Are signs of central sensitisation in acute low back pain a precursor to poor outcome?

David M. Klyne , G. Lorimer Moseley , Michele Sterling , Mary F. Barbe , Paul W. Hodges

PII: S1526-5900(18)30470-X
DOI: https://doi.org/10.1016/j.jpain.2019.03.001
Reference: YJPAI 3715

To appear in: *Journal of Pain*

Received date: 6 September 2018
Revised date: 13 February 2019
Accepted date: 2 March 2019

Please cite this article as: David M. Klyne , G. Lorimer Moseley , Michele Sterling , Mary F. Barbe , Paul W. Hodges , Are signs of central sensitisation in acute low back pain a precursor to poor outcome?, *Journal of Pain* (2019), doi: https://doi.org/10.1016/j.jpain.2019.03.001

Highlights

- Central sensitisation presents in some but not all individuals with acute back pain
- Presence of central sensitisation early does not necessarily precede poor outcome
- Early sensitisation precedes poor outcome when combined with psychological factors

Title: Are signs of central sensitisation in acute low back pain a precursor to poor outcome?

Authors: David M. Klyne[a]; G. Lorimer Moseley[bc]; Michele Sterling[d]; Mary F. Barbe[e]; Paul W. Hodges*[a]

Affiliations: [a]The University of Queensland, NHMRC Centre of Clinical Research Excellence in Spinal Pain, Injury and Health, School of Health and Rehabilitation Sciences, Brisbane, Australia; [b]University of South Australia, Adelaide, Australia; [c]Neuroscience Research Australia, Sydney, Australia; [d]Recover Injury Research Centre, NHMRC CRE in Recovery after Road Traffic Injury, Griffith University, Southport, Australia; [e]Temple University, Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, United States of America.

Disclosures: This research was funded by the National Health and Medical Research Council (NHMRC) of Australia (Project Grant: ID631369; Program Grant: APP1091302). PWH supported by NHMRC Fellowship APP1002190. GLM supported by NHMRC Fellowship ID1061279. MS supported by NHMRC Fellowship APP1002489. There are no conflicts of interest related to this work.

Corresponding author

Address: School of Health and Rehabilitation Sciences, The University of Queensland, Brisbane QLD, Australia 4072

Contact: **Tel/fax –** +61 404 854 589 **E-mail –** p.hodges@uq.edu.au

Abstract

Central sensitisation is considered to have a pathophysiological role in chronic low back pain (LBP). Whether individuals with increased central sensitisation early in their condition are more likely to develop persistent pain or whether it increases over time is unclear. This study aimed to determine whether sensory profiles during acute LBP differ between individuals who did and did not recover by 6-months and to identify subgroups associated with outcomes. Individuals with acute LBP (<2 weeks of onset, N=99) underwent pain threshold (heat/cold/pressure) and conditioned pain modulation (CPM) testing after completing questionnaires related to pain/disability, sleep, and psychological status. Sensory measures were compared during the acute phase (baseline) and longitudinally (baseline/6-months) between unrecovered (≥pain and disability), partially recovered (<pain and/or disability), and recovered (no pain and disability) participants at 6-months. We assessed baseline patterns of sensory sensitivity alone, and with psychological and sleep data, using hierarchical clustering and related the clusters to outcome (pain/disability) at 3- and 6-months. No sensory measure at either time-point differed between groups. Two subgroups were identified that associated with more ("high sensitivity") or less ("high sensitivity and negative psychological state") recovery. These data appear to suggest that central sensitisation during the acute-phase resolves for many, but is a precursor to the transition to chronicity when combined with other psychological features.

Perspective: Central sensitisation signs during early-acute low back pain does not necessarily precede poor outcome, but may be sustained in conjunction with other psychological factors and facilitate pain persistence.

Keywords: Central sensitisation; peripheral sensitisation; hyperalgesia; conditioned pain modulation; transition to chronicity.

1. Introduction

Ongoing enhanced pain sensitivity (hyperalgesia) is a common feature in chronic low back pain (LBP) [100, 125]. Multiple mechanisms contribute to this form of hyperalgesia, most of which involve neural changes that alter processing of nociceptive information [6, 62, 127]. These changes can arise quickly or develop over time in response to "peripheral" or "central" processes that increase neuronal excitability within the central nervous system (CNS). Peripherally, inflammatory agents (e.g., cytokines) in post-injury tissue enhance nociceptor sensitivity, which is called peripheral sensitisation. Centrally, increased responsiveness of spinal nociceptive neurones and their cortical projections can outlast the tissue-based input or be maintained by a normally sub-threshold tissue-based input [58, 124, 126, 127], a situation known as central sensitisation. Central sensitisation involves a range of phenomena and mechanisms that manifest as pain produced in response to normally innocuous stimuli (allodynia) and greater sensitivity to normally noxious stimuli (hyperalgesia) that spreads beyond the originally painful area, sometimes to affect the entire body (generalised hyperalgesia) [72, 79]. Despite evidence of greater central sensitisation across many chronic pain conditions [125], it is unknown whether individuals with more significant signs of central sensitisation in the early acute phase of LBP are more likely to develop persistent pain (i.e., chronic pain), or whether central sensitisation increases later in the acute-to-chronic pain time course.

Evidence of central sensitisation in chronic LBP is conflicting [100]. Generalised hyperalgesia to cutaneous heat and cold [26], cold only [46], pressure [83] or none [8] have been reported. Deficient conditioned pain modulation (CPM; thought to reflect the capacity of endogenous anti-nociceptive mechanisms) [71, 128] has been reported in various chronic pain conditions [2, 51, 87, 111], but studies in chronic LBP are inconclusive [20, 31, 74, 92].

Central sensitisation can be moderated or triggered by psychological or behavioural aspects [5, 22, 36, 78, 103] via shared neural circuitries and interconnected neuro-immune pathways [78]. Both psychological (e.g., depression) and behavioural (e.g., poor sleep) stressors have been associated with measures of central sensitisation [1, 14, 16, 85, 104], and frequently occur together in chronic pain conditions including chronic LBP [29, 52, 81, 123]. Whether or not the coexistence of sensitisation, psychological and/or behavioural features in the early phase of acute LBP is related to poor outcome has not been tested.

This study had four primary objectives. First, we tested whether signs of central sensitisation, measured using a suite of sensory assessments, during the acute-phase of LBP (baseline), differed between individuals who had and had not recovered at 6 months. Second, whether signs of central sensitisation changed over-time (baseline to 6 month) differently for the outcome groups. Third, we compared outcome at 3 and 6 months for four *a priori* defined sub-groups based on our previous findings of presentations of sensory sensitivity in acute LBP [59]. Fourth, we sought to identify whether the addition of psychological and sleep features to pain assessments improved accuracy for prediction of differences in outcomes at 3 or 6 months.

2. Methods

2.1 Participants

One-hundred and twenty-nine people in an acute episode of LBP (66 M, 63 F) aged 28±8 (mean±SD) participated in the study. Of these, 99 completed (51 M, 48 F; aged 30±8 years) and 30 did not complete (non-participants: 15 M, 15 F; aged 26±8 years) follow-up testing at 6 months. 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. Some data from this participant cohort have been reported previously [59].

Participants were recruited and assessed within 2 weeks of onset of an acute episode of LBP that was preceded by at least 1 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. Participants were excluded if they were < 18 or > 50 years old, had a confirmed or suspected serious spinal pathology, had major pain or injury to other body regions in the previous 12 months, or had other major diseases or disorders. To control factors that might influence sensitisation, participants were also excluded if they were using corticosteroids or anti-cytokine therapy. Participants were allowed to use pain

medications that do not affect inflammatory cytokines (i.e., simple analgesics such as paracetamol) and if required could use non-steroidal anti-inflammatory pain medication (e.g., Ibuprofen) provided it ceased five days prior to their laboratory assessments.

Participants reported their "average" level of LBP and LBP-related disability in the past week within 24 h of their first assessment session and each subsequent fortnight for 6 months. LBP was assessed using a numerical rating scale (NRS) anchored with "no pain" at 0 and "worst pain imaginable" at 10 in response to the question: "Please give a number to describe your average pain over the past week". Pain-related disability was assessed using the Roland Morris Disability Questionnaire (RMDQ [99]), 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). In addition to the exclusion criteria listed above, potential participants who reported pain of < 1 on the NRS and/or a score of < 1 on the RMDQ in the week prior to their first assessment session were excluded from the study.

2.3 Procedures

Participants completed a series of online questionnaires related to their general health, demographics, psychological status, and sleep behaviour within 24 hours of their initial 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 random order before assessing CPM. This procedure was replicated 6 months later for follow-up evaluation.

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 and sleep variables: We selected measures of psychological variables with satisfactory psychometric properties that considered the three key domains shown to be relevant in LBP: cognitive (expectations, beliefs, and perceptions' concerning pain) [10, 38, 65, 68], emotional (distress, anxiety, and depression) [88], and behavioural (coping, pain behaviour, and activity/activity avoidance) [38, 65, 68]. The 20-item Center for Epidemiological Studies Depression Scale (CES-D, range: 0–60) [93] was used to assess depressive symptoms (i.e., *emotional domain*) in the past week [64]. The 13-item Pain Catastrophizing Scale (PCS, range: 0–52) was used to assess the presence of catastrophic thought processes related to pain (i.e., *cognitive domain*) [86]. The 11-item 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) attributed to the participants' LBP (i.e., *behavioural domain*) – higher scores indicate higher levels of fear-avoidance beliefs [114]. Unemployed participants were removed from the final FABQ-W dataset. The 10-item Pain Self-Efficacy Questionnaire (PSEQ, range: 0–60) was used to assess the confidence participants had in performing activities while in pain (i.e., *cognitive and behavioural domains*) [77] – higher scores imply a greater confidence in the ability to do things despite pain. With respect to sleep, duration and quality were assessed with the Pittsburgh Sleep Quality Index (PSQI) [15]. The 19-item PSQI and its psychometric properties have been validated in various populations including those with insomnia [3, 17] – higher scores reflect greater sleep complaints. For analyses we used self-reported hours of actual sleep and total PSQI scores (range: 0–21).

2.3.2 Sensory testing

Sensory tests were performed as described previously [59, 60] and outlined briefly below.

