Contributions of Mood, Pain Catastrophizing, and Cold Hyperalgesia in Acute and Chronic Low Back Pain

A Comparison With Pain-free Controls

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Objectives: Quantitative sensory testing (QST) has been used to elucidate the peripheral and central mechanisms that underlie changes in pain sensitivity associated with low back pain (LBP). However, it remains unclear to what degree peripheral and central changes contribute to the generation and maintenance of LBP. The aim of this study was to compare thermal pain sensitivity, measured using QST, in participants with acute LBP, chronic LBP, and pain-free controls.

Materials and Methods: Participant groups with acute LBP (N = 20), chronic LBP (N = 30), and pain-free controls (N = 30) were assessed by thermal QST. The unique contributions of pain-related psychological and QST variables to predict membership to the acute and chronic pain groups were also determined.

Results: We found that participants with chronic LBP demonstrated significantly lower cold pain threshold (CPT) in the primary area of pain (low back) as well as in an area anatomically remote from the primary area of pain (forearm) when compared with controls. Participants with acute LBP did not show significantly elevated pain sensitivity. CPT at the remote site was a significant independent predictor of membership to the chronic pain group, after the adjustment for mood and pain catastrophizing. CPT explained 8% of the total variance of 46% related to group membership.

Discussion: We found evidence for localized and generalized cold hyperalgesia in chronic, but not acute LBP. We might speculate that hyperalgesia develops as a consequence of long-lasting LBP, but prospective studies are needed to confirm this assumption.

Key Words: low back pain, quantitative sensory testing, acute pain, chronic pain, central sensitization

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The search for pathologic causes and prognostic factors of low back pain (LBP) and the related disability has rarely been successful.[1–3] Neither psychological nor pathologic factors explain the majority of the variance in patients' reporting of pain intensity or disability (prediction models explain < 20% of variability).[4,5] Therefore, a better understanding of the mechanisms responsible for pain could have important implications for the clinical diagnosis and treatment of affected patients.[6]

Research on pain mechanisms has increasingly focused on pain sensitization.[7] Sensitization is essentially an augmentation of neural signaling that may occur within the peripheral and/or central nervous system.[8] Peripheral sensitization is thought to be triggered by acute peripheral noxious stimulation or inflammatory processes related to tissue injury or nerve damage, resulting in increased pain sensitivity that is restricted to the site of pain or injury.[9] Parallel to this peripheral phenomenon, intense ongoing peripheral nociceptive input can lead to altered central mechanisms, such as, an immediate-onset and lasting increase in the excitability of dorsal horn pain transmission neurons, referred to as central sensitization.[9,10] Central sensitization may manifest as pain hypersensitivity (eg, allodynia, hyperalgesia, temporal summation [TS]) that can spread to noninjured areas.[8]

Quantitative sensory testing (QST) has been used to elucidate the peripheral and central processing mechanisms that underlie changes in pain sensitivity associated with clinical pain.[11–13] Several studies using QST have found that, compared with pain-free controls, participants with chronic LBP show evidence of pain hypersensitivity with decreased pain threshold at the primary area of pain[14] as well as at sites remote from the primary site of pain.[15–17] Increased pain sensitivity in the primary area of pain (local pain) is considered a sign of predominantly peripheral pain sensitization, whereas pain sensitivity in areas anatomically remote from the primary area of pain is thought to reflect a more central phenomenon.[8,18,19] Furthermore, the assessment of TS, that is, responses to repeated noxious stimuli, for example, noxious heat, is considered a reflection of "wind up" and represents a psychophysical measure of central sensitisation.[20–22]

However, even though QST might facilitate the understanding of the pathophysiology of chronic LBP, reproducible findings specific to the disorder are still pending.[23] At present, it remains unclear to what degree peripheral and central changes contribute to the generation and maintenance of LBP. Furthermore, the time course of changes in nociceptive processing is not known. Even though basic evidence suggests that changes in the central nervous system can occur within hours of injury,[9,10] which possibly explains the findings of local and generalized hyperalgesia demonstrated in patients with whiplash 1 month after injury,[24] studies investigating participants with acute LBP are limited and have found different results.

