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Do chronic low back pain subgroups derived from dynamic quantitative sensory testing exhibit differing multidimensional profiles?

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Abstract

Objectives: The relationship of pain sensitivity with pain and disability in low back pain (LBP) is complicated. It has been suggested increased understanding of dynamic quantitative sensory testing (QST) might be useful in increasing understanding of these relationships. This study aimed to create subgroups based on participant responses to dynamic QST, profile these subgroups based on multidimensional variables (including clinical measures of pain and disability, psychological and lifestyle variables and static QST), and investigate the association of subgroup membership with levels of pain intensity, LBP-related disability and disability risk at 12-month follow up.

Methods: Participants (n=273) with dominant axial chronic non-specific LBP with duration of pain >3 months were included in this study. At baseline, eligible participants completed a self-report questionnaire to collect demographic, clinical, psychological and lifestyle data prior to dynamic and static QST. Dynamic QST measures were conditioned pain modulation (CPM) and temporal summation (TS). At 12-months follow up, clinical data were collected, including pain intensity and LBP-related disability. Sub-groups were formed by cross-tabulation. Analysis was undertaken to profile dynamic QST subgroup on demographic, clinical, psychological, lifestyle and static QST measures. Associations between dynamic QST subgroups and follow-up clinical variables were examined.

Results: Based on dynamic QST, participants were allocated into four subgroups; normal CPM and normal TS (n=34, 12.5%); normal CPM and facilitated TS (n=6, 2.2%); impaired CPM and normal TS (n=186, 68.1%); impaired CPM and facilitated TS (n=47, 17.2%). At baseline no differences were demonstrated between subgroups across most clinical variables, or any psychological or lifestyle measures. The two subgroups with impaired CPM were more likely to have a higher number of painful body areas. Cold pain sensitivity was heightened in both the subgroups with facilitated TS. Subgroups did not differ across pain intensity, LBP-related disability and disability risk stratification at follow-up.

Conclusions: The profiles of people with axial LBP did not vary significantly across dynamic QST subgroups, save for those in groups with impaired CPM being more likely to have more widespread symptoms and those with facilitated TS having heightened cold pain sensitivity. Further, subgroup membership was not related to future pain and disability. The role of dynamic QST profiles in LBP remains unclear. Further work is required to understand the role of pain sensitivity in LBP. The utility of dynamic QST subgrouping might not be in determining of future disability. Future research might focus on treatment modifying effects of dynamic QST subgroups.

Keywords: chronic low back pain; conditioned pain modulation; quantitative sensory testing; subgroups; temporal summation.

Introduction

Low back pain (LBP) is the largest contributor to global morbidity [1, 2]. Chronic LBP (CLBP) is a multidimensional condition influenced by many factors including pain characteristics, genetic, demographic, physical, psychological, social, health and lifestyle [3, 4].

When examined using quantitative sensory testing (QST), people with CLBP have been shown to have

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heightened pain sensitivity compared to healthy controls [5, 6], and differing pain sensitivity profiles have been derived in people with CLBP [7]. However, one recent systematic review suggests static QST (e.g. pain thresholds) may be less helpful for predicting future pain intensity than dynamic QST [8], while another found predominantly non-significant associations between dynamic QST findings and pain intensity and disability [9]. Dynamic QST includes assessment of temporal summation (TS): central nervous system-mediated increasing perception of pain following repetitive noxious stimulation [10]; and conditioned pain modulation (CPM): a surrogate measure of a person's endogenous pain modulation capacity [11]. Combining TS and CPM findings to determine the presence of pro- or anti-nociceptive subgroups has been hypothesised as potentially clinically meaningful [12], however, such subgroups are yet to be thoroughly explored in an LBP cohort.

The exploration of subgroups based upon dynamic QST variables of CPM and TS has been investigated in participants with non-cancer related chronic pain (n=400, 18.8% CLBP) [13]. Four subgroups were determined; normal CPM and normal TS (30%), normal CPM and facilitated TS (11%), impaired CPM and normal TS (37%) and impaired CPM and facilitated TS (21%). Participants with impaired CPM and facilitated TS demonstrated higher average pain intensity and the presence of multiple pain sites. Additionally, between group differences were identified for static QST measures (heat pain threshold [HPT] and pressure pain threshold [PPT]). However, no differences between the subgroups for disability levels or demographic or psychological variables were identified [13]. Considering CLBP is known to be a multidimensional pain condition disorder [3] associated with, for example, differing pain characteristics (e.g. pain provocation with movement [14]) or lifestyle factors (e.g. sleep disturbance [15]), it is appropriate to explore broader multidimensional associations across such subgroups.

To date, no studies have derived subgroups in people with CLBP based upon dynamic QST variables and examined the multidimensional profiles of those subgroups. Therefore, Aim 1 was to subgroup people with CLBP based upon normal/abnormal CPM and TS findings using previously described methods [13]. Using dynamic QST variables to subgroup people with LBP would overcome a limitation reported in literature which has largely focused on testing static QST [16]. Aim 2 was to profile dynamic QST subgroups across a full array of multidimensional variables (pain characteristics, disability levels, psychological factors, lifestyle factors, static QST measures). Aim 3 was to evaluate whether subgroup membership was associated with pain intensity, disability and disability risk at 12-month follow up. Together, Aims 2 and 3 could help inform the clinical utility of subgrouping people based on dynamic QST profiles.