Pain thresholds: Pain thresholds to heat, cold and pressure were measured at two locations: (1) lower back (local) – site at which the participant reported "most" pain on palpation, and (2) thumb/forearm (remote) – thumbnail (PPT) and proximal volar aspect of the forearm (HPT/CPT) on the opposite side of the body to that used to assess pain thresholds at the lower back.

Thermal pain thresholds were tested using a Thermal Sensory Analyzer (TSA 2001, Medoc, Israel) system with a 30 × 30 mm Peltier contact probe. For HPT, the thermode started at 30 °C and increased at rate of 0.7 °C/s with a cut-off of limit of 52 °C. Participants pressed a stop button when they first perceived the stimulus as painful [106]. Five trials were performed at each site (back and forearm), separated by an inter-stimulus interval of 10 s, and the mean of the last three trials was used as the "HPT" [89]. For CPT, the thermode started at 30 °C and decreased at rate of 0.7 °C/s with a cut-off limit of 0 °C. Participants pressed a stop button when they first perceived the stimulus as painful [106]. As for HPT, five trials were performed at each site (10-s inter-stimulus intervals) and the mean of the last three trials was used as the "CPT". For the determination of PPT, a pressure algometer (Somedic A/B, Stockholm, Sweden) with a 1-cm disc-shaped probe head was applied at an increasing rate of ~40 kPa/s. Participants pressed a stop button when the stimulus changed from one of pressure to one of pain [106]. Three trials were performed at each site and a mean score in kPa was calculated.

Conditioned pain modulation: CPM is measured as the difference in pain perceived in response to a noxious stimulus (test stimulus – TS) before and during/after the application of a secondary noxious stimulus (conditioning stimulus – CS). Here, CPM was assessed approximately 20 minutes after assessment of pain thresholds using a parallel paradigm in which a noxious TS was applied before, and then simultaneously with, a CS 30 seconds after onset. PPT, performed in an identical manner to that outlined above, served as the TS. Contact heat delivered by a computerised stimulation device (30 × 30 mm Peltier contact probe) served as the CS. 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 seconds, 30 seconds, 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 NRS. If the reported pain in response to the CS was less than

"45" on the 101-NRS before application of the TS (30 seconds 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 increases or decreases in temperature was required. This procedure ensured the CS was safe and sufficiently intense to induce CPM over a short application time.

Three body regions were selected for testing to explore whether application of the TS/CS to the painful region affects the CPM response: (1) lower back (as for pain thresholds [see above]), (2) forearm (TS – proximal region of the muscle belly of extensor carpi radialis longus; CS – proximal volar aspect), and (3) thumbnail (TS only). Trials were conducted in three test blocks (separated by a 15-minute break [122]) 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

The CPM response for each of the arrangements was calculated as the difference between the TS scores obtained before and during the CS [130]. A higher TS score (i.e., higher pain threshold) during the CS than baseline indicated pain inhibition (positive value). A lower TS score (i.e., lower pain threshold) during the CS than baseline indicated pain facilitation (negative value) [128, 129]. Two final CPM scores were calculated for analysis: (1) average of the CPM responses for TS/CS arrangements using the same anatomy (upper limbs: "CPM-sa"), and (2) average of the CPM responses for TS/CS arrangements using mixed anatomy (back and upper limbs: "CPM-ma"). CPM responses were averaged across multiple testing sites to reduce the potential for spurious findings that may be associated with interpretation of CPM from a single measure [59].

2.4 Statistical analysis

Analyses were performed using Statistica v12 (StatSoft) and Stata v14 (Stata Corp). Significance threshold was set at $\alpha < 0.05$. Data that were not normally distributed (i.e., pain threshold and CPM measures were skewed), as indicated by a Kolmogorov-Smirnov test: $p < 0.05$, were log-transformed. To assess for potential attrition bias due to follow-up loss, baseline questionnaire and sensory data were compared between participants (N = 99) and non-participants (i.e., excluded because they did not provide follow-up data after baseline testing: N = 30) at follow-up using Fisher's exact (categorical variables) or independent t tests (continuous variables).

Participants were categorised based on their 6-month pain (NRS) and disability (RMDQ) status: (1) those with increased or unchanged pain and disability from baseline, or a pain score of ≥ 7/10 (corresponding to severe pain [11]) at 6 months (N = 15, "unrecovered"), (2) those with decreased but not fully resolved pain and/or disability from baseline (N = 65, "partially recovered"), and (3) those with no pain and disability at 6 months (N = 19, "recovered"). Six-month pain and disability status were calculated by separately averaging the final three fortnightly NRS and RMDQ scores (final month: weeks 20, 22, and 24). LBP participants (N = 30) without these data could not be categorised.

Questionnaire data were compared between the unrecovered, partially recovered and recovered LBP groups using Fisher's exact tests (categorical variables) or one-way ANOVAs (continuous variables). Pain thresholds and CPM values (CPM-sa and CPM-ma) were first compared between LBP groups (*group*: unrecovered *vs.* partially recovered *vs.* recovered) for the first aim at baseline using one-way ANOVAs, and then over time (*session*: baseline *vs.* 6 months), for the second aim using repeated measures ANOVAs. These techniques were preferred over others (e.g., linear mixed models) because of the relatively simple study design and complete data set. Bonferroni's test was used for post hoc analysis.

According to our third and fourth aims, cluster analysis was conducted in two ways:

(1) First, for aim three we repeated methods used previously to generate sub-groups based exclusively on sensory data at baseline (i.e., during the acute phase) [59]. Pain threshold (PPT, HPT, and CPT) and CPM (all five individual measures) data were entered into a principal component analysis (PCA)

to reduce the dimensionality of the original data set into a series of linear, non-correlated "principal components" (PCs) [131]. The first PC accounts for the greatest proportion of the variability in the dataset, followed by the second PC, and so forth [97]. PCs with eigenvalues > 1 or above a break in the scree plot ("elbow" criterion: value at which added dimensions no longer explain the data substantially) were retained [21, 50]. Variables with considerable influence on each PC were defined as those with a factor loading $\geq \pm 0.5$ [33]. Unbiased hierarchical clustering (cosine similarity, complete linkage) was performed on the retained PCs (individual participant t-scores converted to Z-scores: each t-score subtracted by the mean of the group and divided by the standard deviation of the group) to determine the existence of sub-groups in acute LBP based on the sensory testing results.

(2) Second, for aim four we explored potential sub-groups based on analysis of data that included psychological and sleep factors, in addition to sensory data, without subjecting data to PCA. Hierarchical clustering (Euclidean distance, complete linkage) was performed on baseline (acute phase) measures of sensitivity (PPT, HPT, and PPT), CPM-sa, CES-D, PCS, and PSQI, with all data standardised to Z-scores. To reduce the risk of spurious groupings, the three psychological variables (FABQ and PSEQ) that were least different ($p>0.0380$) between the unrecovered, partially recovered and recovered groups at baseline were excluded to increase the sample size-to-variable ratio. As an additional post hoc analysis, not to answer the primary questions of the study, we repeated the process using only CES-D, PCS and PSQI data to assess whether sub-groups based on psychological and sleep factors alone (i.e., without sensory data) were associated with measures of outcome.

Clustering was performed using the publicly available Morpheus webtool (https://software.broadinstitute.org/morpheus/). The optimal number of clusters was determined by inspecting the dendrogram/heatmap and limiting the minimum number of participants per cluster to 10. After clustering, one-way ANOVAs or Fisher's exact tests were used to determine which variables differed between the clusters, and whether measures of outcome (pain/disability at 3 and 6 months, and % change in pain and disability from baseline to 6 months), demographics, and the percentages of participants from the three LBP groups differed between clusters.

3. Results

3.1 Comparisons at baseline between participants and non-participants at follow-up

Baseline characteristics were mostly similar between participants and non-participants at follow-up, except for higher disability ($p = 0.020$) and lower pain self-efficacy ($p = 0.022$) in non-participants. Pain thresholds and CPM magnitudes were not different between groups.

3.2 Characteristics at baseline in LBP outcome groups

The three LBP groups based on outcome at 6 months shared similar health and demographic characteristics at baseline. However, *unrecovered* participants had greater depressive symptoms (post hoc: $p = 0.005$) and a lower BMI (post hoc: $p = 0.047$) than *recovered* participants, and both *unrecovered* and *partially recovered* participants had greater pain catastrophizing (post hoc: all $p < 0.009$) and a greater incidence of previous LBP (Fisher's exact: all $p < 0.043$) than *recovered* participants (Table 1).

3.3 Sensory profiles at baseline in LBP outcome groups

Pain thresholds and CPM magnitudes for each LBP outcome group at baseline and 6 months are presented in Fig. 1. One-way ANOVAs of baseline data confirmed that there were no sensory differences during the acute phase for any measure between the three LBP outcome groups (all $p > 0.288$; Table 2).

3.4 Sensory profiles at baseline and 6 months in LBP outcome groups

Repeated measures ANOVAs that compared sensory measures at two time-points revealed a significant *group* × *session* interaction for CPT measured at the arm ($F[2, 87] = 3.3$, $p = 0.040$). Although average sensitivity to cold pain tended to increase over time in *unrecovered* participants and decrease in *partially recovered* and *recovered* participants at 6 months, no significant post hoc differences were found. Sensitivity to pressure (PPT) at the

back was less at 6 months than at baseline in *recovered* participants (main effect: session – F[1, 87] = 6.8, p = 0.011; post hoc: p = 0.049) and sensitivity to heat (HPT) at the back was less at 6 months than at baseline in *partially recovered* participants (main effect: session – F[1, 87] = 7.2, p = 0.009; post hoc: p = 0.019). No *group* differences were found for any measure.

3.5 A priori PCA-based cluster analysis of sensory data at baseline: 3- and 6-month outcome differences between clusters

Results from the PCA-based cluster analysis of sensory variables at baseline replicate our previous findings [59]. Two PCs accounting for 46.4% of the total variation in the sensory data (Table 3) were derived from the PCA and can be summarised as representing the dimensions pain threshold (PC1) and CPM (PC2). Hierarchical clustering based on these PCs revealed four sub-groups with distinct sensory profiles (Fig. 2 and Table 4), which were termed: "high sensitivity" (Cluster 1), "low CPM efficacy" (Cluster 2), "high sensitivity/low CPM efficacy" (Cluster 3), and "low sensitivity/high CPM efficacy" (Cluster 4). Outcome analyses showed that clusters did not differ in terms of pain or disability at 3 months, 6 months, or in the percent change in pain/disability from baseline to 6 months (Table 4). This indicates that baseline pain sensitivity/CPM alone was not related to outcome.

