Low back related leg pain – An investigation of

construct validity of a new classification system

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1 Abstract

2	Background: Leg pain is associated with back pain in 25-65% of all cases and
3	classified as somatic referred pain or radicular pain. However, distinction between the
4	two may be difficult as different pathomechanisms may cause similar patterns of pain.
5	Therefore a pathomechanism based classification system was proposed, with four
6	distinct hierarchical and mutually exclusive categories: Neuropathic Sensitization
7	(NS) comprising major features of neuropathic pain with sensory sensitization;
8	Denervation (D) arising from significant axonal compromise; Peripheral Nerve
9	Sensitization (PNS) with marked nerve trunk mechanosensitivity; and
10	Musculoskeletal (M) with pain referred from musculoskeletal structures.
11	Objective: To investigate construct validity of the classification system
12	Methods: Construct validity was investigated by determining the relationship of
13	nerve functioning with subgroups of patients and asymptomatic controls. Thus
14	somatosensory profiles of subgroups of patients with low back related leg pain
15	(LBRLP) and healthy controls were determined by a comprehensive quantitative
16	sensory test (QST) protocol. It was hypothesized that subgroups of patients and
17	healthy controls would show differences in QST profiles relating to underlying
18	pathomechanisms.
19	Results: 77 subjects with LBRLP were recruited and classified in one of the four
20	groups. Additionally, 18 age and gender matched asymptomatic controls were
21	measured. QST revealed signs of pain hypersensitivity in group NS and sensory
22	deficits in group D whereas Groups PNS and M showed no significant differences
23	when compared to the asymptomatic group.

1	Conclusions: These findings support construct validity for two of the categories of
2	the new classification system, however further research is warranted to achieve
3	construct validation of the classification system as a whole.
4	
5	Keywords: Low back pain, Leg pain, Classification system, Validity, Quantitative

6 Sensory Testing, QST

1 1. Introduction

2	Low back related leg pain (LBRLP) is common with up to 65% of patients with low
3	back pain reporting accompanying leg pain [1, 2]. These cases account for a
4	disproportionately large amount of the costs of medical care and disability
5	compensation caused by low back pain (LBP) [3] as leg pain is associated with more
6	severe pain and disability outcomes [4]. Traditionally, LBRLP is classified as somatic
7	referred pain ("pseudoradicular pain") or projected radicular pain [5]. However,
8	despite advanced diagnostic technology, the distinction between these two entities
9	remains difficult as different structures in the lower back can evoke similar patterns of
10	pain. Pain radiating as far as the toes can stem from intervertebral disks,
11	zygapophyseal joints, muscles, and fascia in addition to the lumbar nerve roots [6-8].
12	
13	Randomized controlled trials investigating the effectiveness of conservative treatment
14	of patients with radiating leg pain show inconsistent findings [9, 10]. One explanation
15	for this could be the failure to correctly classify subjects into homogenous treatment-
16	specific subgroups, with consequent lack of effect due to inappropriate treatment.
17	There are recommendations from the pain literature that for the more complex pain
18	conditions related to nerve injury a classification system based on pathomechanisms
19	offers greater diagnostic and treatment value and may also provide information about
20	the prognosis and natural course of the disorder [11].
21	
22	In order to refine the differentiation of radicular and pseudoradicular pain and hence
23	gain treatment efficacy, we introduced a new mechanism based classification system
24	[12] based on the original classification proposed by Elvey and Hall [13]. The aim of
25	this system is to improve treatment outcome, particularly with respect to identifying

25 this system is to improve treatment outcome, particularly with respect to identifying

