Low back related leg pain – An investigation of construct validity of a new classification system

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Abstract

Background: Leg pain is associated with back pain in 25-65% of all cases and classified as somatic referred pain or radicular pain. However, distinction between the two may be difficult as different pathomechanisms may cause similar patterns of pain. Therefore a pathomechanism based classification system was proposed, with four distinct hierarchical and mutually exclusive categories: Neuropathic Sensitization (NS) comprising major features of neuropathic pain with sensory sensitization; Denervation (D) arising from significant axonal compromise; Peripheral Nerve Sensitization (PNS) with marked nerve trunk mechanosensitivity; and Musculoskeletal (M) with pain referred from musculoskeletal structures.

Objective: To investigate construct validity of the classification system

Methods: Construct validity was investigated by determining the relationship of nerve functioning with subgroups of patients and asymptomatic controls. Thus somatosensory profiles of subgroups of patients with low back related leg pain (LBRLP) and healthy controls were determined by a comprehensive quantitative sensory test (QST) protocol. It was hypothesized that subgroups of patients and healthy controls would show differences in QST profiles relating to underlying pathomechanisms.

Results: 77 subjects with LBRLP were recruited and classified in one of the four groups. Additionally, 18 age and gender matched asymptomatic controls were measured. QST revealed signs of pain hypersensitivity in group NS and sensory deficits in group D whereas Groups PNS and M showed no significant differences when compared to the asymptomatic group.

Conclusions: These findings support construct validity for two of the categories of the new classification system, however further research is warranted to achieve construct validation of the classification system as a whole.

Keywords: Low back pain, Leg pain, Classification system, Validity, Quantitative Sensory Testing, QST

1. Introduction

Low back related leg pain (LBRLP) is common with up to 65% of patients with low back pain reporting accompanying leg pain [1, 2]. These cases account for a disproportionately large amount of the costs of medical care and disability compensation caused by low back pain (LBP) [3] as leg pain is associated with more severe pain and disability outcomes [4]. Traditionally, LBRLP is classified as somatic referred pain ("pseudoradicular pain") or projected radicular pain [5]. However, despite advanced diagnostic technology, the distinction between these two entities remains difficult as different structures in the lower back can evoke similar patterns of pain. Pain radiating as far as the toes can stem from intervertebral disks, zygapophyseal joints, muscles, and fascia in addition to the lumbar nerve roots [6-8].

Randomized controlled trials investigating the effectiveness of conservative treatment of patients with radiating leg pain show inconsistent findings [9, 10]. One explanation for this could be the failure to correctly classify subjects into homogenous treatment-specific subgroups, with consequent lack of effect due to inappropriate treatment. There are recommendations from the pain literature that for the more complex pain conditions related to nerve injury a classification system based on pathomechanisms offers greater diagnostic and treatment value and may also provide information about the prognosis and natural course of the disorder [11].

In order to refine the differentiation of radicular and pseudoradicular pain and hence gain treatment efficacy, we introduced a new mechanism based classification system [12] based on the original classification proposed by Elvey and Hall [13]. The aim of this system is to improve treatment outcome, particularly with respect to identifying

patients most likely to respond to neural mobilization. Depending on the assumed predominance of pathomechanisms, LBRLP is classified into four distinct subgroups. Prioritized, these categories are (Figure 1):

1. Neuropathic Sensitization (NS) comprising major features of neuropathic pain mechanisms with dominant sensory sensitization
2. Denervation (D) caused by significant peripheral axonal compromise with evidence of afferent and / or efferent loss of conduction in the absence of dominant sensory sensitization
3. Peripheral Nerve Sensitization (PNS) presumably arising from nerve trunk inflammation. Patients in this group are characterized by positive nerve provocation tests (e.g. straight leg raise test) without clinical evidence of significant denervation and absent dominant features of neuropathic pain mechanisms.
4. Musculoskeletal (M) with pain referred from non-neural structures such as the disc or facet joints. Patients in this group are characterized by absent features of neuropathic pain mechanisms, absent signs of denervation and negative nerve provocation tests.

This new classification system has demonstrated good interrater reliability with κ = 0.72 [14] and has shown prognostic ability [15]. The objective of the present study was to investigate construct validity of the classification system by determining the relationship of diagnostic groups with the results from Quantitative Sensory Testing (QST) [16].