3.6 Cluster analysis of sensory, psychological, and sleep data at baseline

Hierarchical clustering of sensory, psychological, and sleep data identified three distinct clusters (Fig. 3), termed: "high sensitivity and negative psychological state" (Cluster 1), "high sensitivity" (Cluster 2), and "low sensitivity" (Cluster 3). ANOVAs confirmed variables that differentiated the clusters (Table 5) and post hoc analyses confirmed the between-cluster differences. Clusters 1 and 2 were more sensitive than Cluster 3 to all stimulus types at all anatomical locations (post hoc: all $p < 0.006$), and Cluster 2 was more sensitive to heat pain at the arm than Cluster 1 (post hoc: p = 0.006). Differentiating the two high sensitivity clusters, Cluster 1 also had higher depressive symptoms and pain catastrophizing than Clusters 2 and 3 (post hoc: all $p < 0.004$), and poorer sleep quality than Cluster 3 (post hoc: p = 0.011). Clusters also differed with respect to the percentages of participants in each of the three LBP outcome groups (Fisher's exact: p = 0.047; Fig. 3): Cluster 1 contained more *unrecovered* (29.4%) and less *recovered* (0%) participants,

but similar *partially recovered* participants, than Cluster 2 (*unrecovered* = 7.9%, *partially recovered* = 63.2%, *recovered* = 28.9%; Fisher's exact: p = 0.007).

Measures of pain (NRS) and disability (RMDQ) 3 and 6 months after baseline differed between clusters. Cluster 1 ("high sensitivity and negative psychological state") reported greater pain than Cluster 2 ("high sensitivity"), and greater disability than Clusters 2 and 3 ("low sensitivity") at both time points (post hoc: all $p < 0.042$). In addition, Cluster 1 reported least recovery (% change from baseline to 6 months) and Cluster 2 reported most recovery (post hoc: $p = 0.032$), with respect to pain. However, recovery with respect to disability was not different between clusters. Baseline pain, disability and demographics did not differ between clusters (Table 5).

Clustering of baseline psychological and sleep data, without sensory data, generated four distinct clusters (Table 6). Cluster 1 was characterised by high depressive symptoms, Cluster 2 by high pain catastrophizing, Cluster 3 by low depressive and pain catastrophizing symptoms, and Cluster 4 by poor sleep. Although clusters could be differentiated by disability at baseline, and both pain and disability at 3 months, they were not different with respect pain and disability at 6 months, or the degree of recovery at 6 months.

4. Discussion

Our first three aims were to determine whether recovery at 6 months could be differentiated on the basis of signs of central sensitisation early (baseline) and/or at follow-up (6 months) by comparing individual sensory measures between recovery groups, or by an *a priori* PCA-based cluster analysis of baseline sensory data. Both approaches failed. As a fourth aim we also sought to determine whether adding psychological and sleep features at the acute stage improved differentiation of groups, which they did: those with high sensitivity, high depressive symptoms, catastrophizing and poor sleep

had the poorest outcomes at 3 and 6 months. In contrast, those with high sensitivity but low depressive symptoms, catastrophizing and good sleep had the best outcomes at 3 and 6 months.

4.1 Sensory sensitisation alone is not associated with outcome

No single or combination of measure(s) of pain sensitivity/CPM at baseline could differentiate LBP groups or clusters (PCA-based) with respect to outcome. Few studies have prospectively examined the association between sensory profiles in LBP and outcome. However, there are associated data that seem corroborative. For example, a recent systematic review [70] revealed three studies that took sensory measures (including pain thresholds/CPM) at the back and a remote site in individuals with LBP and related them to outcomes. Those measures did not predict clinically significant pain at 4 months in participants initially assessed after their first primary care visit for a LBP episode (65% ≤ 30 days of LBP onset) [63], or pain intensity at 1 year [75] or work ability at 2 years [80] in participants who already had chronic pain at baseline assessment. Another study investigated whether sensory profiles relate to long-term risk of recurrence: people with recent LBP or no/remitted LBP, who had a low PPT at the back or limbs, had no increased risk of developing future LBP 4 and 8 years later [82]. A systematic review of cross-sectional studies also found no correlation between pain thresholds (pressure, thermal, electrical) and spinal (back, neck) pain, regardless of the test site or the duration of pain [45].

There are examples in other pain conditions where sensory measures do seem to predict outcome. For instance, CPT and PPT were shown to be prognostic in whiplash-associated disorders [107, 115] and lateral epicondylalgia [19], and pre-operative higher pain sensitivity (lower PPT, HPT, electrical PT [120]) and lower CPM efficacy [130] have been associated with greater post-operative pain. The relationships however, may not be as simple as they might seem: one study in acute whiplash injury showed that pain sensitivity does not remain a "predictor" of outcome when accounting for other variables (using multiple regression) including initial symptoms, arousal, and age [98]. Differences in the nature and severity of the injury/condition between studies may explain some of the variation in results. Further, central sensitisation is likely not one phenomena that can be activated and modulated by various

mechanisms, each of which could affect outcomes differently at different times. Hence, sensory tests alone might lack sensitivity to consistently detect the various manifestations of central sensitisation. However, an alternative explanation is that heightened sensitivity is only a precursor to poor outcome for some individuals, and may depend on interaction with other factors, as might be suggested by the current results.

Increased pain sensitivity is one of a number of so-called "sickness responses" that occurs when the body is subjected to an immune challenge such as infection [35, 67, 117]. Similar processes occur with injury. Generalised pain amplification in this context is consistent with a "short-term" survival-enhancing strategy that aids tissue healing (and host defence) by restricting movement and conserving energy until the injury has healed [53, 108, 117]. This is consistent with human and animal studies showing that the cellular and molecular changes associated with central (and peripheral) sensitisation can occur rapidly and alter function dramatically, but are usually relatively short-lasting and reversible [62, 72, 127]. This could also explain why generalised hyperalgesia is evident in acute LBP of < 2 weeks [59], though not associated with outcome. The present data suggest that an increased gain of central neurons (i.e., central sensitisation) resulting in generalised hyperalgesia could be interpreted as an adaptive feature of acute LBP that normally resolves, but may be sustained beyond tissue repair by certain interacting factors.

That early development of central sensitisation is not a determinant of outcome but considered to play a key role in the development of chronic pain presents an apparent paradox. Interactions between the immune and nervous systems may provide insight. Inflammatory agents in damaged tissue increase the excitability of nociceptor terminals (peripheral sensitisation) causing enhanced sensitivity to noxious and non-noxious stimuli at the injured site (primary hyperalgesia) [58, 69, 127]. The ensuing barrage of peripheral inflow can soon trigger changes within the spinal cord that contribute to segmental (central) sensitisation by enhancing excitatory and reducing inhibitory inputs [55, 62, 101, 127]. These changes manifest as hyperalgesia surrounding the injured site (secondary hyperalgesia) and serve a logical protective function [72].

Many of the same inflammatory agents (i.e., cytokines) can spill over into circulation and evoke a systemic inflammatory response [54, 66, 95]. Systemically, cytokines can reach or signal the CNS via a number of routes [4, 90, 91, 112, 118] and activate spinal and brain glial cells [96], which produce a range of substances that are instrumental to setting the stimulus-response profile in nociceptive pathways and adaptive behaviour [117, 121]. Confirmative evidence linking systemic inflammation and pain has come from studies showing a rapid increase in widespread pain sensitivity after administration of inflammatory provoking agents in the periphery of healthy humans and animals [23, 113, 119], which can be attenuated by inhibiting peripheral cytokines [30, 67, 116] or central glia [43, 44, 113, 117]. A dysregulated inflammatory response, locally or systemically, could therefore lead to excessive or ongoing inflammation that facilitates central sensitisation to such an extent that the organism becomes "over protected". It seems highly likely that this neuro-immune upregulation significantly contributes to ongoing enhancement of sensitivity to somatosensory input, characteristic of some chronic pain states [62, 117].

4.2 Sub-groups associated with outcome

Sub-groups generated with the addition of psychological and sleep data had different outcomes. Pain (NRS) and disability (RMDQ) scores at 3 and 6 months were highest and pain recovery (% change from baseline to 6 months) was worst in those with enhanced sensitivity to all stimulus types and locations in combination with high depressive, pain catastrophizing, and sleep (poorer) scores (Cluster 1 – "high sensitivity and negative psychological state"). Conversely, individuals with similarly high sensitivity but lower psychological and sleep scores had the lowest pain/disability at both time points and best recovery at 6 months (Cluster 2 – "high sensitivity"). Individuals with generally low sensitivity (Cluster 3 – "low sensitivity") had similar outcomes to Cluster 2. Although other data suggest a relationship between psychosocial features and transition to chronicity [37 56], the sub-groups based on psychological and sleep variables alone, without the sensory data, were not associated with recovery and outcomes at 6 months. These findings support our view that central sensitisation presents in some but not all individuals with acute LBP, and that its presence in the acute-phase does not necessarily precede poor outcome.

We speculate that psychological influences during acute LBP mediate the maintenance of central sensitisation. Many processes that control pain overlap with those that are considered involved in psychological disorders such as depression [76, 108]. It is perhaps not surprising then that there is high comorbidity between pain, pain catastrophizing and depression, and that each might influence the other [7, 18, 37, 56, 109]. This relationship might in part be explained by underlying inflammatory processes. Six meta-analytic reviews on inflammatory profiles in depression show that pro-inflammatory cytokines are elevated in depressed individuals who are otherwise healthy compared to non-depressed individuals [24, 39, 41, 42, 132]. In addition, increased cytokines have been found to prospectively predict the development of depressive symptoms [27, 28, 32, 110], and vice versa, depression and pain catastrophizing predict increases in cytokines [25, 27, 61]. As described above, many of these cytokines modulate pain and are important in both initiating and maintaining central sensitisation (for review see [76, 108]). Although the mechanisms that link these features are complex and remain to be fully elucidated, the hypothalamic-pituitary-adrenal axis (HPA-axis) and its vulnerability to stress and immune responses may be a common factor [7, 27, 40, 94].