Methods

A longitudinal study was performed with data collected at baseline and 12-month follow-up. Data for this study were obtained from a broader study investigating multidimensional profiling and prognostic modelling of people with CLBP [17, 18], however, dynamic QST subgrouping has not been previously reported for this cohort. Data were collected between November 2012 and January 2014.

Ethical approval for the data collection (Approval Number 112/2012) and analysis in this current study (Approval Number HRE2019-0595) was granted by Curtin University's Human Research Ethics Committee and complied with the Declaration of Helsinki. All participants gave written, informed consent.

Participants were recruited from private pain management, psychology and physiotherapy clinics in Perth, Western Australia and through regional and metropolitan communities in Western Australia via multimedia advertisements.

Inclusion criteria: age 18–70 years inclusive; LBP of ≥3 months duration; dominant axial LBP indicated by ≥60% of the pain in the low back and ≤40% in the legs [19]; average pain intensity in the last week of ≥2 points measured on an 11-point Numerical Rating Scale (NRS) [20]; and LBP-related disability of ≥5 points measured on the Roland-Morris Disability Questionnaire (RMDQ) [21]. Exclusion criteria were: history of extensive spinal surgery (greater than single-level fusion or discectomy); spinal surgery in the previous six months; presence of serious spinal conditions (e.g. acute fracture, cancer, inflammatory arthropathy); diagnosed neurological disease; pain bilaterally over the wrist or dorsum of the hand; pregnancy and inability to comprehend English.

The following variables were collected through questionnaires or physical examination.

Dynamic sensory testing for subgrouping (Aim 1)

Sensory testing was carried out with participants prone in the following order: TS, HPT, cold pain threshold (CPT), PPT, CPM, with each test following immediately on from the next. Standardised testing instructions were used throughout testing [22, 23]. Testing was undertaken in a temperature controlled laboratory.

CPM was tested as follows. The test stimulus, pressure pain, was applied to the most painful lumbar spine region as indicated by the participant using an algometer with a probe size of 1 cm^2 (Somedic AB, Hörby, Sweden). Pressure was gradually increased from 0 kPa at a rate of 50 kPa/s until the participant rated the pressure as pain with an intensity of 6/10 on an 11-point NRS and pressed a button to record the pressure. Noxious heat was utilised as the conditioning stimulus applied to the dorsum of the wrist using a contact thermode (Thermotest, Somedic AB, Hörby, Sweden). The conditioning stimulus commenced at 40 °C, increasing by 1 °C until the participant reported it as intolerable. The tester then reduced the stimulus by 1 °C. This heat conditioning stimulus was subsequently sustained while the test stimulus was re-administered. The following instructions were given: "I am going to apply three further pressure tests to your back. You rated the last pressure

at 6/10. Now I want you to give me a score out of 10 compared to that first rating for each of these next three pressures." These instructions determined whether there was a perceived change in pain intensity for the test stimulus during the conditioning stimulus. There was no explicit instruction to suggest a change in pressure from that initially delivered. Reapplication of the test stimulus was to the same area at the same rate using the predetermined pressure (±10 kPa). An NRS score was reassessed by re-applying the test stimulus at 30, 60 and 90 s. For each test the CPM change score was calculated by subtracting the NRS score reported upon re-application of the test stimulus from the baseline NRS score of 6/10. A mean of the three scores was used for statistical analysis. This inter-stimulus interval has previously been shown to prevent TS of test stimuli [24]. CPM was considered missing in cases where an NRS of 6/10 could not be reached during the application of the base stimulus. Participants were classified as having normal CPM if their score on the NRS decreased by ≥0.5-points and impaired CPM was defined as a decrease <0.5-points on the NRS [25].

A standardised TS protocol [22] was applied at the area of maximal lumbar spine pain using a 26 g nylon monofilament (Aesthesio, DanMic Global, USA). The participant was asked whether the first contact by the filament was painful. If painful, participants were asked to rate this on an 11-point NRS. The filament was then applied at 1 Hz for 30 s [22] after which the participant again rated their perceived pain intensity. The TS change score was calculated by subtracting the NRS score reported after 30 s of stimulation from the baseline NRS score. TS was defined as normal if the NRS score increased by <2-points [26] over the 30 s of stimulation. Facilitated TS was deemed present if the pain intensity rating increased by ≥2-points over the 30 s of stimulation [26].

Baseline profiling variables (Aim 2)

The following variables were primarily selected due to their potential relationship to pain sensitivity and CLBP, because they can be used by clinicians to profile people with QST, and because they represented the multidimensional nature of CLBP. Additional variables were included for demographic purposes.

Demographics: Age in years and sex. Education level was measured by asking participants how many years of formal education they had received. Employment status was collected by asking whether participants were working at the time, including either paid or unpaid work (e.g. student, housewife). Those working were asked the title of their occupation and answers where dichotomised into manual or sedentary occupations based on the Australian and New Zealand Standard Classification of Occupations [27]. Compensation status was measured by a single question from the Fear-Avoidance Beliefs Questionnaire (FABQ) [28] and dichotomised into "yes" and "no".

Pain distribution was measured by asking participants how much LBP they had in relation to leg pain. Percentage was expressed as 100, 80 or 60% LBP [19].

Pain characteristics and disability: Average pain intensity in the last week was measured on the 11-point NRS [20].

To measure pain duration participants were asked "How long have you had your back pain for?" Pain duration was expressed in months.