2. Methods

Study design and hypotheses

This observational, cross-sectional study was designed to investigate construct validity of a new classification system for subjects with LBRLP. Construct validity is based on testing hypotheses about relationships of the instrument under study (i.e. the classification system) with other instruments measuring similar constructs [16]. The construct measured both by the instrument under study (i.e. the classification system) and the reference instrument (QST) is pain mechanisms. We tested the hypothesis that QST parameters will differ between subgroups of subjects with LBRLP and a group of asymptomatic subjects.

Ethical approval

This study was approved by the Human Research Ethics Committee of the Curtin University of Technology. All patients provided written informed consent prior to participating in the study.

Subjects and recruitment

Subjects were recruited at a multidisciplinary pain clinic in Hamburg, Germany. 162 consecutive patients with LBRLP referred for physiotherapy at the clinic were screened for eligibility. To be considered for inclusion subjects were required to be between 18 and 75 years of age, with unilateral LBRLP of more than 6 weeks duration. Exclusion criteria were history of lower quadrant surgery or trauma within the past 6 months, nerve root block within the past four weeks, other neuropathic pathology such as diabetes or polyneuropathies, vascular disease in the lower extremities, inflammatory arthropathies, contraindications to manual therapy techniques and inability to understand written / spoken German. Of the 162 subjects

screened, 77 were eligible and willing to participate (Figure 2). Another 18 age and gender matched healthy volunteers were recruited as control subjects to provide normative data for z-score standardization of QST parameters into standard deviation units for comparison.

Quantitative sensory testing (QST)

A comprehensive battery of QST devices that was developed and validated by the German Research Network on Neuropathic Pain [17] was used as the reference instrument.

This QST battery tests all relevant submodalities of the somatosensory system. Seven tests are used to measure 13 parameters consisting of thermal pain thresholds for cold and hot stimuli; thermal detection thresholds for the perception of cold, warm and thermal sensory limen[1]; paradoxical heat sensations; mechanical pain thresholds for pinprick and blunt pressure; mechanical detection thresholds for touch and vibration; a stimulus-response-function for pinprick sensitivity; dynamic mechanical allodynia for stroking light touch; as well as pain summation to repetitive pinprick stimuli. Thus QST evaluates the function of sensory nerve fibres and their respective pathways [18] by analysing multiple parameters of sensory testing. Thus obtained sensory profiles of patients may exhibit whether dominant features of sensory deficit (loss of function) or sensory hyperexcitability (gain of function) exist, indicative for specific pain mechanisms [19, 20].

The test protocol has been shown to have good test-retest and inter-tester reliability

[1] Thermal sensory limen is the difference in sensory threshold between alternating cold and warm stimuli

[21] as well as acceptable concurrent validity [22-24].

We tested three body regions; the lower back, the dorsum of the foot and the dorsum of the hand. In subjects with LBRLP test sites were within the painful region of the back and on the dorsum of the affected foot. A site remote to the painful regions (dorsum of the ipsilateral hand) was also tested, as changes in the somatosensory system associated with chronic pain have also been reported in body areas remote to the source of pain. It has been shown that these changes manifest in negative signs such as hypoesthesia [25] as well as in positive signs such as pain sensitivity to blunt pressure [26]. The ipsilateral hand was always tested first, followed alternately by foot or back in patient groups. In the control group, testing of the different areas was conducted alternately.

Classification

All symptomatic subjects were classified into one of four groups following a pre-established examination protocol [12] (Figure 1). The assessment protocol includes subjective questions relating to area of pain, duration of symptoms, and aggravating and easing factors. The subjective components of the LANSS questionnaire [27] were incorporated into the subjective assessment to screen for predominantly positive symptoms indicative of sensitization of the somatosensory system. The physical examination included a neurological examination to screen for motor and sensory deficits, neural tissue provocation tests (straight leg raise test; prone knee bend test, active flexion test in standing, nerve palpation) [13] and the objective components for the total LANSS score (altered pin prick sensation and light touch allodynia).

The classification system as a whole has demonstrated good inter-rater reliability [14] as well as predictive ability [15]. The LANSS has demonstrated good discriminate validity [27].