Poor sleep also featured in the "high sensitivity and negative psychological state" cluster (Cluster 1). This concurs with the view that sleep, pain, and psychological features are interrelated and that the direction of causality is bidirectional. Poor/restricted sleep reduces pain thresholds [49, 57, 102] and sleep problems exacerbate existing pain and predict new-onset pain [9, 84]. Psychological factors appear to mediate the association between sleep and pain [81, 85, 104], and conversely, sleep seems to mediate the association between pain and depression [34, 73]. Again, inflammation is thought to be involved. Sleep modulates cytokines by interfering with the HPA-axis and sympathetic nervous system [48, 105], and cytokines modulate sleep by acting on neurons within brain regions implicated in the regulation of sleep-wake behaviour [12, 13, 47]. Overall, disturbance to either sleep, mood, or inflammation could setup a viscous negative cycle between the three that could initiate and/or sustain central sensitisation and hyperalgesia.

4.3 Methodological limitations

A limitation of this study is the potential for attrition bias due to loss to follow-up of some participants. Participants (N = 30) that did not follow-up (here referred to as non-participants), and who were therefore not included in the main analyses, had higher disability and lower pain self-efficacy at baseline than follow-up participants. However, as differences were relatively weak (all $p > 0.020$) and all other variables were similar between groups it is unlikely that our overall findings were influenced by excluding data from participants lost to follow-up. Another consideration of this study is that 15% and 12% of participants reported to be taking simple analgesics (e.g., paracetamol) and/or non-steroidal anti-inflammatory medication at the time of baseline and follow-up testing, respectively. To help control the influence of these factors on sensitisation, participants were instructed cease using medications that affect inflammation at least five days prior to testing.

4.4 Conclusions

This study provides evidence that generalised hyperalgesia consistent with central sensitisation presents early in some individuals during acute LBP, but its presence does not necessarily precede poor outcome at 3 and 6 months. Negative outcomes are more likely, however, with other features such as depressive and pain catastrophizing symptoms in conjunction with signs of central sensitisation. Our work supports that central sensitisation during the acute-phase can be a "normal" adaptive response that resolves for many, but may be exaggerated and/or sustained by other factors. Further studies that test this theory and explore potential mechanisms, including inflammation, will be interesting to follow.

Acknowledgements

This research was funded by the National Health and Medical Research Council (NHMRC) of Australia (Project Grant: ID631369; Program Grant: APP1091302). PWH supported by NHMRC Fellowship APP1002190. GLM supported by NHMRC Fellowship ID1061279. MS supported by

NHMRC Fellowship APP1002489. In the last five years, GLM has received support from Pfizer, Workers' Compensation boards in Australia, North America and Europe, the International Olympic Committee and Port Adelaide Football Club. PWH and GLM receive speaker's fees for lectures on pain and rehabilitation and received royalties for books on pain. The other authors have no conflicts of interest to declare.

5 References

1. Adams LM, Turk DC. Psychosocial factors and central sensitivity syndromes. *Curr Rheumatol Rev.* 11:96-108, 2015

2. Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, Graven-Nielsen T. Sensitization in patients with painful knee osteoarthritis. *Pain.* 149:573-581, 2010

3. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. *J Psychosom Res.* 53:737-740, 2002

4. Banks WA, Kastin AJ, Broadwell RD. Passage of cytokines across the blood-brain barrier. *Neuroimmunomodulation.* 2:241-248, 1995

5. Bardin L, Malfetes N, Newman-Tancredi A, Depoortere R. Chronic restraint stress induces mechanical and cold allodynia, and enhances inflammatory pain in rat: Relevance to human stress-associated painful pathologies. *Behav Brain Res.* 205:360-366, 2009

6. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell.* 139:267-284, 2009

7. Blackburn-Munro G, Blackburn-Munro RE. Chronic pain, chronic stress and depression: coincidence or consequence? *J Neuroendocrinol.* 13:1009-1023, 2001

8. Blumenstiel K, Gerhardt A, Rolke R, Bieber C, Tesarz J, Friederich HC, Eich W, Treede RD. Quantitative sensory testing profiles in chronic back pain are distinct from those in fibromyalgia. *Clin J Pain.* 27:682-690, 2011

9. Boardman HF, Thomas E, Millson DS, Croft PR. The natural history of headache: predictors of onset and recovery. *Cephalalgia.* 26:1080-1088, 2006

10. Boersma K, Linton SJ. How does persistent pain develop? An analysis of the relationship between psychological variables, pain and function across stages of chronicity. *Behav Res Ther.* 43:1495-1507, 2005

11. Boonstra AM, Schiphorst Preuper HR, Balk GA, Stewart RE. Cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain. *Pain.* 155:2545-2550, 2014

12. Breder CD, Dinarello CA, Saper CB. Interleukin-1 Immunoreactive Innervation of the Human Hypothalamus. *Science.* 240:321-324, 1988

13. Breder CD, Tsujimoto M, Terano Y, Scott DW, Saper CB. Distribution and Characterization of Tumor Necrosis Factor-Alpha-Like Immunoreactivity in the Murine Central-Nervous-System. *J Comp Neurol.* 337:543-567, 1993

14. Burton E, Campbell C, Robinson M, Bounds S, Buenaver L, Smith M. Sleep mediates the relationship between central sensitization and clinical pain. *J Pain.* 17:S56-S56, 2016

15. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index - a New Instrument for Psychiatric Practice and Research. *Psychiat Res.* 28:193-213, 1989

16. Campbell CM, Buenaver LF, Finan P, Bounds SC, Redding M, McCauley L, Robinson M, Edwards RR, Smith MT. Sleep, Pain Catastrophizing, and Central Sensitization in Knee Osteoarthritis Patients With and Without Insomnia. *Arthrit Care Res.* 67:1387-1396, 2015

17. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. *J Psychosom Res.* 45:5-13, 1998

18. Chou KL. Reciprocal relationship between pain and depression in older adults: Evidence from the English Longitudinal Study of Ageing. *J Affect Disorders.* 102:115-123, 2007

19. Coombes BK, Bisset L, Vicenzino B. Cold hyperalgesia associated with poorer prognosis in lateral epicondylalgia: a 1-year prognostic study of physical and psychological factors. *Clin J Pain.* 31:30-35, 2015

20. Correa JB, Costa LOP, de Oliveira NTB, Sluka KA, Liebano RE. Central sensitization and changes in conditioned pain modulation in people with chronic nonspecific low back pain: a case-control study. *Exp Brain Res.* 233:2391-2399, 2015

21. Costello AB, W. O. Best Practices in Exploratory Factor Analysis: Four Recommendations for Getting the Most From Your Analysis. *Practical Assessment Research and Evaluation.* 10, 2005

22. Crettaz B, Marziniak M, Willeke P, Young P, Hellhammer D, Stumpf A, Burgmer M. Stress-induced allodynia--evidence of increased pain sensitivity in healthy humans and patients with chronic pain after experimentally induced psychosocial stress. *PLoS One.* 8:e69460, 2013

23. de Goeij M, van Eijk LT, Vanelderen P, Wilder-Smith OH, Vissers KC, van der Hoeven JG, Kox M, Scheffer GJ, Pickkers P. Systemic inflammation decreases pain threshold in humans in vivo. *PLoS One.* 8:e84159, 2013

24. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctot KL. A Meta-Analysis of Cytokines in Major Depression. *Biol Psychiat.* 67:446-457, 2010

25. Edwards RR, Kronfli T, Haythornthwaite JA, Smith MT, Mcguire L, Page GG. Association of catastrophizing with interleukin-6 responses to acute pain. *Pain.* 140:135-144, 2008

26. Edwards RR, Wasan AD, Michna E, Greenbaum S, Ross E, Jamison RN. Elevated pain sensitivity in chronic pain patients at risk for opioid misuse. *J Pain.* 12:953-963, 2011

27. Fasick V, Spengler RN, Samankan S, Nader ND, Ignatowski TA. The hippocampus and TNF: Common links between chronic pain and depression. *Neurosci Biobehav R.* 53:139-159, 2015

28. Felger JC, Lotrich FE. Inflammatory Cytokines in Depression: Neurobiological Mechanisms and Therapeutic Implications. *Neuroscience.* 246:199-229, 2013

29. Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: Dopamine as a putative mechanism. *Sleep Med Rev.* 17:173-183, 2013

30. Follenfant RL, Nakamuracraig M, Henderson B, Higgs GA. Inhibition by Neuropeptides of Interleukin-1-Beta-Induced, Prostaglandin-Independent Hyperalgesia. *Brit J Pharmacol.* 98:41-43, 1989

31. Gerhardt A, Eich W, Treede RD, Tesarz J. Conditioned pain modulation in patients with nonspecific chronic back pain with chronic local pain, chronic widespread pain, and fibromyalgia. *Pain.* 158:430-439, 2017

32. Gimeno D, Kivimaki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A, Kumari M, Lowe GDO, Rumley A, Marmot MG, Ferrie JE. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychol Med.* 39:413-423, 2009

33. Hair JF, Black WC, Babin BJ: Multivariate Data Analysis: A Global Perspective. 7 edition, Pearson Education, London, 2010.