Participants also indicated any areas of pain perceived throughout their entire body on a quantifiable grid-based body chart. Body chart count as indicated by the total number of squares filled in was recorded [29].

Participants were asked to list all medications taken. Analgesic intake was categorised as opioid or non-opioid.

LBP-related disability was measured by the RMDQ [21].

The STarT Back Tool (SBT) was used to stratify participants into low, medium and high-risk of future disability [30]. The tool contains a psychosocial subscale. Participants are stratified as high risk if they score ≥4 points on the psychosocial subscale. As such participants SBT risk profiles will also be used as a proxy psychosocial score at follow up. Higher risk has previously been shown to correlate well with psychological factors in this cohort [31].

Pain summation following repeated spinal bending was examined by asking participants to complete 20 repetitions of forward bending followed by 20 repetitions of backward bending. Forward bending involved picking up a pencil from the floor. Placing the pencil back on the floor counted as another repetition of forward bending. For backward bending participants viewed a marker approximately 60 cm behind them on the ceiling, without turning around, before returning to neutral. Participants received standardised instructions that they could undertake these tasks however they wished, and at whatever speed they wished. To determine the participant's pain response following repeated bending, pain was measured on an 11-point NRS at baseline and after every five repetitions. Based on a ≥2-point change in pain intensity [26] following repeated bending, participants were categorised as having no increase in pain in either direction, a unidirectional increase in pain or a bidirectional increase in pain [14].

Psychological factors: Depression, anxiety and stress were measured with the Depression Anxiety Stress Scale (DASS-21) [32]. Fear avoidance beliefs about physical activity and pain catastrophising were measured with the Fear-Avoidance Beliefs Questionnaire-Physical Activity subscale (FABQ-PA) [28] and the Pain Catastrophising Scale (PCS) [33] respectively.

Lifestyle factors: Sleep disturbance was measured with the Pittsburgh Sleep Quality Index (PSQI) [34].

Body mass index was calculated from height (metres) and weight (kilograms) measurements.

Static sensory testing: Static sensory tests (HPT, CPT, PPT) were applied at the site of greatest lumbar spine pain as specified by the participant, and at the dorsal wrist line. In participants with no wrist pain the non-dominant side was used, however, in the presence of unilateral wrist pain selection was directed to the non-painful side. HPT and CPT were tested using the Thermotest (Somedic AB, Hörby, Sweden). HPT was defined as the temperature at which a warm sensation was first perceived as a sensation of heat and pain. The initial temperature commenced at 32 °C and was increased by 1 °C until maximum temperature (50 °C) was reached or the participant indicated their threshold by pressing a button. CPT was defined as the temperature which a cold sensation was first perceived as a sensation of cold and pain. The initial temperature commenced at 32 °C and was decreased by 1 °C until the participant indicated their threshold by pressing a button or when the lowest temperature of the device was reached (4 °C). PPT was tested using an algometer with a probe size of 1 cm^2 (Somedic AB, Hörby, Sweden), and was considered the point where the perceived sensation changed from pressure to pressure and pain. The pressure was increased at a rate of 50 kPa/s until the

participant indicated their PPT by pressing a button. For HPT, CPT and PPT three measures were taken at both the lumbar spine and wrist with the mean of three measures used for analysis. To minimise the possibility of TS during testing inter-stimulus intervals of 30 s were adopted.

Practically, both static and dynamic sensory testing was carried out with participants prone in the following order: TS, HPT, CPT, PPT, CPM, with each test following immediately on from the next. Standardised testing instructions were used throughout testing [22, 23]. Testing was undertaken in a temperature-controlled laboratory.

One year follow-up measures (Aim 3)

Follow-up measures were collected from the participants 12-months after entry into the study. Participants were contacted by email or mail and completed the following measures: pain intensity (11-point NRS) [20], LBP-related disability (RMDQ) [21] and disability risk stratification (SBT) [30]. Participants also described treatments undertaken (if any) during the follow up period (Supplementary Material 2).

Baseline statistical analysis

Descriptive statistics for the total cohort were calculated for all baseline variables. Descriptive statistics for females vs. males were also calculated for all baseline variables and included as a Supplementary File.

Cross-tabulation was used to subgroup participants according to dynamic QST parameters. The subgroups were: normal CPM and normal TS; normal CPM and facilitated TS; impaired CPM and normal TS; impaired CPM and facilitated TS.

To determine whether associations existed between dynamic QST subgroup membership and the broader multidimensional variables (pain characteristics, disability levels, psychological factors, lifestyle factors and static QST measures) one-way analysis of variance was utilised for normally distributed variables, the Kruskal–Wallis test for those with skewed data, and the Chi-squared test for categorical variables. As the proportion of females/males varied considerably across the subgroups we additionally estimated sex-adjusted associations using linear regression, negative binomial regression or quantile (median) regression depending on data type and distribution are reported for all variables with a p-value of <0.10 on unadjusted analysis. Sex adjusted associations between dynamic QST subgroup membership and the dependent variables were considered significant if the p-value was <0.05.

Follow-up analysis

Participants who completed and did not complete the 12-month follow-up were compared with respect to age, sex, baseline pain intensity (NRS) [20], LBP-related disability (RMDQ) [21], disability risk stratification (SBT) [30] and dynamic QST subgroup using a simple t-test for normally distributed variables, the Mann–Whitney U test for variables with skewed data, or Chi-squared test for categorical variables.

Descriptive statistics were calculated for the follow-up measures with respect to the total cohort and dynamic QST subgroups.