Subjects scoring 12 or more on the LANSS scale were classified as NS. The LANSS questionnaire was designed to detect pain of predominantly neuropathic origin, a cut off score of ≥12 is indicative for a likely contribution of neuropathic pain mechanisms to the patients pain [27]. Mechanisms underlying neuropathic pain may be both central or peripheral [28], however items within the LANSS scale are primarily concerned with identifying positive features of neuropathic pain, such as hyperalgesia and allodynia in areas distant to the lesion which are hall mark signs for central pain mechanisms [29, 30].

In our earlier papers [12, 14] we referred to the group with a LANSS score ≥ 12 as "Central Sensitization". In retrospect, this was not the most appropriate term and was probably misleading. In the present paper we refer to the group with a LANSS scale ≥ 12 as "Neuropathic Sensitization". "Neuropathic" to more adequately reflect the construct of the LANSS scale and "Sensitization" as the LANSS tests primarily for positive signs indicative for gain of function. The only item within the LANSS testing for negative signs is the test for altered pin-prick sensation.

Subjects scoring less than 12 on the LANSS scale and with at least two or more positive tests in two of four different categories: reflexes; muscle power; light touch; or pinprick sensitivity [14] were classified as "Denervation". We chose the term

"Denervation" as it encompasses both ventral (efferent) and dorsal (afferent) root dysfunction.

Subjects in group PNS are characterized by positive nerve provocation tests [31] with a LANSS score < 12 and in the absence of marked neurological deficits. The term "Peripheral Nerve Sensitization" reflects potential peripheral mechanisms such as induction of mechanosensitive sodium channels in the nerve sheath as a consequence of focal inflammation [32]. Nerve mechanosensitivity to pressure and stretch in the absence of nerve damage has been demonstrated in animal nerve inflammation models [33, 34], and can be observed clinically in patients with radiating arm pain [35] or leg pain [36]. The term "Peripheral Nerve Sensitization" describes a pain state with marked nerve mechanosensitivity in the absence of neuropathic pain and denervation.

Group M consists of subjects with a LANSS score < 12, without marked neurological deficits and negative nerve provocation tests. These clinical features indicate "pseudoradicular" or somatic referred pain, as neural involvement in the subjects' pain is unlikely. The main mechanism for somatic referred pain is convergence, where afferent nerve fibers from the leg and from structures in the lower back converge upon the same viscerosomatic neurons in the dorsal horn of the spinal cord [37].

Examiners

Two examiners (AS and KL), trained simultaneously by RR in the use of the QST equipment, carried out all QST testing. The QST examiners were blinded to the results of the physical examination.

Data management

QST data that were not normally distributed were transformed logarithmically before statistical analysis. The numbers of paradoxical heat sensations during the thermal sensory limen procedure, cold pain thresholds, heat pain thresholds and vibration detection thresholds were normally distributed as raw data. All other QST parameters were normally distributed after logarithmical transformation.

To facilitate comparisons between parameters originally measured in different units, normalized data for each of the QST parameters were converted to z-scores using means and SDs from the control group (z-score = $Score_{single\ patient}$ - $Mean_{controls}$ / $SD_{controls}$) [17]. A z-score of zero characterizes a value matching the group mean of the healthy control subjects. Positive z-scores indicate a gain of function where the patient is more sensitive to the tested stimulus compared to controls (hyperalgesia, allodynia, hyperpathia) and negative z-scores indicate the patient has a loss of sensation (hypoesthesia) compared to controls.

One-way ANOVAs and Chi square tests were used to analyze the difference in general measures between groups (Table 1).

Two way ANOVAs were conducted for each QST parameter to test interaction effects of group with body region and between subject main effects (group). The aim was to investigate relationships of QST data with diagnostic groups. Where main effects or interactions were significant, Tukey HSD post hoc tests were used to control for multiple testing. All QST data are presented as Z-scores (mean ± SEM) unless otherwise indicated. SPSS version 17 (SPSS Inc., Chicago, USA) was used for statistical analysis.

3. Results

Subjects

Subjects had a mean age of 48 years and 39% were men. Age, gender, pain duration and proportion of patients with pain below the knee were comparable between groups ($p > 0.50$). Subjects with a score of 12 or more on the LANSS scale [27] were classified as Neuropathic Sensitization (n=20). The remaining symptomatic subjects (n=57) who had a LANSS scale score of less than 12 plus negative signs such as hypoesthesia, muscle weakness or hyporeflexia were classified as Denervation (n=28). Of the remaining 29 symptomatic subjects, 9 exhibited positive neural provocation tests, and were classified as Peripheral Nerve Sensitization. All other subjects were classified as Musculoskeletal (n=20) as there was no suggestion of neural involvement (Figure 1). For detailed subject characteristics please see Table 1.