34. Hamilton NA, Pressman M, Lillis T, Atchley R, Karlson C, Stevens N. Evaluating Evidence for the Role of Sleep in Fibromyalgia: A Test of the Sleep and Pain Diathesis Model. *Cognit Ther Res.* 36:806-814, 2012

35. Hart BL. Biological Basis of the Behavior of Sick Animals. *Neurosci Biobehav R.* 12:123-137, 1988

36. Hassett AL, Clauw DJ. Does psychological stress cause chronic pain? *The Psychiatric clinics of North America.* 34:579-594, 2011

37. Haythornthwaite JA, Clark MR, Pappagallo M, Raja SN. Pain coping strategies play a role in the persistence of pain in post-herpetic neuralgia. *Pain.* 106:453-460, 2003

38. Henschke N, Maher CG, Refshauge KM, Herbert RD, Cumming RG, Bleasel J, York J, Das A, McAuley JH. Prognosis in patients with recent onset low back pain in Australian primary care: inception cohort study. *Brit Med J.* 337, 2008

39. Herbert TB, Cohen S. Depression and Immunity - a Meta-Analytic Review. *Psychol Bull.* 113:472-486, 1993

40. Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin A, Makinson R, Scheimann J, Myers B. Regulation of the Hypothalamic- Pituitary-Adrenocortical Stress Response. *Compr Physiol.* 6:603-621, 2016

41. Hiles SA, Baker AL, de Malmanche T, Attia J. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: Exploring the causes of heterogeneity. *Brain Behavior and Immunity.* 26:1180-1188, 2012

42. Howren MB, Lamkin DM, Suls J. Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis. *Psychosom Med.* 71:171-186, 2009

43. Hua XY, Svensson CI, Matsui T, Fitzsimmons B, Yaksh TL, Webb M. Intrathecal minocycline attenuates peripheral inflammation-induced hyperalgesia by inhibiting p38 MAPK in spinal microglia. *Eur J Neurosci.* 22:2431-2440, 2005

44. Huang CY, Chen YL, Li AH, Lu JC, Wang HL. Minocycline, a microglial inhibitor, blocks spinal CCL2-induced heat hyperalgesia and augmentation of glutamatergic transmission in substantia gelatinosa neurons. *J Neuroinflammation.* 11:7, 2014

45. Hubscher M, Moloney N, Leaver A, Rebbeck T, McAuley JH, Refshauge KM. Relationship between quantitative sensory testing and pain or disability in people with spinal pain-A systematic review and meta-analysis. *Pain.* 154:1497-1504, 2013

46. Hubscher M, Moloney N, Rebbeck T, Traeger A, Refshauge KM. Contributions of mood, pain catastrophizing, and cold hyperalgesia in acute and chronic low back pain: a comparison with pain-free controls. *Clin J Pain.* 30:886-893, 2014

47. Imeri L, Opp MR. How (and why) the immune system makes us sleep. *Nature reviews. Neuroscience.* 10:199-210, 2009

48. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. *Nat Rev Immunol.* 11:625-632, 2011

49. Irwin MR, Olmstead R, Carrillo C, Sadeghi N, FitzGerald JD, Ranganath VK, Nicassio PM. Sleep Loss Exacerbates Fatigue, Depression, and Pain in Rheumatoid Arthritis. *Sleep.* 35:537-543, 2012

50. Jolliffe IT: Choosing a subset of principal components or variables. In: Principal component analysis, Springer-Verlag, New York, 2002.

51. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain.* 114:295-302, 2005

52. Kanaan S, Siengsukon C, Arnold P, Burton D, Emmanuel N, Sharma N. Relationship between sleep quality and functional and psychological symptoms in patients with chronic low back pain. *Physiotherapy.* 101:e713-e714

53. Karshikoff B, Jensen KB, Kosek E, Kalpouzos G, Soop A, Ingvar M, Hoglund CO, Lekander M, Axelsson J. Why sickness hurts: A central mechanism for pain induced by peripheral inflammation. *Brain Behavior and Immunity.* 57:38-46, 2016

54. Kataranovski M, Magic Z, Pejnovic N. Early inflammatory cytokine and acute phase protein response under the stress of thermal injury in rats. *Physiol Res.* 48:473-482, 1999

55. Kawasaki Y, Zhang L, Cheng JK, Ji RR. Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord. *J Neurosci.* 28:5189-5194, 2008

56. Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LM. Psychological aspects of persistent pain: Current state of the science. *J Pain.* 5:195-211, 2004

57. Kelly GA, Blake C, Power CK, O'Keeffe D, Fullen BM. The Association Between Chronic Low Back Pain and Sleep A Systematic Review. *Clinical Journal of Pain.* 27:169-181, 2011

58. Kidd BL, Urban LA. Mechanisms of inflammatory pain. *Br J Anaesth.* 87:3-11, 2001

59. Klyne DM, Moseley GL, Sterling M, Barbe MF, Hodges PW. Individual Variation in Pain Sensitivity and Conditioned Pain Modulation in Acute Low Back Pain: Effect of Stimulus Type, Sleep, and Psychological and Lifestyle Factors. *J Pain.* 2018

60. Klyne DM, Schmid AB, Moseley GL, Sterling M, Hodges PW. Effect of Types and Anatomic Arrangement of Painful Stimuli on Conditioned Pain Modulation. *J Pain.* 16:176-185, 2015

61. Kubera M, Obuchowicz E, Goehler L, Brzeszcz J, Maes M. In animal models, psychosocial stress-induced (neuro)inflammation, apoptosis and reduced neurogenesis are associated to the onset of depression. *Prog Neuro-Psychoph.* 35:744-759, 2011

62. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain.* 10:895-926, 2009

63. LeResche L, Turner JA, Saunders K, Shortreed SM, Von Korff M. Psychophysical tests as predictors of back pain chronicity in primary care. *J Pain.* 14:1663-1670, 2013

64. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging.* 12:277-287, 1997

65. Linton SJ. A review of psychological risk factors in back and neck pain. *Spine (Phila Pa 1976).* 25:1148-1156, 2000

66. Mackiewicz A, Speroff T, Ganapathi MK, I K. Effects of Cytokine Combinations on Acute Phase Protein-Production in 2 Human Hepatoma-Cell Lines. *J Immunol.* 146:3032-3037, 1991

67. Maier SF, Watkins LR. Cytokines for psychologists: Implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychol Rev.* 105:83-107, 1998

68. Mallen CD, Peat G, Thomas E, Dunn KM, Croft PR. Prognostic factors for musculoskeletal pain in primary care: a systematic review. *Brit J Gen Pract.* 57:655-661, 2007

69. Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. *Nat Rev Neurosci.* 6:521-532, 2005

70. Marcuzzi A, Dean CM, Wrigley PJ, Chakiath RJ, Hush JM. Prognostic value of quantitative sensory testing in low back pain: a systematic review of the literature. *J Pain Res.* 9:599-607, 2016

71. Melzack R: Folk medicine and the sensory modulation of pain. 3rd edition, Churchill Livingstone, Edinburgh, 1994.

72. Meyer RA, Ringkamp M, Campbell JN, Raja SN. Neural mechanisms of hyperalgesia after tissue injury. *Johns Hopkins APL Technical Digest (Applied Physics Laboratory).* 26:56-66, 2005

73. Miro E, Martinez MP, Sanchez AI, Prados G, Medina A. When is pain related to emotional distress and daily functioning in fibromyalgia syndrome? The mediating roles of self-efficacy and sleep quality. *Brit J Health Psych.* 16:799-814, 2011

74. Mlekusch S, Neziri AY, Limacher A, Juni P, Arendt-Nielsen L, Curatolo M. Conditioned Pain Modulation in Patients With Acute and Chronic Low Back Pain. *Clin J Pain.* 32:116-121, 2016

75. Mlekusch S, Schliessbach J, Camara RJA, Arendt-Nielsen L, Juni P, Curatolo M. Do Central Hypersensitivity and Altered Pain Modulation Predict the Course of Chronic Low Back and Neck Pain? *Clinical Journal of Pain.* 29:673-680, 2013

76. Nekovarova T, Yamamotova A, Vales K, Stuchlik A, Fricova J, Rokyta R. Common mechanisms of pain and depression: are antidepressants also analgesics? *Front Behav Neurosci.* 8, 2014

77. Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. *Eur J Pain.* 11:153-163, 2007

78. Nijs J, Loggia ML, Polli A, Moens M, Huysmans E, Goudman L, Meeus M, Vanderweeen L, Ickmans K, Clauw D. Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients? *Expert Opin Ther Tar.* 21:817-826, 2017

79. Nijs J, Torres-Cueco R, van Wilgen CP, Girbes EL, Struyf F, Roussel N, van Oosterwijck J, Daenen L, Kuppens K, Vanwerweeen L, Hermans L, Beckwee D, Voogt L, Clark J, Moloney N, Meeus M. Applying modern pain neuroscience in clinical practice: criteria for the classification of central sensitization pain. *Pain Physician.* 17:447-457, 2014

80. Nordeman L, Gunnarsson R, Mannerkorpi K. Prognostic Factors for Work Ability in Women With Chronic Low Back Pain Consulting Primary Health Care A 2-Year Prospective Longitudinal Cohort Study. *Clinical Journal of Pain.* 30:391-398, 2014

81. O'Brien EM, Waxenberg LB, Atchison JW, Gremillion HA, Staud RM, McCrae CS, Robinson ME. Negative Mood Mediates the Effect of Poor Sleep on Pain Among Chronic Pain Patients. *Clinical Journal of Pain.* 26:310-319, 2010

82. O'Neill S, Kjaer P, Graven-Nielsen T, Manniche C, Arendt-Nielsen L. Low pressure pain thresholds are associated with, but does not predispose for, low back pain. *Eur Spine J.* 20:2120-2125, 2011

83. O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. *Eur J Pain.* 11:415-420, 2007

84. Odegard SS, Sand T, Engstrom M, Stovner LJ, Zwart JA, Hagen K. The long-term effect of insomnia on primary headaches: a prospective population-based cohort study (HUNT-2 and HUNT-3). *Headache.* 51:570-580, 2011

85. Onen SH, Alloui A, Gross A, Eschaller A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res.* 10:35-42, 2001

86. Osman A, Barrios FX, Kopper BA, Hauptmann W, Jones J, O'Neill E. Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med.* 20:589-605, 1997

87. Pielsticker A, Haag G, Zaudig M, Lautenbacher S. Impairment of pain inhibition in chronic tension-type headache. *Pain.* 118:215-223, 2005

88. Pincus T, Burton AK, Vogel S, Field AP. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine (Phila Pa 1976).* 27:E109-120, 2002

89. Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. *Pain.* 144:16-19, 2009

90. Quan N, Banks WA. Brain-immune communication pathways. *Brain Behavior and Immunity.* 21:727-735, 2007

91. Quan N, Herkenham M. Connecting cytokines and brain: a review of current issues. *Histol Histopathol.* 17:273-288, 2002