To evaluate whether subgroup membership was associated with levels of pain intensity, disability and disability risk stratification (SBT [30]) at 12-month follow-up data were analysed using one-way analysis of variance for normally distributed variables, the Kruskal–Wallis test for variables with skewed data, or the Chi-squared test for categorical variables.

All analysis was performed with Stata 16.

Results

Participant (n=273) flow through the study is shown in Figure 1. The demographic characteristics of the total cohort (n=273) is presented in Table 1. Baseline descriptive data, stratified by dynamic QST subgroups for female and male participants reported separately, are shown as a supplemental file (Supplementary material 1).

The proportions of participants (n, %) in the derived dynamic QST subgroups at baseline were: normal CPM and normal TS: 34 (12.5); normal CPM and facilitated TS: 6 (2.2); impaired CPM and normal TS: 186 (68.1); impaired CPM and facilitated TS: 47 (17.2). For TS, 267 (97.8%) reported the initial monofilament stimulation as 0/10 on the NRS. CPM and TS change scores for each subgroup are shown in Table 2 and Figure 2.

Sex differed significantly across the four subgroups (χ^2=9.93, p=0.013). Those with impaired CPM and facilitated TS had a higher than expected proportion of females (78.7%). Subsequently sex-adjusted comparisons are reported for all variables with a p-value <0.10 which included pain intensity, pain duration, body chart count, PPT and CPT at the lumbar spine and wrist, and HPT at the wrist (Table 2). After adjusting for sex, number of body chart areas remained different across subgroups (χ^2=9.23, p=0.026), with both groups with impaired CPM having a significantly higher number of areas that those with normal CPM and TS. CPT at the lumbar spine (F [3]=5.36; p=0.001) and wrist (F [3]=4.50; p=0.004) also differed across subgroups (Table 3). Those with normal CPM and facilitated TS (n=6, 2.2%) had higher CPT at the lumbar spine and wrist compared to the other subgroups. Those with impaired CPM and facilitated TS (n=47, 17.2%) also had higher CPT at the lumbar spine than those with impaired CPM and normal TS (n=186, 68.1%).

Of the 273 participants included at baseline 250 participants (91.6%) responded at the 12-month follow-up. The proportion of the 250 participants (n, %) in the dynamic QST subgroups at follow-up were: normal CPM and normal TS: 26 (10.4); normal CPM and facilitated TS: 6 (2.4); impaired CPM and normal TS: 175 (70.0); impaired CPM and facilitated TS: 43 (17.2). There was no difference in age, sex or baseline pain intensity between those who did or did not complete the 12-month follow-up (Table 4). However, participants that did not complete the 12-month

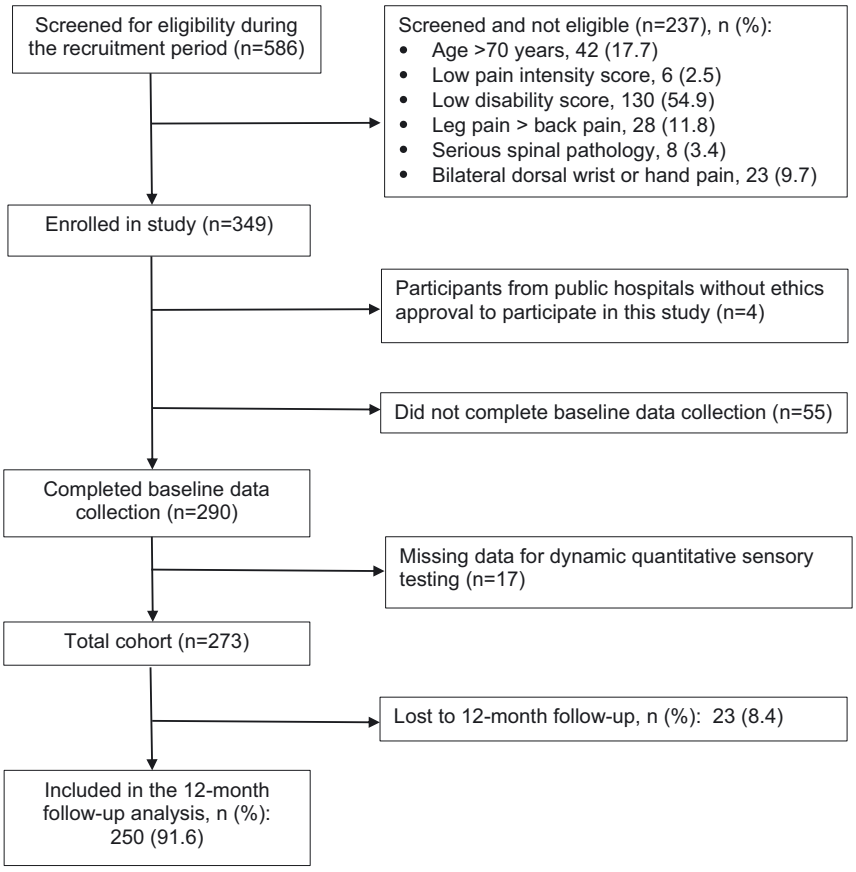


Figure 1: Flow of participants through the study.

follow-up had higher baseline disability (RMDQ median score 11-points vs. 9-points respectively; z=2.02; p=0.043), higher baseline disability risk stratification (high risk allocation 60.9 vs. 29.2 % respectively; X^2=10.54; p=0.005) and were more likely to have normal CPM and normal TS (34.8 vs. 10.4% respectively; X^2=12.13; p=0.016). Subgroup membership was not associated with follow-up pain intensity, LBP-related disability or disability risk stratification (SBT) at 12-months, either unadjusted or adjusted for sex (Table 5).