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To the best of our knowledge, there is only 1 study which compared chronic with acute LBP. This study demonstrated generalized and localized pressure hyperalgesia in participants with chronic LBP, but not with acute LBP.[15] However, this study did not consider pain-related psychological variables (ie, depression, anxiety, catastrophizing) that have been shown to influence patients' reporting of pain and disability[25,26] as well as patients' response to experimental pain induction.[27,28] Furthermore, there is evidence from previous studies in acute whiplash that cold pain might be more sensitive to detect early changes in pain sensitivity.[24] This is consistent with research highlighting cold hyperalgesia as important in the prediction of poor outcomes in whiplash-associated disorder.[29]

It is well accepted that psychological variables, such as depression, stress, anxiety, catastrophic thinking, and fear-avoidance beliefs, are associated with the severity of pain, disability, and poor outcome in LBP[26,30,31] and indeed, may be linked with clinical presentations of sensitization. Current conceptualizations of pain, therefore, incorporate a biopsychosocial approach that considers reciprocal interactions between multiple physiological and psychosocial processes.[32] Wallin et al[28] recently found that pain catastrophizing, anxiety, and depression were strong predictors for cold and heat sensitivity in participants with whiplash-associated disorders. These results suggest that assessment of psychological factors in relation to sensitization in LBP is warranted.

A number of questionnaires have been developed to assess these supposedly different psychological constructs. However, recent research has indicated that there may be conceptual overlap, that is, different questionnaires might be measuring the same construct, which might lead to redundancy.[33,34] In people with chronic LBP, Campbell et al[33] have identified pain-related emotional distress as a factor with the strongest association to LBP patients' outcomes. This factor had high and variable loadings from depression, pain catastrophizing, and fear avoidance, which suggests that they capture all participants' emotional distress, although to a different extent. Given the lack of a validated instrument for measuring emotional distress in people with either acute or chronic LBP more concisely, it is useful to combine measures of important psychological constructs, despite the overlap.

The first aim of this cross-sectional study was to compare thermal pain sensitivity, measured using QST, in participant groups with acute LBP, chronic LBP, and pain-free controls. Second, we aimed to determine the unique contributions of psychological (ie, depression, pain catastrophizing, fear avoidance) and QST variables to predict membership to the acute and chronic pain groups. We hypothesized that: (1) participants with chronic LBP would show elevated local and generalized thermal pain sensitivity compared with those with acute pain and controls; (2) participants with acute LBP would show elevated local and generalized thermal pain sensitivity compared with controls; and (3) thermal pain hypersensitivity would be an independent predictor of group membership.

MATERIALS AND METHODS

Participants

The study was approved by the Human Research Ethics Committees of the University of Sydney and the Sydney Local Health District. Informed consent was obtained from each participant included into the study. Participants were recruited through newspaper advertisements, among students and staff at the University of Sydney as well as from outpatient physiotherapy departments at local hospitals. Participants were eligible if they met the following inclusion criteria: age older than 18 years, both sexes, LBP lasting for >24 hours but <6 weeks, and preceded by a period of at least 1 month without pain (acute pain, with and without previous episodes) or chronic LBP (pain lasting ≥ 3 mo), which can be continuous or intermittent (present on at least half of the days), pain in the lumbar spine with or without radiation to the lower limb, pain intensity (current or during the past week) ≥ 3 of 10 (numeric rating scale [NRS]). Acute and chronic LBP were defined based on recommendations of the International Association for the Study of Pain,[35] the Cochrane Back Review Group,[36] and de Vet et al.[37]

In addition, age-matched and sex-matched pain-free controls were recruited. Inclusion criteria were: age older than 18 years, no episode of LBP (lasting >48 h) in the last 6 months, and no significant pain, that is, ≥ 1 of 10 (NRS), lasting >48 hours in the last 6 months.

The following exclusion criteria were applied: inability to read and/or understand English, any known serious pathology such as cancer, stroke, fracture, osteoporosis, inflammatory disease (eg, rheumatoid arthritis, ankylosing spondylitis, discitis, arachnoiditis), peripheral neuropathy associated with diabetes or chemotherapy, psychiatric and neurological disorders (eg, major depression, migraine, multiple sclerosis, Parkinson disease, Alzheimer disease), trauma within the last 6 months, or any spinal surgery.