92. Rabey M, Poon C, Wray J, Thamajaree C, East R, Slater H. Pro-nociceptive and anti-nociceptive effects of a conditioned pain modulation protocol in participants with chronic low back pain and healthy control subjects. *Man Ther.* 20:763-768, 2015

93. Radloff LS. The CES-D Scale: a new self-report depression scale for research in the general population *Appl Psychol Meas.* 1:385-401, 1977

94. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol.* 27:24-31, 2006

95. Ramadori G, Christ B. Cytokines and the hepatic acute-phase response. *Semin Liver Dis.* 19:141-155, 1999

96. Ren K, Dubner R. Interactions between the immune and nervous systems in pain. *Nat Med.* 16:1267-1276, 2010

97. Ringner M. What is principal component analysis? *Nat Biotechnol.* 26:303-304, 2008

98. Ritchie C, Hendrikz J, Kenardy J, Sterling M. Derivation of a clinical prediction rule to identify both chronic moderate/severe disability and full recovery following whiplash injury. *Pain.* 154:2198-2206, 2013

99. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. *Spine (Phila Pa 1976).* 8:141-144, 1983

100. Roussel NA, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp R. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clin J Pain.* 29:625-638, 2013

101. Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, Bonventre JV, Woolf CJ. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. *Nature.* 410:471-475, 2001

102. Schey R, Dickman R, Parthasarathy S, Quan SF, Wendel C, Merchant J, Powers J, Han B, Van Handel D, Fass R. Sleep deprivation is hyperalgesic in patients with Gastroesophageal reflux disease. *Gastroenterology.* 133:1787-1795, 2007

103. Schuh-Hofer S, Wodarski R, Pfau DB, Caspani O, Magerl W, Kennedy JD, Treede RD. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. *Pain.* 154:1613-1621, 2013

104. Sivertsen B, Lallukka T, Petrie KJ, Steingrimsdottir OA, Stubhaug A, Nielsen CS. Sleep and pain sensitivity in adults. *Pain.* 156:1433-1439, 2015

105. Slavich GM, Irwin MR. From Stress to Inflammation and Major Depressive Disorder: A Social Signal Transduction Theory of Depression. *Psychol Bull.* 140:774-815, 2014

106. Sterling M. Testing for sensory hypersensitivity or central hyperexcitability associated with cervical spine pain. *J Manip Physiol Ther.* 31:534-539, 2008

107. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. *Pain.* 104:509-517, 2003

108. Strouse TB. The Relationship Between Cytokines and Pain/Depression. *Curr Pain Headache Rep.* 11:98-103, 2007

109. Sullivan MJL, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, Lefebvre JC. Theoretical perspectives on the relation between catastrophizing and pain. *Clinical Journal of Pain.* 17:52-64, 2001

110. van den Biggelaar AH, Gussekloo J, de Craen AJ, Frolich M, Stek ML, van der Mast RC, Westendorp RG. Inflammation and interleukin-1 signaling network contribute to depressive symptoms but not cognitive decline in old age. *Exp Gerontol.* 42:693-701, 2007

111. van Wijk G, Veldhuijzen DS. Perspective on diffuse noxious inhibitory controls as a model of endogenous pain modulation in clinical pain syndromes. *J Pain.* 11:408-419, 2010

112. Varatharaj A, Galea I. The blood-brain barrier in systemic inflammation. *Brain Behavior and Immunity.* 60:1-12, 2017

113. Vega-Avelaira D, Ballesteros JJ, Lopez-Garcia JA. Inflammation-induced hyperalgesia and spinal microglia reactivity in neonatal rats. *Eur J Pain.* 17:1180-1188, 2013

114. Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A Fear-Avoidance Beliefs Questionnaire (Fabq) and the Role of Fear-Avoidance Beliefs in Chronic Low-Back-Pain and Disability. *Pain.* 52:157-168, 1993

115. Walton DM, Macdermid JC, Nielson W, Teasell RW, Reese H, Levesque L. Pressure pain threshold testing demonstrates predictive ability in people with acute whiplash. *J Orthop Sports Phys Ther.* 41:658-665, 2011

116. Wang CJ, Song SY, Zhang Y, Ge YL, Fang XZ, Huang TF, Du J, Gao J. Inhibition of the Rho/Rho kinase pathway prevents lipopolysaccharide-induced hyperalgesia and the release of TNF-alpha and IL-1 beta in the mouse spinal cord. *Sci Rep-Uk.* 5, 2015

117. Watkins LR, Maier SF. Immune regulation of central nervous system functions: from sickness responses to pathological pain. *J Intern Med.* 257:139-155, 2005

118. Watkins LR, Maier SF, Goehler LE. Cytokine-to-Brain Communication - a Review and Analysis of Alternative Mechanisms. *Life Sci.* 57:1011-1026, 1995

119. Wegner A, Elsenbruch S, Maluck J, Grigoleit JS, Engler H, Jager M, Spreitzer I, Schedlowski M, Benson S. Inflammation-induced hyperalgesia: effects of timing, dosage, and negative affect on somatic pain sensitivity in human experimental endotoxemia. *Brain Behav Immun.* 41:46-54, 2014

120. Werner MU, Mjobo HN, Nielsen PR, Rudin A. Prediction of postoperative pain: a systematic review of predictive experimental pain studies. *Anesthesiology.* 112:1494-1502, 2010

121. Wieseler-Frank J, Maier SF, Watkins LR. Central proinflammatory cytokines and pain enhancement. *Neurosignals.* 14:166-174, 2005

122. Willer JC, Roby A, Le Bars D. Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. *Brain.* 107 (Pt 4):1095-1112, 1984

123. Wilson HD, Robinson JP, Turk DC. Toward the Identification of Symptom Patterns in People With Fibromyalgia. *Arthrit Rheum-Arthr.* 61:527-534, 2009

124. Woolf CJ. Evidence for a Central Component of Post-Injury Pain Hypersensitivity. *Nature.* 306:686-688, 1983

125. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain.* 152:S2-15, 2011

126. Woolf CJ, Costigan M. Transcriptional and posttranslational plasticity and the generation of inflammatory pain. *Proc Natl Acad Sci U S A.* 96:7723-7730, 1999

127. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science.* 288:1765-1769, 2000

128. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O. Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain.* 14:339, 2010

129. Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, Landau R, Marchand S, Matre D, Nilsen KB, Stubhaug A, Treede RD, Wilder-Smith OH. Recommendations on practice of conditioned pain modulation (CPM) testing. *Eur J Pain.* 19:805-806, 2015

130. Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain.* 138:22-28, 2008

131. Yeung KY, Ruzzo WL. Principal component analysis for clustering gene expression data. *Bioinformatics.* 17:763-774, 2001

132. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K. The relationship of depression and stressors to immunological assays: A meta-analytic review. *Brain Behavior and Immunity.* 15:199-226, 2001

Figure captions

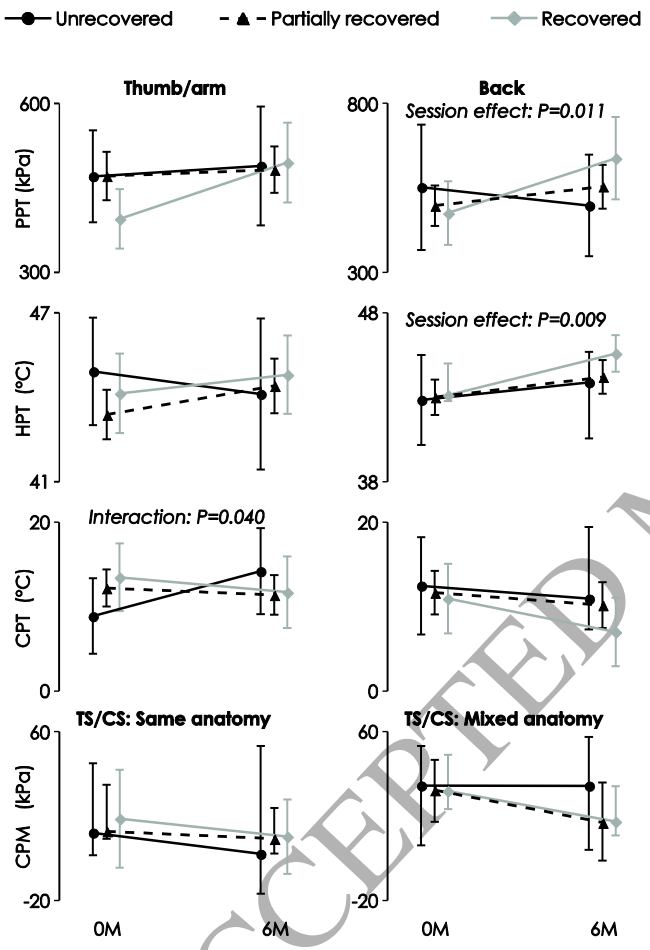

Fig. 1. Baseline and 6 month pain thresholds and conditioned pain modulation magnitudes in participants with low back pain divided into those who were *unrecovered* (≥ pain and disability), *partially recovered* (< pain and/or disability), and *recovered* (no pain and disability) at 6 months. Significant interactions (*group* × *session*) and effects (*session*) derived using repeated measures ANOVAs are shown. Conditioned pain modulation is expressed as the average response to test and conditioning stimuli applied to either the "same" (upper limbs) or "mixed" (upper limb and back) anatomy. Error bars represent 95% confidence intervals. PPT – pressure pain threshold; HPT – heat pain threshold; CPT – cold pain threshold; CPM – conditioned pain modulation; TS – test stimulus; CS – conditioning stimulus.