Table 1: Demographic characteristics total cohort.[a]

Variable	Total cohort n=273[b]
Age, year	50 (37–60)
Sex, n, % female	163 (59.7)
Percent LBP (vs. leg pain), n, %	
100%	136 (49.8)
80%	103 (37.7)
60%	34 (12.5)
Education level[1], year, mean, SD	14.8 (3.6)
Employment status, n, % yes working	212 (77.7)
Occupation[2], n, %	
Manual	66 (25.5)
Sedentary	165 (63.7)
Not working	28 (10.8)
Compensation status[3], n, % yes compensated	42 (15.7)

LBP, low back pain. [a]Values represent median (interquartile range) unless otherwise indicated. [b]n=273; except where there are missing data. **Missing data:** Educational level[1] = 14 missing; occupation[2] = 14 missing; compensation status[3] = six missing.

Discussion

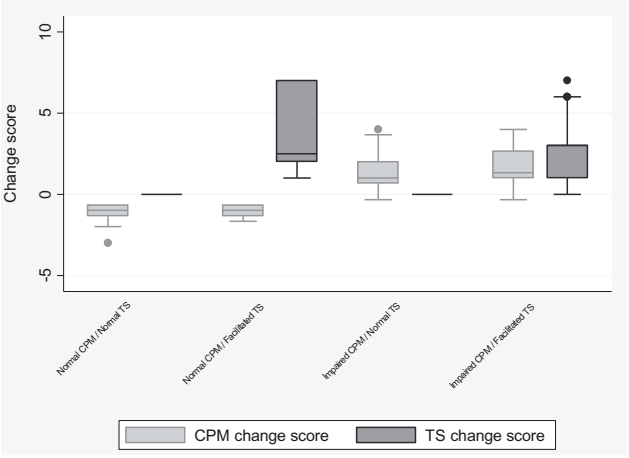
This study utilised dynamic QST findings to characterise subgroups within a large cohort with axial CLBP and explored differences between these subgroups across multidimensional characteristics and outcomes at 12-month follow-up. Across the derived subgroups there were no sex-adjusted associations with pain intensity, disability levels, psychological or lifestyle variables at baseline. Number of pain areas was greater in the two subgroups with impaired CPM. Cold pain sensitivity was heightened in both subgroups with facilitated TS, however, the subgroup with normal CPM and facilitated TS was small (n=6) and findings should be interpreted with caution.

Strengths of the study included a large cohort exclusively with axial CLBP who were well characterised across multiple dimensions relevant to pain, and with a low

Table 2: Baseline comparisons between dynamic quantitative sensory testing subgroups, unadjusted for sex.

Variable	Dynamic QST subgroup[f]					
	Total cohort n=273[f]	Normal CPM/normal TS n=34 (12.5%)	Normal CPM/facilitated TS n=6 (2.2%)	Impaired CPM/normal TS n=186 (68.1%)	Impaired CPM/facilitated TS n=47 (17.2%)	p-Value
Dynamic quantitative sensory testing						
CPM change score (NRS), mean, SD	1.0 (1.3)	−1.1 (0.6)	−1.1 (0.4)	1.2 (1.0)	1.5 (1.2)	
TS change score, NRS	0.0 (0.0–0.0)	0.0 (0.0–0.0)	2.5 (2.0–7.0)	0.0 (0.0–0.0)	3.0 (1.0–3.0)	
Sex, female n, %[h]	166 (57.2)	16 (47.1)	3 (50.0)	107 (57.5)	37 (78.7)	**0.01**
Pain characteristics & disability						
Pain intensity (NRS), mean, SD[f]	5.8 (1.9)	5.1 (2.0)[a]	5.3 (1.6)[ab]	6.0 (1.8)[b]	5.8 (2.0)[ab]	**0.07**
Pain duration[1], months[g]	120 (42–240)	120 (24–180)[ab]	67 (24–120)[ab]	120 (51–240)[a]	84 (24–180)[b]	**0.06**
Body chart count[g]	13 (7–21)	7 (4–13)[a]	13 (8–17)[abc]	14 (7–21)[bc]	14 (8–25)[c]	**0.003**
Opioids, n, % yes opioid use[e]	43 (15.8)	2 (5.9)	2 (33.3)	29 (15.6)	10 (21.3)	0.17
Disability (RMDQ)[g]	9 (6–13)	9 (6–11)	10 (5–11)	9 (6–13)	8 (6–12)	0.64
SBT risk subgroup, n, %[h]						0.26
Low risk	76 (27.8)	13 (38.2)	3 (50.0)	48 (25.8)	12 (25.5)	
Medium risk	110 (40.3)	12 (35.3)	0 (0.0)	80 (43.0)	18 (38.3)	
High risk	87 (31.9)	9 (26.5)	3 (50.0)	58 (31.2)	17 (36.2)	
Pain summation following repeated bending, n, %[h]						0.15
No increase in pain	135 (49.5)	23 (67.7)	2 (33.3)	90 (48.4)	20 (42.6)	
Unidirectional increase in pain	104 (38.1)	9 (26.5)	3 (50.0)	75 (40.3)	17 (36.2)	
Bidirectional increase in pain	34 (12.5)	2 (5.9)	1 (16.7)	21 (11.3)	10 (21.3)	
Psychological variables						
Depression (DASS-21)[g]	6 (2–14)	6 (2–14)	9 (6–10)	6 (2–14)	8 (2–16)	0.74
Anxiety (DASS-21)[g]	4 (2–8)	2 (0–8)	6 (4–10)	4 (2–8)	4 (2–8)	0.32
Stress (DASS-21)[g]	12 (6–20)	10 (6–20)	19 (10–22)	12 (6–18)	14 (8–20)	0.27
Fear avoidance beliefs (FABQ-PA)[g]	15 (11–19)	16 (12–20)	9 (3–18)	15 (11–19)	15 (10–19)	0.38
Pain catastrophising[2] (PCS total)[g]	18 (10–27)	15 (8–24)	17 (7–24)	18 (10–28)	16 (9–31)	0.76
Lifestyle variables						
Sleep quality[3] (PQSI total)[g]	9 (6–12)	9 (5–11)	9 (6–11)	9 (7–12)	9 (7–12)	0.52
Body mass index[c]	26 (24–29)	26 (23–31)	24 (24–30)	26 (24–29)	25 (23–30)	0.84
Static QST variables						
Pressure pain threshold (lumbar), kPa[g]	257 (160–423)	321 (202–422)[a]	115 (93–268)[b]	264 (176–445)[ac]	163 (73–336)[bd]	**0.001**
Pressure pain threshold (wrist), kPa[g]	268 (177–340)	276 (191–383)[a]	145 (137–184)[b]	271 (189–362)[ac]	257 (153–312)[d]	**0.009**
Heat pain threshold (lumbar), °C[g]	43 (39–46)	44 (42–46)	38 (34–44)	42 (39–45)	43 (37–45)	0.16
Heat pain threshold (wrist), °C[g]	45 (43–48)	46 (44–48)[a]	40 (35–45)[b]	46 (43–48)[ac]	43 (41–46)[bd]	**0.004**
Cold pain threshold (lumbar), °C[g]	4 (4–24)	4 (4–9)[a]	26 (17–29)[b]	4 (4–23)[ac]	10 (4–27)[bd]	**0.001**
Cold pain threshold (wrist), °C[g]	5 (4–13)	4 (4–11)[a]	14 (8–27)[b]	5 (4–12)[ac]	10 (4–21)[bd]	**0.006**

