9	**<0.001**
Disability severity[b]	4.8 (3.3)	1–14	7.0 (4.4)	1–21	**0.015**
Sleep hours per night (h)	7.0 (1.2)	4–9	6.9 (1.3)	4–10	0.496
Sleep quality[c]	6.3 (2.8)	1–12	6.6 (3.3)	1–15	0.644
Poor sleeper (%)[d]	53.6	-	59.1	-	0.607
Depressive symptoms[e]	14.8 (10.5)	0–39	13.4 (8.5)	0–37	0.491
Clinically sig. depression (%)[f]	39.3	-	33.0	-	0.538
Fear avoidance (work)[g]	12.1 (8.7)	0–27	12.1 (9.8)	0–36	0.998
Fear avoidance (activity)[h]	13.5 (5.5)	0–24	15.1 (5.5)	0–24	0.165
Pain self-efficacy[i]	46.1 (10.6)	14–60	44.1 (10.7)	18–60	0.444
Pain catastrophizing[j]:	10.4 (7.8)	1–34	14.5 (10.8)	0–49	0.060
Rumination	3.6 (3.1)	0–12	5.0 (4.2)	0–16	0.096
Magnification	3.1 (2.1)	0–9	3.5 (2.8)	0–12	0.400
Helplessness	3.7 (3.3)	0–13	5.9 (5.0)	0–21	**0.029**

[a]Scored on a 0 to 10 numerical rating scale (0 = no pain, 10 = worst pain imaginable)

[b]Scored using the 24-item Roland Morris Disability Questionnaire. Higher scores reflect greater disability.

[c]Scored using the 19-item Pittsburgh Sleep Quality Index. Higher scores reflect poorer sleep.

[d]Interpreted from the Pittsburgh Sleep Quality Index. A global sum of "6" or greater indicates a "poor" sleeper

[e]Scored using the 20-item Epidemiological Studies of Depression Scale. Higher scores reflect greater depressive symptoms.

[f]Interpreted from the Epidemiological Studies of Depression Scale. Scores greater than 15 indicate clinically significant depressive symptoms.

[g]Scored using the 5-item Fear Avoidance Beliefs Questionnaire-Work. Higher scores indicate higher levels of fear-avoidance beliefs related to work.

[h]Scored using the 11-item Fear Avoidance Beliefs Questionnaire-Physical Activity. Higher scores indicate higher levels of fear-avoidance beliefs related to physical activity.

[i]Scored using the 10-item Pain Self-Efficacy Questionnaire. Higher scores reflect stronger self-efficacy beliefs with respect to performing activities while in pain.

[j]Scored using the 13-item Pain Catastrophizing Scale. Higher scores reflect greater pain-related catastrophizing. Components of the questionnaire include rumination, magnification and helplessness.

Significant values are in bold font.

Table 4. Principal component analysis of pain threshold and conditioned pain modulation data in low back pain participants.

Sensory test	PC 1	PC 2	PC3
PPT - thumb	**0.67**	-0.03	0.17
PPT - back	**0.70**	0.06	0.10
HPT - forearm	**0.74**	-0.06	-0.36
HPT - back	**0.80**	0.03	-0.17
CPT - forearm	**-0.73**	0.13	0.06
CPT - back	**-0.76**	-0.01	-0.01
CPM (TS-thumb/CS-forearm)	-0.21	**0.69**	-0.31
CPM (TS-forearm/CS-forearm)	0.20	**0.55**	0.03
CPM (TS-thumb/CS-back)	-0.05	**0.67**	0.28
CPM (TS-forearm/CS-back)	0.29	0.05	**0.79**
CPM (TS-back/CS-forearm)	0.28	**0.50**	-0.11
% of variance	31.9	13.8	9.2
Cumulative % of variance	31.9	45.7	54.8

Two of the first three principal components shown were retained (no shading). Variable loading on each principal component was considered significant if ≥±0.5 (highlighted in bold). PPT, pressure pain threshold; HPT, heat pain threshold; CPT, cold pain threshold; CPM, conditioned pain modulation; TS, test stimulus; CS, conditioning stimulus.

Table 5. Sensory, clinical and demographic measures for the four low back pain subgroups identified by PCA-based hierarchical clustering and the control group.