QST findings

Results showed relationships between QST data and diagnostic groups as there were differences in QST parameters between groups across the tested body regions (group main effect) (Table 2). All group main effects were between symptomatic subject groups and the asymptomatic group. No significant differences were found between the four symptomatic subject groups. Warm detection threshold was the only parameter where the difference between groups varied significantly according to region (significant group by region interaction), however no group main effects could be detected for this parameter (Table 2). Allodynia was rare, there was one outlier with severe allodynia over the back and paradoxical heat sensation was generally more frequent at the affected foot for group Denervation, although these differences were not significant at group level (Figure 3). Significant main effects for region

across groups were not further analysed nor discussed, as these do not relate to the research question.

QST procedures reveal differences between groups Neuropathic Sensitization, Denervation and controls

The complete sensory profiles of the diagnostic groups Neuropathic Sensitization, Denervation, Peripheral Nerve Sensitization, and Musculoskeletal over the foot, lumbar spine, and dorsum of the hand are displayed in Figure 3. When comparing symptomatic subject groups and asymptomatic controls, we found significant group main effects for cold pain threshold, mechanical detection threshold, mechanical pain threshold and mechanical pain sensitivity (Table 2).

Post hoc analysis with correction for multiple testing (Tukey HSD) for group main effects revealed that group Neuropathic Sensitization had hyperalgesia to cold (CPT) and to pinprick (MPT, MPS, all $p<0.05$). Group Denervation also showed cold hyperalgesia and in addition higher mechanical detection threshold indicating mechanical hypaesthesia (MDT, $p<0.05$). For mean differences, F and p values, please see Table 2.

4. Discussion

The results supported construct validity, as relationships between QST data and diagnostic groups could be demonstrated. QST parameters differed between two groups of subjects with leg pain and the group of asymptomatic subjects: Subjects in group Neuropathic Sensitization showed marked signs of pain hypersensitivity, while sensory deficits were most pronounced in group Denervation. The QST findings in

these two groups match the presumed underlying pathomechanisms: Dominant neuropathic pain mechanisms with sensory sensitization in group Neuropathic Sensitization and mechanisms responsible for loss of conduction in group Denervation. In contrast, groups Peripheral Nerve Sensitization and Musculoskeletal were not significantly different to healthy controls across all QST parameters.

Decreased mechanical pain thresholds and cold hyperalgesia as observed in group Neuropathic Sensitization are signs consistent with central sensitization [28]. Central sensitization may arise as a result of a number of different mechanisms. Diminished control of pain including cell death of inhibitory interneurons in the dorsal horn may contribute to enhanced pain processing [28] as well as changed descending modulatory mechanisms from the brain stem [38, 39]. Additionally, secondary changes in cortical and subcortical brain regions, triggered by cognitions, emotions and attention may further add to central sensitization and development of spontaneous activity and pain [40, 41]. Another mechanism potentially contributing to augmentation of central pain processing is deafferentation: Clinical and QST examinations revealed deficits in large fibre function not only in group Denervation but also in group Neuropathic Sensitization, indicating nerve fibre damage that for the latter group may have induced secondary sensitization of higher order nociceptive neurons [42]. QST findings from patients with other conditions thought to involve central sensitization such as whiplash associated disorders [43], LBP [44] or fibromyalgia [45] have also shown increased sensitivity to thermal and mechanical pain stimuli consistent with findings in the present study. Central sensitization of the nociceptive system is one of the main mechanisms contributing to neuropathic pain [46].

Increased mechanical detection thresholds were found in group Denervation when compared to healthy controls, this was most pronounced over the foot. Additionally, although not significant, group Denervation showed the most pronounced deficits in vibration, cold and warm detection over the foot (Fig. 3), consistent with a loss of conduction. One possible explanation for the significantly elevated mechanical detection threshold found in group Denervation could be mechanical compression of the nerve root caused by prolapsed IVD tissue, osteophytes, facet joint hypertrophy or ligamentum flavum hypertrophy [47]. Also chemical irritation of the nerve roots may have similar effects. Proinflammatory cytokines such as tumor necrosis factor α released from nucleus pulposus cells or from inflamed arthritic facet joints can enter the epidural space, contact nerve roots and thereby induce radicular symptoms with large and small fibre deficits [48, 49].