QST, Quantitative Sensory Testing; CPM, Conditioned pain Modulation; TS, Temporal Summation; NRS, Numerical Rating Scale; RMDQ, Roland-Morris Disability Questionnaire; SBT, STarT Back Tool; DASS-21, Depression Anxiety Stress Scale-21; FABQ-PA, Fear Avoidance Beliefs Questionnaire – Physical Activity; PCS, Pain Catastrophising Scale; PQSI, Pittsburgh Sleep Quality Index. Values represent median (interquartile range) unless otherwise indicated. [e]Pearson Chi squared. [f]one-way Analysis of Variance (ANOVA). [g]Kruskal–Wallis test. [h]Fisher's Exact test. Superscript letters indicate a significant difference between groups ($p<0.05$) i.e. results with different letters are significantly different. Variables for sex adjusted analyses if $p<0.10$ (indicated in bold). **Missing data:** n=273; except where there are missing data. Pain duration[1] = 2 and 2 missing respectively from impaired CPM/normal TS group and impaired CPM/facilitated TS group. Pain catastrophising[2] = 1 missing from normal CPM/normal TS group. Sleep quality[3] = 2, 8, and 1 missing respectively from normal CPM/normal TS group, impaired CPM/normal TS group, and impaired CPM/facilitated TS group.



CPM: conditioned pain modulation, TS: temporal summation

Figure 2: Conditioned pain modulation and temporal summation change scores for the four dynamic quantitative sensory testing subgroups.

attrition rate at 12-month follow-up. This provided specific advantages over the study by Vaegter and Graven-Nielsen [13] which was not LBP specific and was limited in the profiling variables it included. One limitation of this study is that the nylon monofilament used to assess TS was not re-calibrated between every participant and we cannot exclude the possibility that the monofilament may have functioned slightly differently with changes in humidity. Also, multiple comparisons in this study increase the possibility of type I error. However, with little research to date examining subgroups based upon dynamic QST this is a relatively exploratory study. Therefore, when profiling subgroups it may be more appropriate to maintain p-values such that there may be a greater chance of a type I error, but less chance of a type II error [35]. As such, no correction for multiple comparisons was deemed necessary.

Only one study has previously attempted subgrouping based on dynamic QST measures. Vaegter and Graven-Nielsen [13] formed the same dynamic QST subgroups in a cohort with chronic non-cancer pain. The subgroup with impaired CPM and facilitated TS demonstrated higher average pain intensity, more widespread pain and heightened heat pain sensitivity. The subgroup with impaired CPM and normal TS also had heightened heat pain sensitivity compared to those with normal CPM and normal TS. There may be numerous reasons for the different findings between these two studies. Firstly, the methods utilised for testing CPM and TS differed between studies. Vaegter and Graven-Nielsen [13] utilised repeated cuff pressure stimuli to test TS, and cuff pressure as both the conditioning and test stimuli for CPM testing. There is no gold standard CPM testing protocol [36]. There is also no consensus on categorising CPM or TS as normal or impaired based upon cut-off scores, and these differed in our study from the cut-off scores utilised by Vaegter and Graven-Nielsen [13]. However, the cut-off scores chosen in the current study were consistent with a previous LBP cohort study (CPM) [25] and the minimum clinically important difference on an 11-point NRS (TS) [26]. Finally,

Table 3: Baseline sex adjusted comparisons between dynamic quantitative sensory testing subgroups.