Variable	Cluster 1: High Sensitivity (N=34)	Cluster 2: Low CPM efficacy (N=33)	Cluster 3: High Sensitivity/Low CPM Efficacy (N=27)	Cluster 4: Low Sensitivity/High CPM Efficacy (N=31)	Controls (N=74)	Main Effect (P)
Sensory						
PPT – thumb (kPa)†	**381.5 (111.1)****	594.1 (153.6)	**366.1 (110.1)****	535.6 (154.3)	494.51 (168.2)	**<0.001**
PPT – back (kPa)†	**359.8 (153.8)*****	639.0 (258.8)	**368.0 (153.0)*****	661.9 (276)	607.86 (239.2)	**<0.001**
HPT – arm (°C)†	**41.5 (4.0)*****	46.0 (2.5)	**41.7 (3.4)*****	45.8 (1.7)	45.2 (3.1)	**<0.001**
HPT – back (°C)†	**40.8 (3.6)*****	45.9 (3.3)	**40.4 (3.9)*****	46.2 (2.1)	45.8 (3.0)	**<0.001**
CPT – arm (°C)	**17.9 (7.1)*****	5.3 (5.6)	**16.4 (7.3)****	6.8 (7.1)	8.9 (8.9)	**<0.001**
CPT – back (°C)	**16.7 (8.7)*****	4.6 (7.7)	**17.8 (7.8)*****	4.6 (8.6)	4.7 (7.3)	**<0.001**
CPM (TS-thumb/CS-arm)†	58.7 (44.5)	**-48.8 (67.0)*****	-17.3 (41.7)	38.3 (58.4)	19.9 (66.8)	**<0.001**
CPM (TS-arm/CS-arm)†	40.5 (42.0)	6.3 (35.9)	**4.2 (49.4)•**	68.0 (78.8)	46.8 (80.1)	**<0.001**
CPM (TS-thumb/CS-back)†	42.5 (52.0)	**-37.9 (65.1)****	**-30.8 (68.9)***	50.0 (73.9)	18.3 (77.2)	**<0.001**
CPM (TS-arm/CS-back)†	15.5 (81.9)	49.0 (66.9)	1.2 (67.8)	40.1 (85.3)	41.9 (69.2)	**0.028**
CPM (TS-back/CS-arm)†	55.2 (47.9)	32.1 (87.5)	**-2.9 (70.5)****	118.2 (89.6)	72.7 (111.8)	**<0.001**
Clinical						
Pain intensity (NRS)	**5.1 (1.7)*****	**5.0 (2.0)*****	**5.2 (1.9)*****	**4.9 (1.9)*****	0.0 (0.0)	**<0.001**

Disability (RMDQ)	**5.3 (3.6)*** **	**5.8 (4.3)*** **	**7.3 (4.7)*** **	**7.9 (4.1)*** **	0.0 (0.0)	**<0.001**
Demographic						
Age (yrs)	26.8 (7.4)	**31.5 (7.1)***	27.3 (9.6)	30.6 (7.7)	26.6 (6.5)	**0.006**
Sex (male, %)	35.3	63.6	40.7	58.1	39.2	0.056
BMI (kg/m^2)	23.1 (3.2)	24.2 (3.9)	24.6 (4.4)	24.7 (3.8)	22.7 (4.4)	0.074
Previous/current smoker (%)	35.3	20.3	40.7	38.7	20.5	0.080

Variables were compared across all four clusters using one-way ANOVAs (continuous variables), Kruskal-Wallis (CPT – arm; CPT – back) or chi-squared tests (categorical variables).

†P-value is calculated after log-transformation.

Continuous data described as mean ±SD. Categorical data described as number (%).

Values in bold font are significantly different from the control group (post-hoc: clusters 1–4 *vs* control, •p=0.056; *p<0.05; **p<0.01; ***p<0.001).

Table 6. Association of factors on pain thresholds in response to pressure (PPT) and heat (HPT) at the forearm/thumb and back.

Variable	PPT-thumb	PPT-back	HPT-forearm	HPT-back
Age (yrs)	-	-	0.17 (0.03–0.31)*	-
Sex (male, %)	0.29 (0.15–0.42)***	0.28 (0.15–0.42)***	-	-
Pain intensity (NRS)	-	-0.19 (-0.33– -0.05)**	-0.22 (-0.36– -0.08)**	-0.23 (-0.38–0.08)**
5+ drinks monthly[a]	0.31 (0.0–0.52)**	-	-	0.23 (0.09–0.44)*
PSQI: sleep efficiency 65-75%[b]	-	-	-	0.38 (0.12–0.65)**
PSQI: sleep disturbance <1 times/w[c]				0.36 (0.12–0.61)**
PSQI: daytime dysfunction 1-2 times/w[d]	-	-	-	0.27 (0.04–0.49)*
PSQI: sleep med. <1 times/w[e]	-	0.43 (0.17–0.68)**	-	-
CES-D: total score	-	-0.17 (-0.31– -0.03)*	-	-
Pain catastrophizing	-	-	-	-0.17 (-0.31– -0.02)*
Overall fit (R^2)	**0.12**	**0.23**	**0.07**	**0.25**