Procedures

Demographic and Clinical Assessment

NRS (0 = no pain, 10 = unbearable) was applied to obtain the present, and average back pain intensity within the last 7 days. Furthermore, participants were asked to complete the following validated psychological, pain, and disability self-report questionnaires: (1) the short-form Depression Anxiety Stress Scales (DASS-21)[38,39]; (2) the Fear-Avoidance Beliefs Questionnaire (FABQ)[40]; (3) the Pain Catastrophizing Scale (PCS)[41]; and the Roland Morris Disability Questionnaire (RMDQ).[42]

The DASS-21[39] is a short version of the 42-item questionnaire developed by Lovibond and Lovibond.[38] The 21-item instrument consists of three 7-item subscales designed to measure negative aspects of mood, that is, depression, anxiety, and stress. The extent to which each statement applied to the respondent over the past week is graded on a 4-point scale, with the end points 0 "did not apply to me at all" and 3 "applied to me very much, or most of the time." The item scores from each subscale are summed and multiplied by 2. Subscale scores range from 0 to 42 with higher values indicating greater severity of mood disturbance.

The FABQ is a 7-point rating scale (0 "completely disagree" to 6 "completely agree") which consists of 2 subscales to measure fear-avoidance beliefs about physical activity (4 items) and work (7 items) in patients with LBP. The subscales comprise of statements about the impact of actual or anticipated normal work or physical activities, such as bending, lifting, walking or driving, on the respondent's back pain. Each subscale is scored separately by adding up the respective responses. The subscales have a range of 0 to 24 for physical activities and 0 to 42 for work

with higher score representing stronger fear-avoidance beliefs.[40]

The PCS is a 13-item instrument that evaluates 3 dimensions of catastrophic thinking, that is, rumination, magnification, and helplessness, related to pain. Completion of the scale involves the respondent indicating to what degree each of the listed statements on thoughts and feelings applies to them when experiencing pain, on 5-point scales with the end points 0 "not at all" and 4 "all the time." The PCS total score is computed by summing all item scores and ranges from 0 to 5, with higher values showing more severe catastrophizing. The RMDQ consists of 24 items referring specifically to a range of physical functions that are affected by LBP. Respondents are asked to tick those statements that apply to them on that day. The score of the RMDQ is the total number of items checked, that is, from 0 to 24, with higher scores reflecting greater levels of disability.[42] The following basic demographic and socioeconomic variables were also recorded: age, sex, medication use, presence of leg and/or foot pain (self-report), and educational level.

QST

Thermal pain threshold and tolerance (heat/cold) and TS of heat pain were measured by a single, appropriately trained investigator (approximately 45 h practical training and research experience) using a thermal sensory testing system with a thermode size of $25 \times 50\,mm^2$ (MSA Thermal Stimulator, Somedic, Sweden) and standardized instructions. Thermal QST is supposed to assess superficial pain thresholds by stimulation of heat and cold receptors in the skin. [43] Sensory testing was conducted at 2 body sites: on the surface of the low back (patients: at the most painful site, ie, over muscle tissue or muscle tissue and spinal structures; controls: mid-line over the spinous process of L4 and adjacent muscle tissue), and at a distal site, the volar surface of the forearm, the latter as a marker of possible central sensitization. The order of the different tests and stimulation sites, that is, lower back and left or right forearm, was randomized.

Thermal thresholds and tolerance: Participants received a continuously ascending or descending stimulus which started at 32°C and either increased or decreased at a rate of 1°C/s. They were given a switch to terminate the stimulus when the temperature reached their pain threshold, that is, when the stimulus started to become painful. To assess heat/cold pain tolerance (HPTol/CPTol), participants were asked to stop the stimulus when it became so painful that they wished it to stop.[44] Three trials were performed and the average temperature was used as threshold or tolerance. Lower and upper temperature limits were set at 4°C and 50°C.

TS of heat pain: One sequence of 10 consecutive heat pulses of < 1-second duration at an interstimulus interval of 0.33 Hz were delivered. The temperature of the heat pulses increased from 41°C as a baseline temperature for interstimulus to a maximum of 47°C at a rate of 10°C/s.[44,45] Participants were asked to rate the pain intensity of each heat pulse on an NRS (0 = no pain, 10 = unbearable). Mean pain ratings for the 10 stimuli[46] and the fifth pain rating minus the first pain rating[44] in each TS sequence were used for the analysis.

Statistical Analysis

The normality of the data was tested using the Kolmogorov-Smirnov test. Because most variables were not normally distributed, group differences for demographic and psychological factors (ie, age, LBP duration, pain intensity RMDQ, DASS-21, FABQ, PCS) and all QST variables were determined using the Kruskal-Wallis test, followed by Bonferroni-Holm adjusted Mann-Whitney *U* tests as post hoc analyses. Categorical variables were compared using χ^2 tests.