1	patients most likely to respond to neural mobilization. Depending on the assumed
2	predominance of pathomechanisms, LBRLP is classified into four distinct subgroups.
3	Prioritized, these categories are (Figure 1):
4	1. Neuropathic Sensitization (NS) comprising major features of neuropathic pain
5	mechanisms with dominant sensory sensitization
6	2. Denervation (D) caused by significant peripheral axonal compromise with
7	evidence of afferent and / or efferent loss of conduction in the absence of
8	dominant sensory sensitization
9	3. Peripheral Nerve Sensitization (PNS) presumably arising from nerve trunk
10	inflammation. Patients in this group are characterized by positive nerve
11	provocation tests (e.g. straight leg raise test) without clinical evidence of
12	significant denervation and absent dominant features of neuropathic pain
13	mechanisms.
14	4. Musculoskeletal (M) with pain referred from non-neural structures such as the
15	disc or facet joints. Patients in this group are characterized by absent features
16	of neuropathic pain mechanisms, absent signs of denervation and negative
17	nerve provocation tests.
18	
19	This new classification system has demonstrated good interrater reliability with $\kappa =$
20	0.72 [14] and has shown prognostic ability [15]. The objective of the present study
21	was to investigate construct validity of the classification system by determining the
22	relationship of diagnostic groups with the results from Quantitative Sensory Testing
23	(QST) [16].
24	

1 **2.** Methods

2 Study design and hypotheses

3 This observational, cross-sectional study was designed to investigate construct 4 validity of a new classification system for subjects with LBRLP. Construct validity is 5 based on testing hypotheses about relationships of the instrument under study (i.e. the 6 classification system) with other instruments measuring similar constructs [16]. The 7 construct measured both by the instrument under study (i.e. the classification system) 8 and the reference instrument (QST) is pain mechanisms. We tested the hypothesis that 9 QST parameters will differ between subgroups of subjects with LBRLP and a group 10 of asymptomatic subjects.

11 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.

15 Subjects and recruitment

16 Subjects were recruited at a multidisciplinary pain clinic in Hamburg, Germany. 162 17 consecutive patients with LBRLP referred for physiotherapy at the clinic were 18 screened for eligibility. To be considered for inclusion subjects were required to be 19 between 18 and 75 years of age, with unilateral LBRLP of more than 6 weeks 20 duration. Exclusion criteria were history of lower quadrant surgery or trauma within 21 the past 6 months, nerve root block within the past four weeks, other neuropathic 22 pathology such as diabetes or polyneuropathies, vascular disease in the lower 23 extremities, inflammatory arthropathies, contraindications to manual therapy 24 techniques and inability to understand written / spoken German. Of the 162 subjects

1	screened, 77 were eligible and willing to participate (Figure 2). Another 18 age and
2	gender matched healthy volunteers were recruited as control subjects to provide
3	normative data for z-score standardization of QST parameters into standard deviation
4	units for comparison.
5	Quantitative sensory testing (QST)
6	A comprehensive battery of QST devices that was developed and validated by the
7	German Research Network on Neuropathic Pain [17] was used as the reference
8	instrument.
9	
10	This QST battery tests all relevant submodalities of the somatosensory system.
11	Seven tests are used to measure 13 parameters consisting of thermal pain thresholds
12	for cold and hot stimuli; thermal detection thresholds for the perception of cold, warm
13	and thermal sensory limen ¹ ; paradoxical heat sensations; mechanical pain thresholds
14	for pinprick and blunt pressure; mechanical detection thresholds for touch and
15	vibration; a stimulus-response-function for pinprick sensitivity; dynamic mechanical
16	allodynia for stroking light touch; as well as pain summation to repetitive pinprick
17	stimuli. Thus QST evaluates the function of sensory nerve fibres and their respective
18	pathways [18] by analysing multiple parameters of sensory testing. Thus obtained
19	sensory profiles of patients may exhibit whether dominant features of sensory deficit
20	(loss of function) or sensory hyperexcitability (gain of function) exist, indicative for
21	specific pain mechanisms [19, 20].
$\gamma\gamma$	

22

23 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

1 [21] as well as acceptable concurrent validity [22-24].

2

3 We tested three body regions; the lower back, the dorsum of the foot and the dorsum 4 of the hand. In subjects with LBRLP test sites were within the painful region of the 5 back and on the dorsum of the affected foot. A site remote to the painful regions 6 (dorsum of the ipsilateral hand) was also tested, as changes in the somatosensory 7 system associated with chronic pain have also been reported in body areas remote to 8 the source of pain. It has been shown that these changes manifest in negative signs 9 such as hypoesthesia [25] as well as in positive signs such as pain sensitivity to blunt 10 pressure [26]. The ipsilateral hand was always tested first, followed alternately by foot 11 or back in patient groups. In the control group, testing of the different areas was 12 conducted alternately.