Variable	Dynamic QST subgroup[g]				p-Value
	Normal CPM/normal TS n=34 (12.5%)	Normal CPM/facilitated TS n=6 (2.2%)	Impaired CPM/normal TS n=186 (68.1%)	Impaired CPM/facilitated TS n=47 (17.2%)	
Pain characteristics					
Pain intensity (NRS); sex adjusted mean [95% CI][e]	5.1 [4.5, 5.7]	5.3 [3.9, 6.8]	6.0 [5.7, 6.2]	5.8 [5.2, 6.3]	0.08
Pain duration[1], months[f]	137 [93, 180]	116 [27, 205]	176 [151, 200]	146 [152, 200]	0.29
Body chart count[f]	11.2 [8.6,13.8][a]	12.8 [5.8, 19.9][abc]	16.3 [14.7, 17.8][bc]	16.5 [13.3, 19.6][bc]	0.026
Static QST variables					
Pressure pain threshold (lumbar), kPa[g]	278 [194, 363]	169 [–32, 370]	280 [244, 316]	210 [138, 283]	0.29
Pressure pain threshold (wrist), kPa[g]	255 [202, 309]	155 [28, 283]	260 [237, 283]	261 [215, 307]	0.47
Heat pain threshold (wrist), °C[g]	46 [44, 47]	44 [40, 47]	45 [45, 46]	44 [43, 46]	0.20
Cold pain threshold (lumbar), °C[g]	5 [0, 9][a]	24 [14, 35][b]	5 [3, 7][ac]	9 [5, 13][acd]	0.001
Cold pain threshold (wrist), °C[g]	6 [4, 9][a]	16 [10, 22][b]	6 [5, 7][ac]	8 [6, 10][ac]	0.004

QST, quantitative sensory testing; CPM, conditioned pain modulation; TS, temporal summation; NRS, Numerical Rating Scale. Values represent sex adjusted mean and 95% confidence intervals. Superscript letters (a, b, c) indicated a significant difference between groups ($p<0.05$) i.e. results with different letters are significantly different. [e]linear regression, [f] negative binomial regression, [g]quantile (median) regression.
Missing data: n=273; except where there are missing data. Pain duration[1] = 2 and two missing respectively from impaired CPM/normal TS group and impaired CPM/facilitated TS group.

Table 4: Baseline characteristics for participants who completed and did not complete the 12-month follow-up.[a]

Variable	Completer n=250 (91.6%)	Non-completer[b] n=23 (8.4%)	p-Value
Age, year	50 (38–60)	49 (33–58)	0.28
Sex, n, % female	152 (60.8)	11 (47.8)	0.22
Pain intensity (NRS), mean, SD; range 0–10	5.8 (1.9)	5.8 (1.7)	0.93
Disability (RMDQ); range 0–24	9 (6–13)	11 (7–15)	**0.043**
SBT risk subgroup, n, %			**0.005**
Low risk	74 (29.6)	2 (8.7)	
Medium risk	103 (41.2)	7 (30.4)	
High risk	73 (29.2)	14 (60.9)	
Dynamic QST subgroup, n, %; Fisher's Exact test			**0.016**
Group 1 (normal CPM/normal TS)	26 (10.4)	8 (34.8)	
Group 2 (normal CPM/facilitated TS)	6 (2.4)	0.0 (0.0)	
Group 3 (impaired CPM/normal TS)	175 (70.0)	11 (47.8)	
Group 4 (impaired CPM/facilitated TS)	43 (17.2)	4 (17.4)	

NRS, Numerical Rating Scale; RMDQ, Roland Morris Disability Questionnaire; SBT, STarT Back Tool; QST, quantitative sensory testing; CPM, conditioned pain modulation; TS, temporal summation. [a]Values represent median (interquartile range) unless otherwise indicated. Evaluation of differences between responders and non-responders were performed using an independent t-test, Mann-Whitney U test or Chi-squared test (Pearson's test unless otherwise indicated) depending on data type and distribution. Boldface indicates statistical significance ($p<0.05$). [b]Lost to follow-up by dynamic QST subgroup: eight from Group 1 (normal CPM/normal TS), zero from Group 2 (normal CPM/facilitated TS), 11 from Group 3 (impaired CPM/normal TS), and four from Group 4 (impaired CPM/facilitated TS).

the proportion of participants per subgroup differed compared to Vaegter and Graven-Nielsen [13]. The studies were similar with the largest subgroup being those with impaired CPM and normal TS (68.1 vs. 37.0%) and our smallest subgroup with normal CPM and facilitated TS (2.2%) was also the smallest (11.2%) for Vaegter and Graven-Nielsen [13]. Our study may suggest that CLBP populations more commonly exhibit impaired CPM than other chronic non-cancer pain complaints, but the findings may also reflect methodological differences, highlighting the difficulty in comparing studies without standardised testing protocols for dynamic QST. Similar to the findings from our study, the subgroups derived by Vaegter and Graven-Nielsen [13] did not differ across disability level, pain catastrophising or fear of movement. The lack of association between the derived subgroups and pain and disability levels is probably also consistent with previous systematic reviews [9, 16]. Finally, the risk