Data represent regression coefficients (95% confidence intervals) of various factors demonstrating an association with pressure and heat pain thresholds (log transformed) using stepwise linear regression models. Only significant factors are shown (*p<0.05; **p<0.01; ***p<0.001): [a]frequency at which 5 or more alcoholic drinks are consumed in a single drinking session, [b]average amount of sleep as a percentage of total time spent in bed per night in the last month, [c]frequency of sleep disturbances in the last month, [d]frequency of sleep-related daytime dysfunction experienced in the last month, [e]frequency of sleep medication use to help sleep in the last month.

Table 7. Predictors of a low cold pain threshold (bottom tertile: >14.9°C) as opposed to a high cold pain threshold (top tertile: <4.4°C) at the forearm and back.

Variable	CPT-forearm	CPT-back
Age (yrs)	-	-0.09 (-0.17– -0.02)*
Pain intensity (NRS)	-	0.32 (0.13–0.50)***
≥5 drinks[a]	3.22 (1.78–4.65)***	-
Drink freq 2-3 times/w[b]	1.00 (0.08–1.93)*	1.25 (0.18–2.33)*
5+ drinks monthly[c]	-	-1.46 (-2.84– -0.07)*
PSQI: sleep hours[d]	0.41 (0.05–0.76)*	-
PSQI: sleep disturbance ≥1 times/w[e]	4.52 (3.48–5.56)***	4.23 (3.09–5.36)***
PSQI: daytime dysfunction ≥1 times/w[f]	-4.93 (-6.31– -3.56)***	-5.34 (-6.85– -3.83)***
Somers' D	**0.54**	**0.66**

Data represent the log odds (95% confidence intervals) for various factors predictive (negatively or positively) of a cold pain threshold >14.9°C (low-CPT) based on stepwise logistic regression models. Only significant factors are shown (*p<0.05; **p<0.01; ***p<0.001): [a]number of alcoholic drinks typically consumed when drinking, [b]frequency at which alcohol is consumed, [c]frequency at which 5 or more alcoholic drinks are consumed in a single drinking session, [d]average number of hours slept per night in the last month, [e]frequency of sleep disturbances in the last month, [f]frequency of sleep-related daytime dysfunction experienced in the last month.

Table 8. Predictors of facilitatory conditioned pain modulation (CPM value <0) for different test stimulus (TS) and conditioning stimulus (CS) configurations.

	Stimuli Configuration				
Variable	**TS-thumb/CS-forearm**	**TS-forearm/CS-forearm**	**TS-thumb/CS-back**	**TS-forearm/CS-back**	**TS-back/CS-forearm**
Sex (male, %)	0.41 (0.08–0.73)*	-	-	-	0.38 (0.01–0.76)*
Disability (RMDQ)	-	0.09 (0.01–0.17)*	-	-	-
Smoke now/ever	-	-	-	0.53 (0.17–.89)**	-
≥5 drinks[a]	-3.20 (-4.37– -2.02)***	3.41 (2.24–4.60)***	-3.28 (-4.37– -2.19)***	3.28 (2.04–4.52)***	2.34 (0.65–4.02)**
Drink freq 2-3 times/w[b]	-	0.77 (0.04–1.49)*	-	-	-
5+ drinks <monthly[c]	-0.68 (-1.29– -0.06)*	-	-	-	-
PSQI: sleep latency >60 min[d]	-	-	-	-	1.15 (0.10–2.19)*
PSQI: sleep disturbance ≥1 times/w[e]	4.40 (3.65–5.15)***	3.88 (3.09–4.67)***	4.20 (3.45–4.95)***	4.23 (3.45–5.01)***	7.83 (6.98–8.68)***
PSQI: daytime dysfunction ≥1 times/w[f]	-	-	-4.02 (-4.99– -3.05)***	-	-
Somers' D	**0.40**	**0.40**	**0.22**	**0.35**	**0.42**

Data represent the log odds (95% confidence intervals) for various factors predictive (negatively or positively) of facilitatory CPM based on stepwise logistic regression models. Only significant factors are shown (*p<0.05; **p<0.01; ***p<0.001): [a] number of alcoholic drinks typically consumed when drinking, [b]frequency at which alcohol is consumed, [c]frequency at which 5 or more alcoholic drinks are consumed in a single drinking session,

[d]average time taken to fall asleep per night in the last month, [e]frequency of sleep disturbances in the last month, [f]frequency of sleep-related daytime dysfunction experienced in the last month.