A recent study [25] compared somatosensory profiles of subjects with somatic referred pain (n=15) with subjects with radicular pain (n=12) and found that both were significantly different to a healthy control group. The authors hypothesized that mild root compression or an inflammatory perturbation of nerve roots in people with pseudoradicular pain as well as in people with radicular pain may explain this phenomenon. In contrast, the present study showed, in comparison to healthy controls, no significant sensory dysfunction in groups Peripheral Nerve Sensitization and Musculoskeletal, which are clinically comparable to patients with "pseudoradicular symptoms". The reason for this may lie in a more differentiated subclassification of subjects and consequently higher within group homogeneity.

Some limitations should be pointed out. First of all, interaction effects between group and body region could not be demonstrated. This indicates that only generalized sensory changes over the entire body could be shown, but not localized changes. Also, statistical analysis of QST data revealed significant differences only between two of the four symptomatic groups and the asymptomatic group. This implies, firstly, that construct validity could only be demonstrated for two of the groups, but not for the classification as a whole. Secondly, the fact that no differences were found between patient groups weakens conclusions in regard to construct validity. One possible explanation is that group Peripheral Nerve Sensitization was unexpectedly small with higher standard errors as a result. In addition, it is well known that psychosocial factors such as hypervigilance or catastrophizing significantly influence pain perception, however data in this respect were not available for the present study.

5. Conclusion

The results of this study provide preliminary evidence for the construct validity for two of the four groups used in the new classification system as significant differences of QST determined sensory and pain thresholds in groups Neuropathic Sensitization and Denervation when compared to a group of asymptomatic subjects were shown. These differences match presumed underlying mechanisms: Sensory deficits in group Denervation and pain hypersensitivity in group Neuropathic Sensitization. Future research should include assessment of further psychosocial covariates such as catastrophizing or hypervigilance and focus on achieving equal group sizes.

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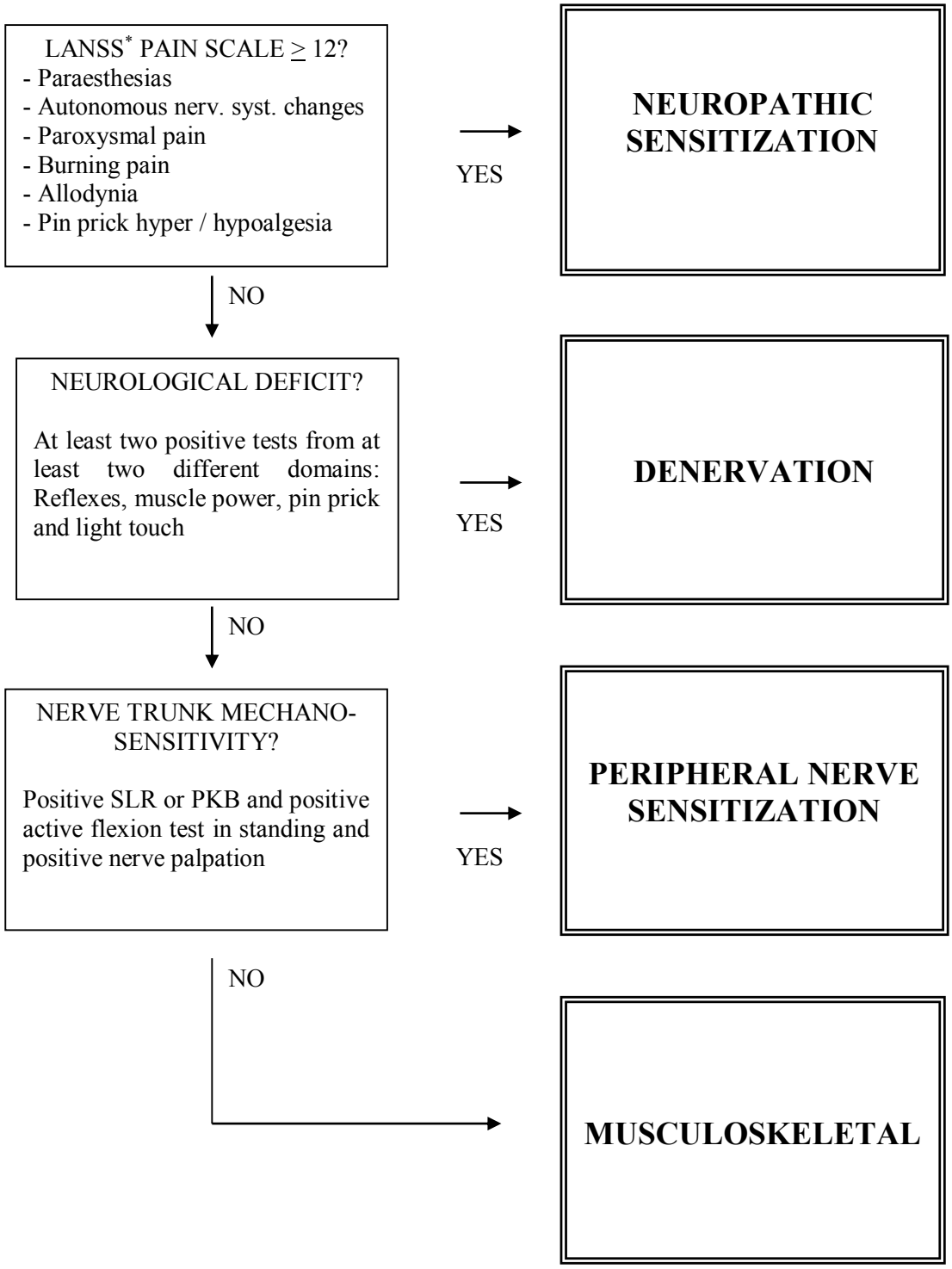
Figure 1: Classification algorithm