Three binary logistic regression models were built on the basis of significant variables to determine variables that best predict group membership (dependent variable). The first 2 models compared participants with acute or chronic pain with pain-free controls, and the third model compared participants with acute and chronic pain. In these models, psychological factors (ie, depression, catastrophizing) were considered first, followed by QST variables that were entered in a forward stepwise manner. This regression model permits the unique influence of QST variables to be evaluated, after accounting for the contribution of psychological factors. We examined bivariate Pearson correlations between the explanatory variables and the β-coefficient SE to explore potential influences of collinearity. For each regression model, a minimum number of 10 cases per candidate predictor variable was ensured.[47,48]

For all analyses, significance was set at $P < 0.05$. All statistical computations were made with SPSS 20.0.

RESULTS

A total of 132 individuals were screened for study eligibility. From a total of 83 potentially eligible participants, 80 provided consent and were included into the study. The main proportion (91%) of included participants was recruited from the community. The number of participants recruited from outpatient physiotherapy departments at local hospitals was equally distributed between the acute (N = 4) and chronic (N = 3) pain groups. Samples' demographic and descriptive data are depicted in Table 1 with results from between-group comparisons of QST variables presented in Table 2. There were no significant group differences in age, sex, and education. Both pain groups did not differ in pain intensity and seem representative for LBP patients seeking consultation in primary care in terms of pain intensity.[31,49,50] Participants with acute or chronic pain showed significantly higher levels of depression than pain-free controls. Participants with acute pain demonstrated significantly higher depression scores than those with chronic pain. Catastrophizing scores were significantly higher in participants with chronic pain but not with acute pain compared with controls. With regards to the QST variables, significantly lower cold pain thresholds (CPTs) at both sites (low back, forearm) were found in participants with chronic pain when compared with controls. Participants with chronic pain also showed significantly lower CPTol at the forearm than controls. In participants with acute pain, there was also a nonsignificant trend towards a markedly lower CPT at the forearm compared with pain-free controls. No significant group differences were identified for heat pain threshold (HPT), HPTol, or TS. Furthermore, no significant differences were found between participants with acute pain versus chronic pain or pain-free participants for any QST variable. Results of the binary logistic regression models are presented in Tables 3 to 5.

TABLE 1. Sample Descriptives

Variables	Chronic LBP	Acute LBP	Controls
No.	30	20	30
Age (median [IQR]) (y)	30.6 (21.8-35.0)	26.8 (22.0-32.5)	28.0 (21.8-31.0)
Sex (female) (n [%])	15 (50.0)	12 (60.0)	17 (56.7)
Taking analgesics (n [%])	7 (23.3)	7 (35.0)	
Postschool education (n [%])			
Basic or skilled vocational qualification	5 (16.1)	3 (15.0)	
Undergraduate or associate diploma	3 (10.0)	2 (10.0)	
Bachelor degree or higher	16 (51.6)	10 (50.0)	24 (80)
LBP duration (median [IQR]) (wk)	96 (31.0-240.0)	4.0 (3.0-5.0)	
Current pain intensity, NRS*	4.0 (1.9)	4.6 (1.9)	0
Average pain intensity last week, NRS*	4.9 (1.4)	5.2 (1.4)	0
Referred leg and/or foot pain (n [%])	11 (36.7)	4 (33.3)	
RMDQ‡	5.1 (3.3)	6.2 (4.8)	
DASS-21 total score (median [IQR])	18.0 (7.5-32.0)#	38.0 (16.0-87.0)#†	6.0 (1.5-14.5)
DASS-21 (depression)§ (median [IQR])	2.0 (4.0-6.0)#	9.0 (1.5-28.0)#†	0 (0.0-4.0)
DASS-21 (anxiety)§ (median [IQR])	5.0 (0.0-8.0)#	6.0 (0.0-19.0)#	0.0 (0.0-2.5)
DASS-21 (stress)§ (median [IQR])	9 (3.5-18.0)#	18 (9.5-35.0)#†	3 (0.0-8.0)
FABQ (physical activities)‖	12.2 (6.3)	12.35 (6.2)	
FABQ (work)¶	11.9 (10.8)	13.85 (8.3)	
PCS**	15.6 (9.9)#	13.8 (8.3)	9.4 (7.5)

Data are mean ± SD unless otherwise indicated.
*Range: 0 (no pain) to 10 (worst pain possible).
‡Range: 0 (no disability) to 24 (high disability).
§Range: (no depression/anxiety/stress) to 42 (high depression/anxiety/stress).
‖Range: 0 (no fear-avoidance beliefs) to 24 (strong fear-avoidance beliefs).
¶Range: 0 (no fear-avoidance beliefs) to 42 (strong fear-avoidance beliefs).
**Range: 0 (no catastrophizing) to 52 (severe catastrophizing).
#$P < 0.05$ versus controls.
†$P < 0.05$ versus chronic.
DASS-21 indicates Depression Anxiety and Stress Scale; FABQ, Fear-Avoidance Beliefs Questionnaire; IQR, interquartile range; LBP, low back pain; NRS, numeric rating scale; PCS, Pain Catastrophizing Scale; RMDQ, Roland-Morris Disability Questionnaire.