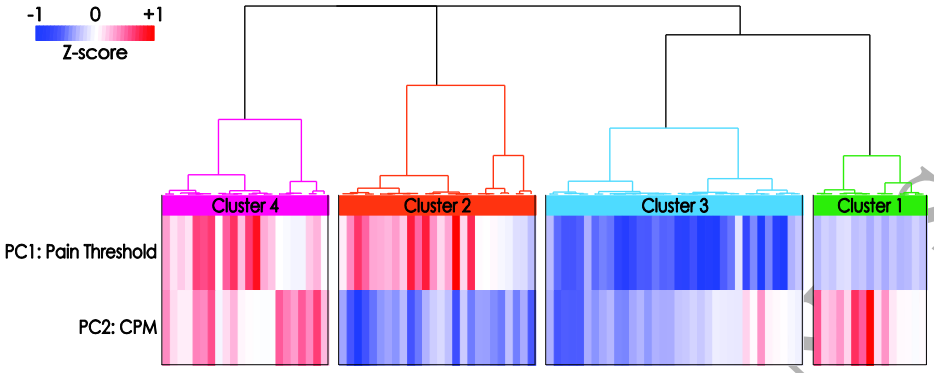

Fig. 2. Hierarchical clustering of acute low back pain individuals based on principle component analysis of sensory data. Results are displayed as a heatmap and dendrogram in which the normalised (Z-scores) principle component (PC) scores are represented by shades of red (positive) and blue (negative). 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).

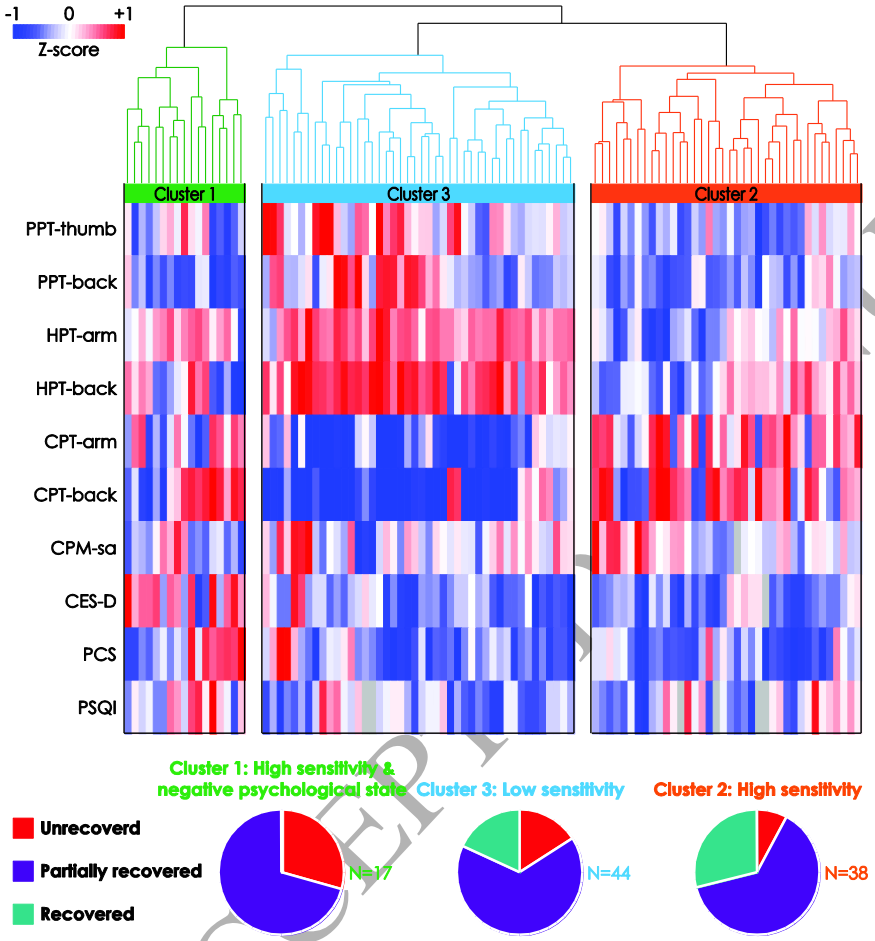

Fig. 3. Heatmap depicting normalised (Z-scores) sensory, psychological, and sleep measures at baseline in participants with low back pain. Each column represents an individual participant and each row represents a variable. Red indicates that the variable value is higher and blue indicates lower. With respect to pain thresholds, a lower value (i.e., temperature or pressure) reflects a lower PPT and HPT (i.e., more sensitive; blue) but a higher CPT (i.e., less sensitive; red). Participants were classified into three distinct clusters using unbiased hierarchical clustering, represented by the dendrogram at the top: Cluster 1 – "high sensitivity & negative psychological state", Cluster 2 – "high sensitivity", and Cluster 3 – "low sensitivity". The percentages of participants in the unrecovered, partially recovered, and recovered groups in each of the three clusters are represented in the pie charts at the bottom. PPT – pressure pain threshold; HPT – heat pain threshold; CPT – cold pain threshold; CPM-sa – conditioned pain modulation (same anatomy); CES-D – Center for Epidemiological Studies Depression Scale; PCS – Pain Catastrophizing Scale; PSQI – Pittsburgh Sleep Quality Index.

Table 1. Baseline characteristics for unrecovered (N = 15), partially recovered (N = 65), and recovered (N = 19) participants.

	Unrecovered		Partially recovered		Recovered		
Characteristic	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**P-value**
Age (yrs)	27.3 (6.6)	19–41	29.8 (7.9)	18–50	30.6 (8.8)	20–49	0.461
Sex (male, %)	53.3	-	53.8	-	42.1	-	0.694
BMI (kg/m^2)	22.9 (3.1)	16.7–27.1	24.0 (3.8)	16.9–39.2	26.2 (4.7)	19.9–37.0	**0.034**
Current smoker (%)	0.0	-	6.3	-	5.3	-	0.999
Previous/current smoker (%)	60.0	-	32.8	-	31.6	-	0.151
Previous LBP (%)	100.00	-	93.8	-	73.7	-	**0.020**
Pain (NRS)	4.5 (1.5)	3–8	5.0 (2.0)	1–9	4.1 (1.9)	1–7	0.171
Disability (RMDQ)	6.1 (4.1)	1–16	6.5 (4.6)	0–21	5.5 (4.1)	1–18	0.668
Depressive symptom (CES-D)	18.2 (10.7)	3–34	12.7 (8.0)	0–36	9.1 (6.5)	0–20	**0.007**
Fear-avoidance beliefs (activity) (FABQ)	14.6 (3.8)	10–21	15.2 (5.6)	1–24	13.2 (6.4)	0–22	0.385
Fear-avoidance beliefs (work) (FABQ)	9.7 (10.2)	0–32	11.8 (6.4)	0–28	9.9 (9.4)	0–36	0.589
Pain catastrophizing (PCS)	14.4 (8.8)	3–34	13.9 (9.3)	0–37	5.4 (4.2)	1–16	< **0.001**
Pain self-efficacy (PSEQ)	46.4 (10.1)	27–60	44.9 (10.2)	14–60	48.3 (11.7)	28–60	0.608
Sleep hours/night (hours, PSQI)	7.1 (1.3)	4–9	6.6 (1.2)	4–9	7.2 (1.2)	5–9	0.174
Sleep quality (PSQI)	10.1 (4.1)	4–18	9.2 (3.2)	4–17	7.9 (3.0)	3–12	0.178

Variable (characteristic) means (±SD) were compared between unrecovered, partially recovered, and recovered low back pain participants using one-way ANOVAs (continuous variables) or Fisher's exact tests (categorical variables).

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

BMI – body mass index; LBP – low back pain; NRS – numerical rating scale; RMDQ – Roland Morris Disability Questionnaire; CES-D – Center for Epidemiological Studies Depression Scale; FABQ – Fear-Avoidance Beliefs Questionnaire; PCS – Pain Catastrophizing Scale; PSEQ – Pain Self-Efficacy Questionnaire; PSQI – Pittsburgh Sleep Quality Index.

Significant values are in bold font.

Table 2. Pain threshold and conditioned pain modulation measures for unrecovered (N = 15), partially recovered (N = 65), and recovered (N = 19) participants at baseline (acute phase).

	Unrecovered		Partially recovered		Recovered		
Characteristic	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**P-value**
PPT – thumb (kPa)	470.7 (159.4)	194.3–687.7	471.1 (174.3)	129.7–829.0	395.0 (116.2)	225.0–703.7	0.229
PPT – back (kPa)	551.5 (362.3)	85.3–1148.7	496.8 (242.7)	136.3–1052.0	475.1 (205.9)	188.0–1035.0	0.940
HPT – forearm (°C)	44.9 (3.7)	35.1–48.9	43.4 (3.6)	34.4–50.2	44.1 (3.1)	36.3–50.4	0.277
HPT – back (°C)	42.8 (5.2)	36.1–48.4	43.0 (4.2)	33.5–49.3	43.9 (2.4)	40.2–48.4	0.979
CPT – forearm (°C)	8.9 (8.7)	0.0–24.4	12.2 (8.9)	0.0–27.7	13.5 (8.8)	0.0–28.7	0.307
CPT – back (°C)	12.4 (11.2)	0.00–27.8	11.6 (10.5)	0.0–27.9	10.9 (9.1)	0.0–28.1	0.963
CPM-sa	23.3 (42.6)	-36.2–112.8	22.0 (51.4)	-92.2–132.2	18.7 (49.5)	-48.7–139.3	0.961
CPM-ma	29.7 (45.7)	-39.2–122.1	36.2 (51.9)	-57.6–157.9	32.0 (31.4)	-36.6–88.7	0.870

Variable means (±SD) were compared after log-transformation between unrecovered, partially recovered, and recovered low back pain participants using one-way ANOVAs.

PPT – pressure pain threshold; HPT – heat pain threshold; CPT – cold pain threshold; CPM-sa – average conditioned pain modulation response when test and conditioning stimuli were applied to the same anatomy (i.e., upper limbs); CPM-ma – average conditioned pain modulation response when test and conditioning stimuli were applied to mixed anatomy (i.e., upper limb and back).

Table 3. Principal component analysis of pain threshold and conditioned pain modulation data in acute low back pain participants.

Sensory test	PC 1	PC 2	PC3
PPT – thumb	**0.64**	-0.15	0.32
PPT – back	**0.70**	-0.07	0.16
HPT – forearm	**0.71**	0.10	-0.32
HPT – back	**0.77**	0.21	-0.20
CPT – forearm	**-0.75**	-0.01	0.19
CPT – back	**-0.76**	-0.13	0.14
CPM (TS-thumb/CS-forearm)	-0.31	**0.72**	-0.23
CPM (TS-forearm/CS-forearm)	0.23	**0.52**	-0.06
CPM (TS-thumb/CS-back)	-0.29	**0.65**	0.32
CPM (TS-forearm/CS-back)	0.38	-0.08	**0.51**
CPM (TS-back/CS-forearm)	0.32	0.40	0.49
% of variance	32.9	13.4	9.0
Cumulative % of variance	32.9	46.4	55.4

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 4. Means for each of the measures used (*clustering variables*: sensory) and not used (*characteristics*: pain and disability at baseline, 3 and 6 months, and demographics) in the PCA-based cluster analysis across the four clusters.