Figure 1.

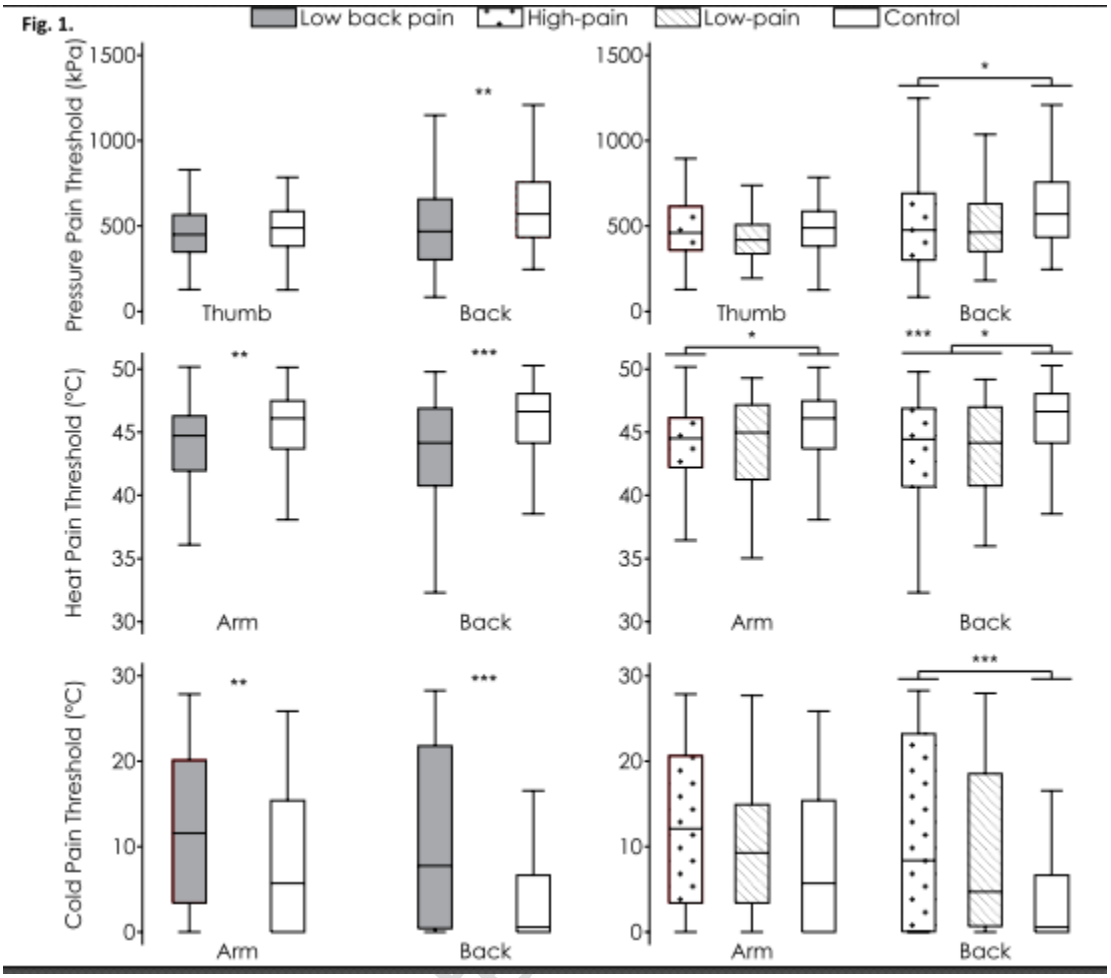

Figure 2.