The first model (Table 3) predicted membership to the acute pain group versus chronic LBP participants with the DASS-21 total score being the only independent variable. The DASS-21 total score correctly classified 90% of the participants with chronic pain and 35% of those with acute pain. The model accounted for 19% in the variance

TABLE 2. QST Variables

	Median (Interquartile Range)			Mean (SD)			*P**			
QST Variable	Chronic LBP	Acute LBP	Controls	Chronic LBP	Acute LBP	Controls	All Groups	Chronic vs. Acute	Acute vs. Controls	Chronic vs. Controls
Back										
CPT (°C)	7.7 (4.0-21.9)	4.0 (4.0-11.9)	4.0 (4.0-9.3)	12.3 (9.3)	8.5 (7.4)	7.5 (6.3)	0.045#	0.221	0.326	0.013†
CPTol (°C)	4.0 (4.0-5.4)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	5.9 (4.2)	5.2 (4.9)	4.5 (1.8)	0.156	0.323	0.505	0.058
HPT (°C)	47.4 (44.8-49.0)	46.9 (44.1-49.0)	47.6 (45.6-49.6)	46.9 (2.4)	46.4 (2.9)	47.0 (2.8)	0.530	0.488	0.312	0.501
HPTol (°C)	50.0 (49.3-50.0)	50.0 (49.4-50.0)	50.0 (49.6-50.0)	49.5 (0.8)	49.1 (2.0)	49.4 (1.1)	0.687	0.478	0.413	0.973
TS‡	4.2 (2.3-5.7)	4.7 (2.7-7.7)	4.0 (1.0-5.7)	4.0 (2.4)	5.0 (2.8)	3.6 (2.5)	0.173	0.184	0.065	0.563
TS§	0.0 (−2.0-1.0)	−0.5 (−1.0-0.8)	0.0 (−0.3-1.0)	−0.2 (1.9)	−0.5 (1.4)	0.2 (1.2)	0.341	0.550	0.107	0.482
Forearm										
CPT (°C)	10.8 (6.0-21.6)	10.3 (4.0-19.8)	4.5 (4.0-14.0)	13.9 (8.7)	11.9 (7.7)	8.1 (5.8)	0.011#	0.397	0.084	0.003†
CPTol (°C)	4.0 (4.0-6.4)	4.0 (4.0-4.6)	4.0 (4.0-4.0)	6.1 (4.3)	7.1 (7.0)	4.3 (1.2)	0.044#	0.763	0.058	0.013†
HPT (°C)	46.6 (44.5-48.2)	46.9 (44.5-48.9)	47.3 (45.0-48.3)	46.1 (2.9)	46.1 (3.3)	46.5 (2.7)	0.828	0.866	0.607	0.610
HPTol (°C)	49.5 (48.6-50.0)	50 (48.6-50.0)	49.9 (49.4-50.0)	49.0 (1.5)	48.9 (2.7)	49.4 (1.3)	0.569	0.778	0.546	0.289
TS‡	4.0 (2.0-5.3)	4.7 (2.7−7.7)	3.7 (1.0-5.4)	3.7 (2.3)	5.1 (2.7)	3.5 (2.5)	0.127	0.090	0.064	0.646
TS§	0.0 (−1.0−1.0)	−1.0 (−1.0−0.0)	0.0 (−0.25−0.0)	0.1 (1.9)	−0.9 (1.3)	−0.3 (0.7)	0.039#	0.034	0.019	0.529

*Results from Kruskal-Wallis test and Bonferroni-Holm adjusted Mann-Whitney *U*-tests.
‡Mean pain ratings (numeric rating scale; NRS) at 47°C.
§5th pain rating minus 1st pain rating (numeric rating scale; NRS) at 47°C.
#$P < 0.05$.
†$P < 0.016$.
CPT indicates cold pain threshold; CPTol, cold pain tolerance; HPT, heat pain threshold; HPTol, heat pain tolerance; LBP, low back pain; QST, quantitative sensory testing; TS, temporal summation.