*LANSS: Leeds Assessment of Neuropathic Symptoms and Signs [27]

Figure 2: Participant flow diagram

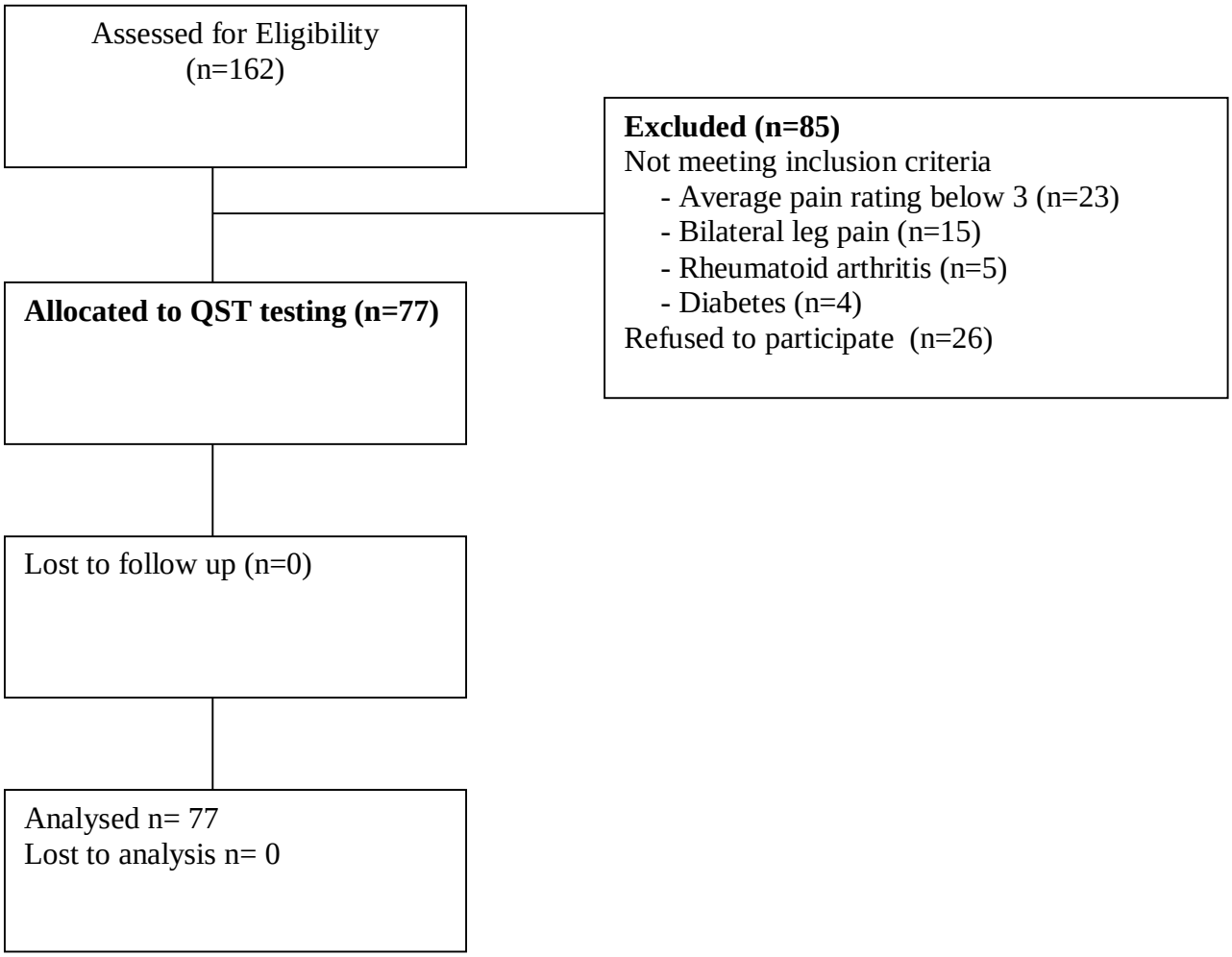
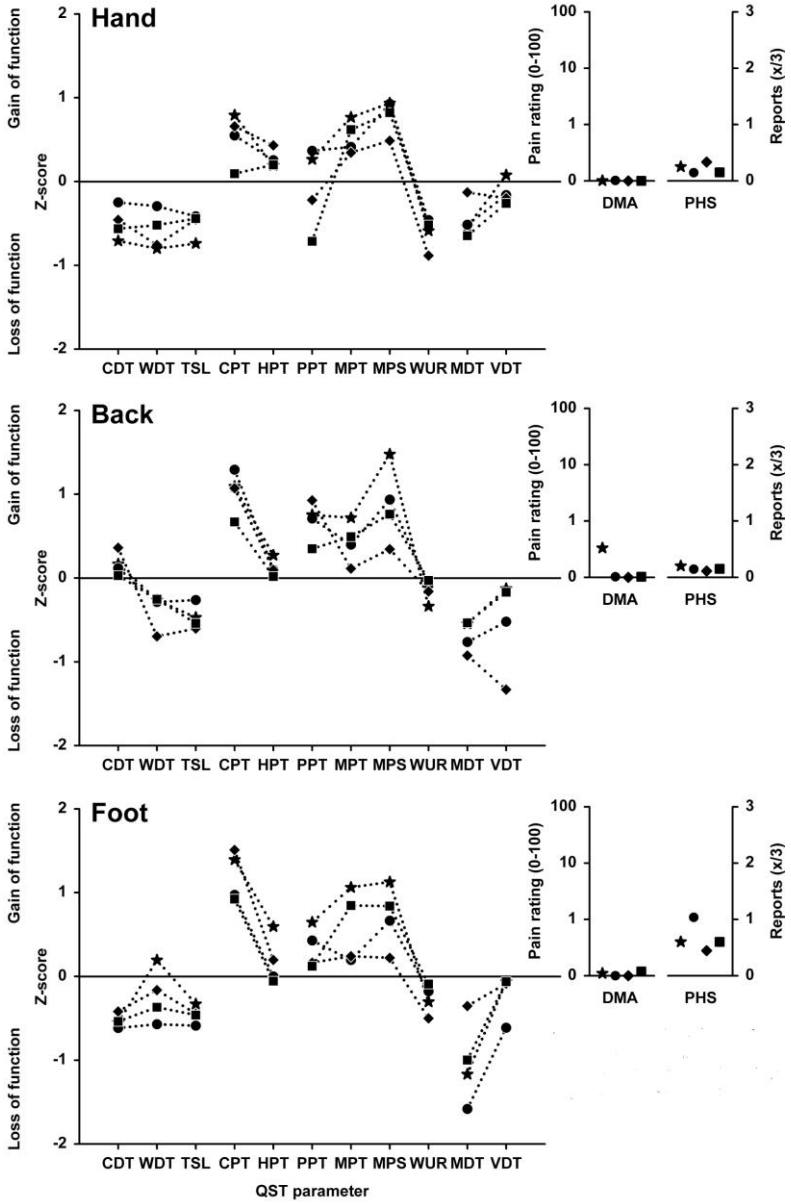


Figure 3: QST profiles



★ Group Neuropathic Sensitization
● Group Denervation
◆ Group Peripheral Nerve Sensitization
■ Group Musculoskeletal

CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind up ratio; MDT, mechanical detection threshold; VDT, vibration detection threshold; PHS, paradoxical heat sensation; DMA, dynamic mechanical allodynia.