Variable	Cluster 1: High Sensitivity (N = 15)	Cluster 2: Low CPM efficacy (N = 26)	Cluster 3: High Sensitivity/Low CPM Efficacy (N = 34)	Cluster 4: Low Sensitivity/High CPM Efficacy (N = 22)	P-value
Clustering variables					
PPT – thumb (kPa)	395.2 (74.6)	588.6 (147.3)	351.4 (127.7)	515.5 (147.5)	< **0.001**
PPT – back (kPa)	456.6 (143.7)	647.5 (276.3)	327.1 (139.1)	633.0 (274.1)	< **0.001**
HPT – forearm (°C)	44.2 (2.5)	45.6 (2.4)	40.7 (3.4)	45.7 (2.2)	< **0.001**
HPT – back (°C)	43.1 (2.8)	45.0 (3.7)	39.5 (3.2)	46.5 (1.8)	< **0.001**
CPT – forearm (°C)	14.6 (7.7)	6.7 (6.4)	18.7 (6.7)	5.2 (6.5)	< **0.001**
CPT – back (°C)	11.7 (7.5)	6.5 (8.6)	20.1 (7.4)	3.9 (7.9)	< **0.001**
CPM (TS-thumb/CS-forearm)	85.6 (50.1)	-47.8 (74.0)	14.2 (44.9)	31.7 (59.9)	< **0.001**
CPM (TS-forearm/CS-forearm)	44.8 (52.4)	6.8 (36.4)	15.7 (40.1)	77.6 (80.3)	< **0.001**
CPM (TS-thumb/CS-back)	67.2 (85.5)	-45.2 (63.6)	14.5 (44.4)	36.2 (70.8)	< **0.001**
CPM (TS-forearm/CS-back)	27.7 (76.1)	68.8 (98.5)	13.7 (36.7)	42.3 (85.3)	**0.030**
CPM (TS-back/CS-forearm)	77.4 (59.3)	41.2 (85.0)	5.0 (67.2)	118.2 (89.6)	< **0.001**
Characteristics					
Pain intensity: baseline	4.8 (1.9)	5.1 (2.1)	4.6 (1.8)	4.8 (1.9)	0.839
Disability: baseline	4.4 (3.4)	6.6 (4.4)	6.4 (4.6)	7.2 (4.7)	0.293
Pain intensity: 3 months	2.4 (2.0)	3.0 (2.6)	2.7 (2.4)	2.2 (1.9)	0.702
Disability: 3 months	1.9 (2.1)	3.4 (3.0)	3.8 (4.5)	3.0 (3.3)	0.401
Pain intensity: 6 months	2.4 (2.1)	3.0 (2.5)	2.2 (1.9)	2.2 (2.0)	0.290
Disability: 6 months	2.8 (3.3)	3.4 (3.8)	3.1 (4.2)	3.1 (3.9)	0.618

% change in pain[†]	-42.5 (38.8)	-33.3 (44.3)	-44.8 (39.1)	-44.8 (37.3)	0.849
% change in disability[†]	-28.8 (56.8)	-39.6 (47.6)	-42.5 (50.5)	-40.9 (51.5)	0.691
Age (yrs)	31.2 (10.1)	32.1 (6.8)	26.8 (7.3)	30.5 (7.3)	**0.045**
Sex (male, %)	40.0	65.4	50.0	50.0	0.431
BMI (kg/m^2)	24.8 (3.2)	24.5 (3.7)	24.2 (4.9)	23.9 (3.2)	0.904
Previous LBP (%)	93.3	100.0	85.3	86.4	0.152

Variables were compared across all four clusters using one-way ANOVAs (continuous variables) or Fisher's exact tests (categorical variables).

Sensory (pain threshold and conditioned pain modulation) measures were compared after log-transformation.

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

[†]Calculated as the percent change in pain/disability from baseline to 6 months.

Refer to Tables 1-3 for a full description of other measures.

Significant values are in bold font.

Table 5. Means for each of the measures used (*clustering variables*: sensory, psychological, and sleep) and not used (*characteristics*: pain and disability at baseline, 3 and 6 months, and demographics) in the cluster analysis across the three clusters.

Variable	Cluster 1: High sensitivity & negative psychological state (N = 17)	Cluster 2: High sensitivity (N = 38)	Cluster 3: Low sensitivity (N = 44)	P-value
Clustering variables:				
PPT – thumb (kPa)	410.4 (159.7)	376.8 (114.6)	542.9 (162.2)	< **0.001**
PPT – back (kPa)	326.6 (167.5)	421.7 (172.7)	636.8 (277.2)	< **0.001**
HPT – forearm (°C)	44.0 (2.7)	41.0 (3.3)	46.1 (2.0)	< **0.001**
HPT – back (°C)	40.4 (4.5)	41.2 (3.2)	45.9 (2.8)	< **0.001**
CPT – forearm (°C)	13.7 (8.1)	18.2 (7.0)	5.8 (6.2)	< **0.001**
CPT – back (°C)	16.5 (9.6)	17.5 (8.5)	4.7 (7.3)	< **0.001**
CPM-sa	35.2 (44.2)	20.7 (43.5)	17.0 (55.3)	0.333
CES-D	22.6 (10.1)	10.4 (6.2)	11.1 (7.0)	< **0.001**
PCS	19.5 (11.1)	10.3 (7.2)	11.3 (8.5)	**0.001**
PSQI	10.9 (3.5)	9.2 (3.5)	8.2 (2.9)	**0.014**
Characteristics				
Pain intensity: baseline	5.1 (2.3)	4.4 (1.9)	4.9 (1.8)	0.403
Disability: baseline	8.1 (4.2)	5.4 (4.0)	6.3 (4.7)	0.111
Pain intensity: 3 months	4.0 (1.4)	2.0 (2.3)	2.6 (2.3)	**0.012**
Disability: 3 months	5.9 (4.5)	2.3 (3.3)	2.9 (2.9)	< **0.001**
Pain intensity: 6 months	3.6 (2.0)	1.8 (1.9)	2.6 (2.2)	**0.011**
Disability: 6 months	5.7 (5.0)	1.9 (2.9)	3.1 (3.5)	**0.002**
% change in pain[†]	-21.9 (32.9)	-51.8 (39.0)	-39.9 (41.7)	**0.036**

% change in disability[†]	-27.8 (37.7)	-49.2 (51.3)	-36.8 (53.2)	0.294
Age (yrs)	29.9 (10.1)	28.3 (8.3)	30.5 (6.4)	0.435
Sex (male, %)	29.4	50.0	61.4	0.092
BMI (kg/m^2)	22.9 (2.7)	24.6 (4.9)	24.4 (3.5)	0.328
Previous LBP (%)	94.1	86.8	93.2	0.645

Variables were compared across all four clusters using one-way ANOVAs (continuous variables) or Fisher's exact tests (categorical variables).
Sensory (pain threshold and conditioned pain modulation) measures were compared after log-transformation.
Continuous data described as mean ±SD. Categorical data described as number (%).
[†]Calculated as the percent change in pain/disability from baseline to 6 months.
Refer to Tables 1-3 for a full description of other measures.
Significant values are in bold font.

Table 6. Means for each of the measures used (*clustering variables*: psychological and sleep) and not used (*characteristics*: pain and disability at baseline, 3 and 6 months, and demographics) in the cluster analysis across the four clusters.

Variable	Cluster 1: (N = 20)	Cluster 2: (N = 23)	Cluster 3: (N = 17)	Cluster 4: (N = 39)	P-value
Clustering variables:					
CES-D	24.5 (5.1)	13.4 (7.9)	6.1 (4.7)	9.4 (4.7)	< **0.001**
PCS	13.7 (7.10)	24.0 (7.1)	7.9 (4.3)	6.6 (4.5)	< **0.001**
PSQI	9.0 (3.8)	8.4 (2.5)	5.1 (1.1)	11.1 (2.4)	< **0.001**
Characteristics					
Pain intensity: baseline	4.6 (2.0)	5.6 (2.1)	4.8 (1.8)	4.3 (1.7)	0.102
Disability: baseline	7.1 (4.0)	8.3 (4.4)	6.8 (5.5)	4.4 (3.1)	**0.004**
Pain intensity: 3 months	2.7 (2.0)	3.5 (1.6)	2.3 (2.5)	2.0 (1.6)	**0.036**
Disability: 3 months	4.4 (5.3)	4.6 (3.7)	2.2 (2.7)	2.1 (2.3)	**0.018**
Pain intensity: 6 months	2.7 (2.2)	3.3 (2.0)	2.0 (2.3)	2.0 (1.8)	0.111
Disability: 6 months	3.8 (4.8)	4.0 (3.7)	2.6 (3.4)	2.4 (3.2)	0.314
% change in pain[†]	-33.8 (39.9)	-29.9 (34.8)	-55.9 (41.6)	-45.7 (39.7)	0.157
% change in disability[†]	-40.9 (54.7)	-40.7 (37.3)	-45.1 (51.3)	-36.9 (53.2)	0.956
Age (yrs)	29.7 (7.5)	27.0 (7.2)	30.6 (6.9)	30.6 (8.3)	0.324
Sex (male, %)	20.0	52.2	52.9	66.7	**0.008**
BMI (kg/m^2)	24.9 (5.2)	22.9 (3.3)	24.2 (4.1)	24.6 (3.3)	0.325
Previous LBP (%)	85.0	91.3	94.1	92.3	0.778

Variables were compared across all four clusters using one-way ANOVAs (continuous variables) or Fisher's exact tests (categorical variables). Continuous data described as mean ±SD. Categorical data described as number (%).

[†]Calculated as the percent change in pain/disability from baseline to 6 months.

Refer to Tables 1-3 for a full description of other measures.

Significant values are in bold font.