TABLE 3. Results of the Binary Logistic Regression for Variables Predicting Membership to the Acute Pain Group Compared With Chronic Pain (Reference Group)

Variables	R^2	*B*	SE	*P*	OR (95% CI)
First model	0.19			< 0.01	
DASS-21 total score		−0.03	0.01	0.01	0.98 (0.96, 1.00)

B indicates unstandardized β-coefficient; CI, confidence interval; DASS-21, Depression Anxiety and Stress Scale; OR, odds ratio; R^2, Nagelkerke coefficient of determination.

between groups. The odds ratio (OR) was smaller than one indicating that lower DASS-21 total scores were related to less likelihood of being in the acute pain group.

The second model (Table 4) predicted membership to the acute pain group versus pain-free participants with the DASS-21 total score also being the only independent variable. The DASS-21 total score correctly classified 96.7% of the participants with acute pain and 70% of the controls. This model explained 59% of the variance between groups. The OR was >1 indicating that increased DASS-21 total scores were associated with an increased likelihood of being in the acute pain group.

The third model (Table 5) predicted membership to the chronic pain group versus pain-free participants with the DASS-21 total score, PCS score, and CPT (forearm) being the independent variables. Together, these variables correctly classified 76.7% of the participants with chronic pain and 73.3% of the controls. CPT (forearm) made a significant contribution to the classification of participants after controlling for DASS-21 total score and PCS. DASS-21 total score and PCS explained 38% of the variance related to group membership. Adding CPT (forearm) to the model explained another 8% in the variance related to group membership (total variance 46%). The OR of DASS, PCS, and CPT (forearm) were all >1 suggesting that increases in these variables were related to an increased chance of being in the chronic pain group. The moderate bivariate correlation between DASS-21 and PCS ($r = 0.31$, $P < 0.01$) and β-coefficient SEs <2 (Table 5) indicate that collinearity was not a problem.

DISCUSSION

The main finding of our study was that participants with chronic, but not acute, LBP demonstrated significantly lower CPT in the primary area of pain (low back) as well as in an area anatomically remote from the primary area of pain (forearm) when compared with controls. CPT at the remote site was a significant independent predictor of membership to the chronic pain group (with pain-free controls as reference group), after the adjustment for mood (DASS-21) and pain catastrophizing (PCS).

TABLE 4. Results of the Binary Logistic Regression for Variables Predicting Membership to the Acute Pain Group Compared With Pain-free Controls (Reference Group)

Variables	R^2	*B*	SE	*P*	OR (95% CI)
First model	0.59			< 0.01	
DASS-21 total score		0.12	0.04	0.004	1.13 (1.04, 1.23)

B indicates unstandardized β-coefficient; CI, confidence interval; DASS-21, Depression Anxiety and Stress Scale; OR, odds ratio; R^2, Nagelkerke coefficient of determination.

There are a number of other cross-sectional studies comparing participants with chronic LBP and pain-free controls. Blumenstiel et al[14] found that participants with chronic LBP showed increased pain sensitivity to pressure at the back, but not at the dorsum of the hand. They reported no group differences for wind-up of pain (TS), CPT, or HPT. These findings were interpreted as reflective of a deep (ie, muscles, joints) and localized change in pain sensitivity with no signs of central sensitization. In contrast, O'Neill and colleagues[15,17] demonstrated increased pressure pain sensitivity at the back as well as at the brachioradialis and tibialis anterior muscles in participants with chronic LBP. Puta et al[16] tested thermal (CPT, HPT), pressure, and mechanical pain thresholds as well as wind-up of pain (TS), but found that their cohort demonstrated sensitivity to only 2 of the parameters; heat pain at the back and mechanical pain over the palmar aspect of the hand. In summary, previous studies have demonstrated localized and generalized mechanical hyperalgesia as well as localized pain hypersensitivity to heat. In addition, our study is the first demonstrating a reduced CPT at both the primary area of pain and at a remote site; however, we did not find significant heat pain sensitivity at either site. Consistent with previous findings, we also did not find evidence for TS. Our finding that reductions in CPT did occur in participants with chronic but not acute pain is in line with a study from O'Neill et al[15] demonstrating generalized and localized pressure hyperalgesia in participants with chronic LBP, but not with acute LBP. We might speculate that, in many people, hyperalgesia develops as a consequence of chronic LBP, but further prospective studies are needed to confirm this assumption, in particular against the background of the nonsignificant trend toward lower CPT at the forearm in participants with acute pain.