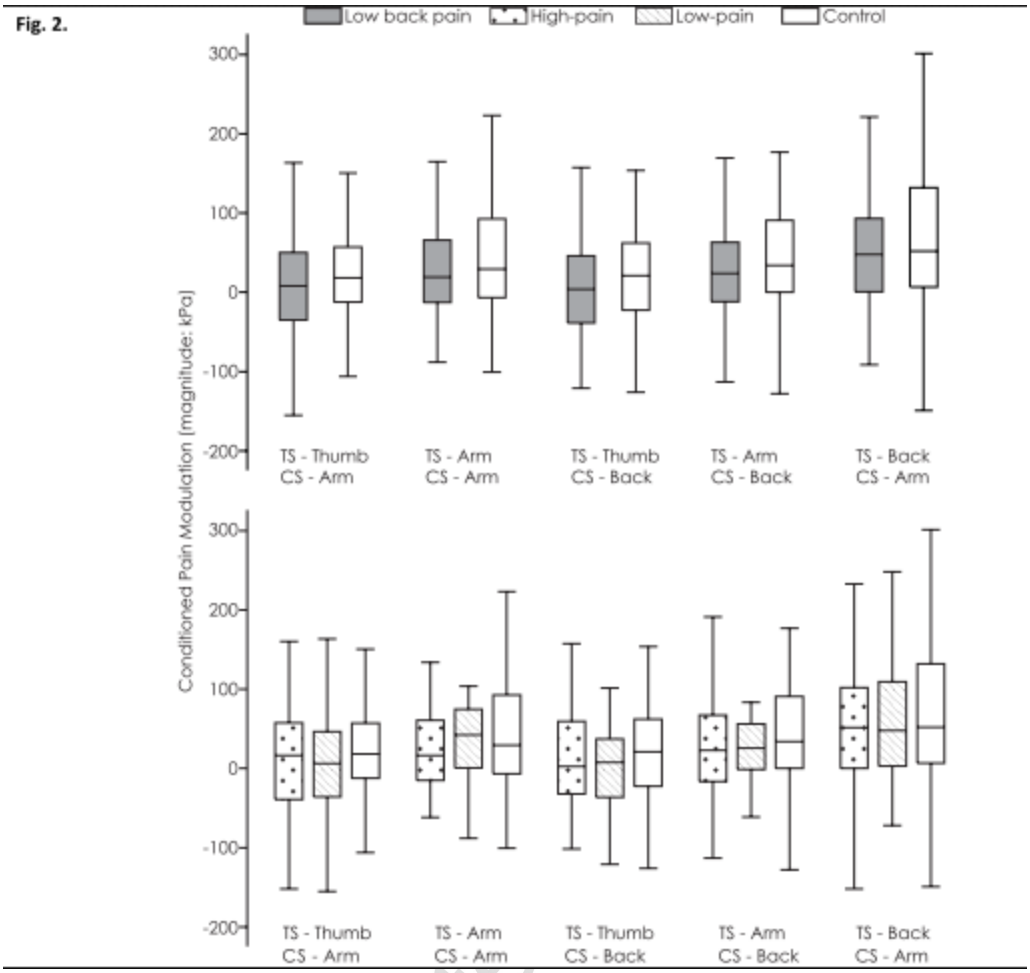

Figure 3.

Fig. 3.

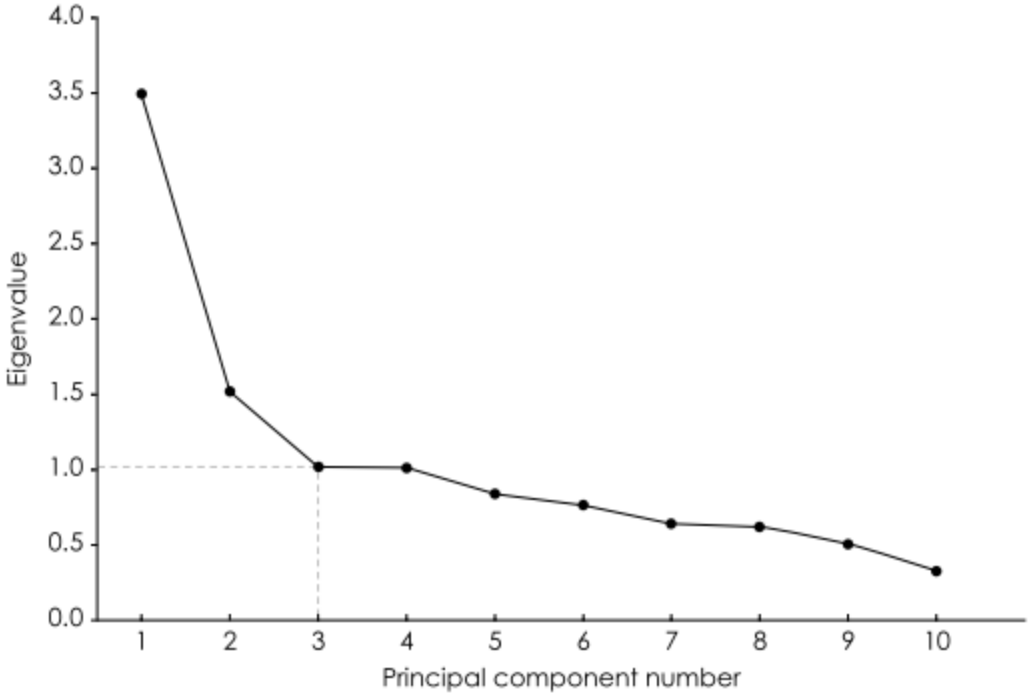

Figure 4.