13 Classification

14 All symptomatic subjects were classified into one of four groups following a pre-15 established examination protocol [12] (Figure 1). The assessment protocol includes 16 subjective questions relating to area of pain, duration of symptoms, and aggravating 17 and easing factors. The subjective components of the LANSS questionnaire [27] were 18 incorporated into the subjective assessment to screen for predominantly positive 19 symptoms indicative of sensitization of the somatosensory system. The physical 20 examination included a neurological examination to screen for motor and sensory 21 deficits, neural tissue provocation tests (straight leg raise test; prone knee bend test, 22 active flexion test in standing, nerve palpation) [13] and the objective components for 23 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].

4

5 Subjects scoring 12 or more on the LANSS scale were classified as NS. The LANSS 6 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 7 8 to the patients pain [27]. Mechanisms underlying neuropathic pain may be both 9 central or peripheral [28], however items within the LANSS scale are primarily 10 concerned with identifying positive features of neuropathic pain, such as hyperalgesia 11 and allodynia in areas distant to the lesion which are hall mark signs for central pain 12 mechanisms [29, 30]. 13 14 In our earlier papers [12, 14] we referred to the group with a LANSS score ≥ 12 as 15 "Central Sensitization". In retrospect, this was not the most appropriate term and was

16 probably misleading. In the present paper we refer to the group with a LANSS scale \geq

17 12 as "Neuropathic Sensitization". "Neuropathic" to more adequately reflect the

18 construct of the LANSS scale and "Sensitization" as the LANSS tests primarily for

19 positive signs indicative for gain of function. The only item within the LANSS testing

20 for negative signs is the test for altered pin-prick sensation.

21

22 Subjects scoring less than 12 on the LANSS scale and with at least two or more

23 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.

3

4 Subjects in group PNS are characterized by positive nerve provocation tests [31] with 5 a LANSS score < 12 and in the absence of marked neurological deficits. The term 6 "Peripheral Nerve Sensitization" reflects potential peripheral mechanisms such as 7 induction of mechanosensitive sodium channels in the nerve sheath as a consequence 8 of focal inflammation [32]. Nerve mechanosensitivity to pressure and stretch in the 9 absence of nerve damage has been demonstrated in animal nerve inflammation 10 models [33, 34], and can be observed clinically in patients with radiating arm pain 11 [35] or leg pain [36]. The term "Peripheral Nerve Sensitization" describes a pain state 12 with marked nerve mechanosensitivity in the absence of neuropathic pain and 13 denervation. 14 15 Group M consists of subjects with a LANSS score < 12, without marked neurological 16 deficits and negative nerve provocation tests. These clinical features indicate "pseudoradicular" or somatic referred pain, as neural involvement in the subjects' 17 18 pain is unlikely. The main mechanism for somatic referred pain is convergence, where 19 afferent nerve fibers from the leg and from structures in the lower back converge upon

20 the same viscerosomatic neurons in the dorsal horn of the spinal cord [37].

21 Examiners

22 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

24 results of the physical examination.

1 Data management

2	QST data that were not normally distributed were transformed logarithmically before
3	statistical analysis. The numbers of paradoxical heat sensations during the thermal
4	sensory limen procedure, cold pain thresholds, heat pain thresholds and vibration
5	detection thresholds were normally distributed as raw data. All other QST parameters
6	were normally distributed after logarithmical transformation.
7	To facilitate comparisons between parameters originally measured in different units,
8	normalized data for each of the QST parameters were converted to z-scores using
9	means and SDs from the control group (z-score = Score _{single patient} - Mean _{controls} /
10	SD _{controls}) [17]. A z-score of zero characterizes a value matching the group mean of
11	the healthy control subjects. Positive z-scores indicate a gain of function where the
12	patient is more sensitive to the tested stimulus compared to controls (hyperalgesia,
13	allodynia, hyperpathia) and negative z-scores indicate the patient has a loss of
14	sensation (hypoesthesia) compared to controls.
15	
16	One-way ANOVAs and Chi square tests were used to analyze the difference in
17	general measures between groups (Table 1).
18	Two way ANOVAs were conducted for each QST parameter to test interaction effects
19	of group with body region and between subject main effects (group). The aim was to
20	investigate relationships of QST data with diagnostic groups. Where main effects or
21	interactions were significant, Tukey HSD post hoc tests were used to control for
22	multiple testing. All QST data are presented as Z-scores (mean \pm SEM) unless
23	otherwise indicated. SPSS version 17 (SPSS Inc., Chicago, USA) was used for
24	statistical analysis.