Even though our knowledge about the mechanisms underlying cold pain hypersensitivity is still incomplete, changes in central pain processing[24,29] and pain-related psychological variables[28] might play a role. In rodents, studies have found that acute and chronic stress results in allodynia and hyperalgesia in response to cold and heat.[51–53] Wallin et al[28] recently found that variables such as pain catastrophizing, anxiety, and depression were strong predictors for CPT and HPT in participants with whiplash-associated disorders. In our study, participants with chronic pain demonstrated increased scores on the PCS as well as the DASS-21 scales when compared with pain-free controls. Exploratory bivariate correlation analyses demonstrated a moderate relationship between the DASS-21 stress subscale and CPT at the back ($r = 0.63$, $P < 0.01$) or CPT at the forearm ($r = 0.45$, $P = 0.01$). It might thus be speculated that stress in individuals with chronic LBP predicts CPT, but this should be ascertained in future studies.

Higher DASS-21 scores in the acute pain group compared with the chronic pain group might indicate processes of acceptance in adjustment to chronic pain. Nicholas and Asghari,[54] for instance, have shown that greater chronic pain acceptance correlated with less severe depression. Our finding that participants differed in DASS-21 scores, but not in cold pain, indicates that the relationship between both variables depends on the pain duration. Indeed, exploratory bivariate correlation analyses demonstrated no correlation between CPT and DASS-21 total score or

TABLE 5. Results of the Binary Logistic Regression for Variables Predicting Membership to the Chronic Pain Group Compared With Pain-free Controls (Reference Group)

Variables	R^2	*B*	SE	*P*	OR (95% CI)
First model	0.38			< 0.01	
DASS-21 total score		0.10	0.03	< 0.01	1.11 (1.03, 1.19)
PCS		0.09	0.04	0.02	1.09 (1.01, 1.18
Second model	0.46			0.02	
DASS-21 total score		−0.09	0.04	0.02	1.09 (1.01, 1.18)
PCS		−0.10	0.04	0.01	1.11 (1.02, 1.20)
CPT forearm			0.05	0.04	1.11 (1.00, 1.23)

B indicates unstandardized β-coefficient; CI, confidence interval; CPT, cold pain threshold; DASS-21, Depression Anxiety and Stress Scale; OR, odds ratio; PCS, Pain Castrophizing Scale; R^2, Nagelkerke coefficient of determination.

subscales ($r = 0.18$ to 0.31, $P > 0.18$) in participants with acute pain, but significant correlations in chronic pain ($r = 0.52$ to 0.63, $P < 0.01$). It might thus be speculated that emotional distress predicts cold hyperalgesia in chronic pain only, but this should be ascertained in future studies.

Furthermore, it might be speculated that our finding of increased sensitivity to cold at the forearm reflects a more central phenomenon as sensitivity in areas anatomically remote from the primary area of pain has been suggested as a marker of central sensitization.[14,24] However, as established criteria for determining the presence of central sensitization are lacking[55] care must be taken when interpreting QST findings as reflective of sensitization, in the absence of other clinical information.[56]

Even though the exact physiological mechanism of central sensitization currently remains elusive, TS and endogenous pain modulation systems have been proposed as important contributing factors.[57] TS refers to the progressive augmentation of C-fiber-evoked responses of dorsal horn nociceptive neurons (wind up), mediated by *N*-methyl-D-aspartate receptor mechanisms.[22,58] Endogenous pain modulation systems include the activity of both inhibitory and facilitatory centers in the brainstem that modulate the excitatory state of dorsal horn neurons and involve serotonergic, noradrenergic, and opioidergic inhibitory pathways.[59] Our finding of generalized cold hyperalgesia accompanied by unchanged TS suggests that deficient endogenous pain modulation might be the contributing factor to generalized pain sensitivity in chronic LBP.

The fact that we did not find group differences in response to heat pain might point toward differences in the cerebral processing of noxious heat and noxious cold, despite the commonalities in peripheral mediation and dorsal horn mechanisms.[60] Preliminary electrophysiological studies have identified thalamic neurons that respond specifically to noxious heat or noxious cold and others that respond to both modalities.[61,62] Furthermore, brain imaging studies have shown that heat and cold pain, while involving the same cortical regions, were associated with different activation patterns.[62,63] In summary, the presence of cold hypersensitivity, but not heat sensitivity, in this study could be a sign of specific brain reorganization in chronic LBP, but this remains speculative and has to be confirmed in future studies, potentially combining QST and brain imaging.