The graphs in Figure 3 display the variance of group means (groups NS, D, PNS and M) from the mean of the asymptomatic controls in standardized units (z-scores). Positive z-scores indicate a gain of function, negative z-scores indicate a loss of function.

Table 1*: Demographic and clinical data by diagnostic classification for subjects with LBRLP*

	Total	***Neuropathic Sensitization***	***Denervation***	***Peripheral Nerve Sensitization***	***Musculo-skeletal***	***p value[a]***
n (%)	77	20 (26)	28 (36)	9 (12)	20 (26)	
Age	47.8 (13.1)	47.5 (13.4)	48.2 (12.2)	44.3 (14.0)	49.2 (14.2)	.83[a]
Gender (% male)	40	35	39	41	45	.92[b]
Pain below knee (%)	76.3	80.0	71.4	88.9	73.7	.71[b]
Pain duration (months)[§]	7.5 (4.0)	7.0 (5.1)	7.3 (3.3)	6.0 (2.8)	10.7 (4.3)	.76[c]

Values presented are means (Standard deviations) or percentage unless otherwise indicated
[§] Median (interquartile range)
[a] One-way ANOVA;
[b] χ^2 test
[c] Kruskall Wallis test

Table 2: Statistics from two-way Analysis of variance comparing z-scores for QST parameters between four symptomatic groups and one asymptomatic group over different body regions

QST parameter	***Group main effects***		***Tukey HSD post hoc for group main effects***				***Body region main effects***		***Inter-action region by group***	
	F-value	*p-value*	*Mean difference (z-score)*	*p-value*	*95% Confidence Interval upper bound*	*lower bound*	*F-value*	*p-value*	*F-value*	*p-value*
CDT	0.7	0.563					14.5	0.001	1.3	0.234
WDT	1.1	0.374					2.9	0.062	2.1	0.042
TSL	1.9	0.342					0.1	0.654	1.3	0.361
CPT	3.3	**0.015**					7.5	0.001	1.0	0.428
C-NS			-1.09	**0.019**	-2.06	-0.12				
C-D			-0.94	**0.038**	-1.84	-0.03				
C-PNS			-1.08	0.108	-2.3	0.14				
C-M			-0.56	0.495	-1.53	0.41				
HPT	0.5	0.891					0.6	0.845	0.9	0.531
MDT	3.7	**0.007**					4.1	0.02	1.6	0.354
C-NS			0.7509	0.058	-0.012	1.52				
C-D			.9543	**0.003**	0.24	1.67				
C-PNS			0.4689	0.659	-0.5	1.43				
C-M			0.7188	0.078	-0.05	1.49				
MPT	3.9	**0.006**					0.6	0.540	0.7	0.789
C-NS			-.8482	**0.005**	-1.51	-0.18				
C-D			-0.3347	0.561	-0.95	0.28				
C-PNS			-0.2325	0.937	-1.07	0.60				
C-M			-0.652	0.058	-1.32	0.01				
MPS	2.5	**0.047**					0.6	0.550	0.7	0.703
C-NS			-1.1798	**0.033**	-2.29	-0.06				
C-D			-0.8415	0.168	-1.88	0.2				
C-PNS			-0.3507	0.957	-1.75	1.05				
C-M			-0.8075	0.267	-1.92	0.31				
WUR	0.4	0.493					4.9	0.001	0.9	0.910
VDT	1.3	0.260					2.6	.083	1.6	0.131
PPT	2.0	0.287					8.7	0.001	1.8	0.405
DMA	1.0	0.745					1.5	0.734	.7	0.820
PHS	1.6	0.541					1.2	0.816	.9	0.690

CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind up ratio; MDT, mechanical detection threshold; VDT, vibration detection threshold; PHS, paradoxical heat sensation; DMA, dynamic mechanical allodynia.
C- Control group
NS – Group Neuropathic Sensitization
D – Group Denervation
PNS – Group Peripheral Nerve Sensitization
M – Group Muskuloskeletal