1 **3. Results**

2 Subjects

21

3	Subjects had a mean age of 48 years and 39% were men. Age, gender, pain duration
4	and proportion of patients with pain below the knee were comparable between groups
5	($p > 0.50$). Subjects with a score of 12 or more on the LANSS scale [27] were
6	classified as Neuropathic Sensitization (n=20). The remaining symptomatic subjects
7	(n=57) who had a LANSS scale score of less than 12 plus negative signs such as
8	hypoesthesia, muscle weakness or hyporeflexia were classified as Denervation
9	(n=28). Of the remaining 29 symptomatic subjects, 9 exhibited positive neural
10	provocation tests, and were classified as Peripheral Nerve Sensitization. All other
11	subjects were classified as Musculoskeletal (n=20) as there was no suggestion of
12	neural involvement (Figure 1). For detailed subject characteristics please see Table 1.
13	QST findings
14	Results showed relationships between QST data and diagnostic groups as there were
15	differences in QST parameters between groups across the tested body regions (group
16	main effect) (Table 2). All group main effects were between symptomatic subject
17	groups and the asymptomatic group. No significant differences were found between
18	the four symptomatic subject groups. Warm detection threshold was the only

19 parameter where the difference between groups varied significantly according to

20 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

22 with severe allodynia over the back and paradoxical heat sensation was generally

23 more frequent at the affected foot for group Denervation, although these differences

24 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.

3 *QST procedures reveal differences between groups Neuropathic Sensitization,*

4 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).

11

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.

18

19 **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.

6

7 Decreased mechanical pain thresholds and cold hyperalgesia as observed in group 8 Neuropathic Sensitization are signs consistent with central sensitization [28]. Central 9 sensitization may arise as a result of a number of different mechanisms. Diminished 10 control of pain including cell death of inhibitory interneurons in the dorsal horn may 11 contribute to enhanced pain processing [28] as well as changed descending 12 modulatory mechanisms from the brain stem [38, 39]. Additionally, secondary 13 changes in cortical and subcortical brain regions, triggered by cognitions, emotions 14 and attention may further add to central sensitization and development of spontaneous 15 activity and pain [40, 41]. Another mechanism potentially contributing to 16 augmentation of central pain processing is deafferentation: Clinical and QST 17 examinations revealed deficits in large fibre function not only in group Denervation 18 but also in group Neuropathic Sensitization, indicating nerve fibre damage that for the 19 latter group may have induced secondary sensitization of higher order nociceptive 20 neurons [42]. QST findings from patients with other conditions thought to involve 21 central sensitization such as whiplash associated disorders [43], LBP [44] or 22 fibromyalgia [45] have also shown increased sensitivity to thermal and mechanical 23 pain stimuli consistent with findings in the present study. Central sensitization of the 24 nociceptive system is one of the main mechanisms contributing to neuropathic pain 25 [46].

1

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

14

15 A recent study [25] compared somatosensory profiles of subjects with somatic 16 referred pain (n=15) with subjects with radicular pain (n=12) and found that both 17 were significantly different to a healthy control group. The authors hypothesized that 18 mild root compression or an inflammatory perturbation of nerve roots in people with 19 pseudoradicular pain as well as in people with radicular pain may explain this 20 phenomenon. In contrast, the present study showed, in comparison to healthy 21 controls, no significant sensory dysfunction in groups Peripheral Nerve Sensitization 22 and Musculoskeletal, which are clinically comparable to patients with 23 "pseudoradicular symptoms". The reason for this may lie in a more differentiated 24 subclassification of subjects and consequently higher within group homogeneity.