Even though we found statistically significant lower CPT in participants with chronic LBP compared with pain-free controls, it has to be acknowledged that the corresponding interquartile ranges overlap substantially, suggesting that groups did not differ much. This might be an inherent problem to some QST measures as previous investigations have also found substantial variability in thermal pain thresholds in pain-free people.[64]

Another explanation for minor group differences might be the fact that in some of the participants with chronic pain, central processes did not significantly contribute to cold hyperalgesia. Results from a recent clinical study involving 464 people with chronic LBP identified 106 (23%) of the participants as having central sensitization as their dominant pain mechanism, with the remaining 358 (77%) deemed (clinically) to present with a dominance of nociceptive or peripheral neuropathic pain.[65] If the results from Smart et al[65] are generalizable, it is quite conceivable that a significant proportion of included participants in our and previous studies did not present with clinical manifestations of central sensitization and as such, rather small group differences would be expected. It would be interesting to investigate cold hyperalgesia in a subgroup of people who are deemed to have evidence of central sensitization on the basis of valid (clinical) assessment and compare their results to pain-free controls.

There are several limitations that should be acknowledged. First, due to the cross-sectional design of our study, no causal inference about the associations found can be drawn. It is unclear whether psychological distress, catastrophizing, and cold hyperalgesia are risk factors for the development of chronic LBP or develop as a consequence of persistent pain. Second, blinding of the assessor to group membership was not possible. Third, TS was the only dynamic QST measure employed in this study. It has recently been suggested that the assessment of descending pain modulation, via dynamic QST measures, and pain magnitude rating for suprathreshold stimuli might facilitate our understanding of a sensitized nociceptive system.[66] Fourth, our data point toward possible ceiling/flooring effects, especially for the pain tolerance measures. As ceiling/flooring effects are dependent on the population studied, it is conceivable that the discriminative ability of CPTol and/or HPTol varies among different subsets of the LBP population. For instance, as indicated above, it could be speculated that ceiling/flooring effects are not present in participants with higher levels of central sensitization relative to our study population. The same might apply to subsets with worse disability status, higher depression scores, higher age, etc. However, even though ceiling effects of CPT have been reported for pain-free controls,[67] there are currently no data available in acute/chronic LBP that might allow between study comparisons. Fifth, given the relatively high proportion of participants recruited from the community, our findings might not unrestrictedly apply to patients seeking care for their LBP. Both pain groups did

not differ in pain intensity and seem representative for LBP patients seeking consultation in primary care in terms of pain intensity.[31,49,50] Finally, we have to acknowledge that the sample size of our group with acute LBP was relatively small and this might limit the power to demonstrate significant differences compared with the chronic LBP group or pain-free controls.

Our finding of generalized cold hypersensitivity in patients with chronic LBP has clinical implications. Measures of pain perception, like QST, appear to provide useful information to the clinical picture of LBP. Such information, when combined with established psychosocial measures, adds another dimension to the assessment of what is a complex and heterogenous clinical problem. Preliminary evidence suggests that early signs of cold hyperalgesia, in addition to high scores on psychosocial measures, can be predictive of poor outcome,[24] however, more work is required to evaluate this in LBP. Each of these constructs may require more specific targeted interventions if identified in an individual patient. In addition, preliminary research has indicated that people with chronic pain might respond differently to treatment, that is, increased pain sensitivity after exercise, when compared with pain-free controls.[68] Thus, it might be useful to investigate the moderating and mediating effects of pain sensitivity in future treatment trials. In line with recent emphasis on targeted treatment for LBP,[69] further work on QST measures could produce data to help identify valid subgroups.

In conclusion, the present study demonstrated, for the first time, increased localized and generalized cold hyperalgesia in people with chronic LBP compared with pain-free controls. Even though mood and pain catastrophizing explained the biggest part in the variance in group membership, CPT at the remote site was a significant independent predictor of membership to the chronic pain group. However, while CPT can help to discriminate between groups (chronic pain vs. no pain), the ability of CPT to predict the intensity of the pain or the severity of disability in patients seems limited.[56] As we did not find cold hyperalgesia in participants with acute pain, it might be speculated that sensory changes develop over time and become manifest only in chronic LBP. Future prospective studies are needed to determine the ability of CPT to contribute to outcome prediction in acute LBP. These studies should consider clinical assessment of sensitization and psychological distress, as well as measures of descending pain modulation and suprathreshold pain magnitude rating.

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