Table 5: Follow-up comparisons between dynamic quantitative sensory testing subgroups (unadjusted for sex).[a]

Follow-up measure	Total cohort n=250	Dynamic QST subgroup[b] Normal CPM/normal TS n=26 (10.4%)	Normal CPM/facilitated TS n=6 (2.4%)	Impaired CPM/normal TS n=175 (70.0%)	Impaired CPM/facilitated TS n=43 (17.2%)	p-Value
Pain intensity (NRS), mean, (SD); range 0–10	4.1 (2.1)	4.2 (1.9)	2.5 (1.9)	4.2 (2.2)	4.1 (2.2)	0.30
Disability (RMDQ); range 0–24	4 (2–8)	5 (3–9)	4 (0–8)	4 (2–8)	4 (2–8)	0.84
SBT risk subgroup, n, %						0.55
Low risk	159 (63.6)	18 (69.2)	6 (100.0)	107 (61.1)	28 (65.1)	
Medium risk	55 (22.0)	3 (11.5)	0 (0.0)	43 (24.6)	9 (20.9)	
High risk	36 (14.4)	5 (19.2)	0 (0.0)	25 (14.3)	6 (14.0)	

QST, quantitative sensory testing; CPM, conditioned pain modulation; TS, temporal summation; NRS, Numerical Rating Scale; RMDQ, Roland-Morris Disability Questionnaire; SBT, STarT Back Tool. [a]Values represent median (interquartile range) unless otherwise indicated. Evaluation of dynamic QST subgroup differences were performed using a one-way Analysis of Variance (ANOVA), Kruskal-Wallis test, or Chi-squared test (Fisher's Exact Test) depending on data type and distribution. [b]n=250; lost to follow-up by dynamic QST subgroup: eight from normal CPM/normal TS group, zero from normal CPM/facilitated TS group, 11 from impaired CPM/normal TS group, and four from impaired CPM/facilitated TS group.

of type II error must be acknowledged as the sample size of each subgroup may have limited the power of the study to detect differences across profiling variables.

In our study, those participants with impaired CPM and facilitated TS demonstrated greater cold pain sensitivity at the lumbar spine than those with impaired CPM and normal TS. Taking into consideration that the small subgroup with facilitated TS (but normal CPM) also had heightened cold pain sensitivity may suggest an association between TS and cold pain sensitivity. Indeed, post-hoc analysis suggests a weak correlation between TS change score and CPT (Lumbar, Spearman's rho=0.26; wrist, Spearman's rho=0.22). While impaired CPM and facilitated TS may indicate altered descending nociceptive modulation, the drivers of such heightened pain sensitivity may be related to variables not investigated in this study, e.g. physical activity levels, genetics etc., and this postulate requires further examination.

Our findings suggest dynamic QST subgroups do not explain pain intensity and LBP-related disability at baseline or 12-month follow-up. This is consistent with previous multidimensional prognostic modelling of this cohort where CPM and TS were not identified as prognostic factors [18]. The clinical utility of QST measures (static, dynamic or subgroups thereof) may not be in their ability to predict future pain and disability, but rather in their modification of treatment effects [37]. Yarnitsky [38] has detailed early evidence that people with dynamic QST profiles characterised by impaired CPM may benefit from specific pharmacological interventions targeting underlying mechanisms (e.g. Tapentadol), while those with facilitated TS may benefit from other medications (e.g. ketamine). Further investigation of these subgroups as treatment effect modifiers may be warranted.

Our study found a difference in body chart count across subgroups, with the two subgroups with impaired CPM more likely to have a higher body area count compared to those with normal dynamic QST responses. In contrast, Vaegter and Graven-Nielsen [13] found that only the subgroup with impaired CPM and facilitated TS had significantly higher number of pain areas compared to the other subgroups, with the authors suggesting this combination might be a biomarker for widespread pain. This disparity between studies could be attributed to the different cohort profiles. Approximately 85% of the cohort utilised by Vaegter and Graven-Nielsen [13] presented with widespread pain or multiple spinal areas of pain, whereas our cohort presented dominantly with axial CLBP. The methodology for measuring this variable also differed between the two studies. Another study has investigated CPM in people with more localised CLBP vs. those with CLBP and more widespread pain [39]. Their findings were consistent with the present study, that impaired CPM is associated with more widespread pain. Unfortunately that study did not also test for TS, somewhat limiting comparison.

This is the first study that considered the relationship between dynamic QST subgroups and pain intensity, LBP-related disability and disability risk stratification at two points in time. At 12-month follow-up, subgroups did not differ across these variables. The 12-month follow-up analysis did not consider what interventions the cohort had received during this period, which may have influenced outcomes. It is unknown whether cold sensitivity findings persisted at 12-month follow-up as static QST measures were not collected. Furthermore, participants lost to follow-up had higher baseline disability and disability risk stratification and were more likely to have normal CPM and normal TS which may have influenced the results.

Overall, our findings suggest that within a cohort with CLBP a subgroup with impaired CPM and facilitated TS demonstrated heightened cold pain sensitivity. Additionally, those with impaired CPM are likely to have more widespread symptoms. These data suggest altered descending nociceptive modulation, however, the drivers of this heightened pain sensitivity require further examination. While sensory profile may act as a treatment effect modifier, future research examining the effectiveness of targeted interventions to address specific sensory phenotypes is needed.

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