25

1 Some limitations should be pointed out. First of all, interaction effects between group 2 and body region could not be demonstrated. This indicates that only generalized 3 sensory changes over the entire body could be shown, but not localized changes. Also, 4 statistical analysis of QST data revealed significant differences only between two of 5 the four symptomatic groups and the asymptomatic group. This implies, firstly, that 6 construct validity could only be demonstrated for two of the groups, but not for the 7 classification as a whole. Secondly, the fact that no differences were found between 8 patient groups weakens conclusions in regard to construct validity. One possible 9 explanation is that group Peripheral Nerve Sensitization was unexpectedly small with 10 higher standard errors as a result. In addition, it is well known that psychosocial 11 factors such as hypervigilance or catastrophizing significantly influence pain 12 perception, however data in this respect were not available for the present study.

13 **5.** Conclusion

The results of this study provide preliminary evidence for the construct validity for 14 15 two of the four groups used in the new classification system as significant differences 16 of QST determined sensory and pain thresholds in groups Neuropathic Sensitization 17 and Denervation when compared to a group of asymptomatic subjects were shown. 18 These differences match presumed underlying mechanisms: Sensory deficits in group 19 Denervation and pain hypersensitivity in group Neuropathic Sensitization. Future 20 research should include assessment of further psychosocial covariates such as 21 catastrophizing or hypervigilance and focus on achieving equal group sizes.

22

23

6. References

[1] Selim AJ, Ren XS, Fincke G, Deyo RA, Rogers W, Miller D, et al. The importance of radiating leg pain in assessing health outcomes among patients with low back pain. Results from the Veterans Health Study. Spine. 1998 Feb 15;23(4):470-4.

[2] Freynhagen R, Baron R, Gockel U, Tölle TR. Screening of neuropathic pain components in patients with chronic back pain associated with nerve compression: a prospective observational study (MIPORT) Curr Med Res Op. 2006;22:529 - 37.

[3] Ren XS, Selim AJ, Fincke G, Deyo RA, Linzer , Lee A, et al. Assessment of functional status, low back disability, and use of diagnostic imaging in patients with low back pain and radiating leg pain. J Clin Epidemiol. 1999 Nov;52(11):1063-71.

[4] Hill JC, Konstantinou K, Egbewale BE, Dunn KM, Lewis M, van der Windt D. Clinical Outcomes Among Low Back Pain Consulters With Referred Leg Pain In Primary Care. Spine (Phila Pa 1976). 2011 Feb 24;Epub ahead of print.

[5] Merskey H, Bogduk N. Classification of Chronic Pain. 2nd ed. Merskey H, Bogduk N, editors. Seattle: IASP Press; 1994.

[6] O'Neill CW, Kurgansky ME, Derby R, Ryan DP. Disc stimulation and patterns of referred pain. Spine. 2002;27(24):2776-81.

[7] Travell JG, Simons DG. The Lower Extremities. Philadelphia: Lippincott Williams & Wilkins; 1983.

[8] Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. Clinical features of patients with pain stemming from the lumbar zygapophysial joints. Is the lumbar facet syndrome a clinical entity? Spine. 1994 May 15;19(10):1132-7.

[9] Vroomen PC, de Krom MC, Slofstra PD, Knottnerus JA. Conservative treatment of sciatica: a systematic review. J Spinal Disord. 2000 Dec;13(6):463-9.

[10] Luijsterburg PA, Verhagen AP, Ostelo RW, van Os TA, Peul WC, Koes BW. Effectiveness of conservative treatments for the lumbosacral radicular syndrome: a systematic review. Eur Spine J. 2007 Jul;16(7):881-99.

[11] Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. Life Sci. 2004 Apr 9;74(21):2605-10.

[12] Schäfer A, Hall T, Briffa K. Classification of low back-related leg pain - A proposed patho-mechanism-based approach. Man Ther. 2009 Dec 31;14(2):222-30.

[13] Elvey RL, Hall TM. Neural tissue evaluation and treatment. In: Donatelli R, editor. Physical Therapy of the Shoulder. 3rd ed. New York ; Philadelphia: Churchill Livingstone; 1997. p. 131-52.

[14] Schäfer A, Hall T, Lüdtke K, Mallwitz J, Briffa K. Interrater reliability of a new classification system for patients with low back related leg pain. J Man Manip Ther. 2009;17(2):109-17.

[15] Schäfer A, Hall T, Müller G, Briffa K. Outcomes differ between subgroups of patients with low back and leg pain following neural manual therapy: a prospective cohort study. Eur Spine J. 2011 Mar;20(3):482-90.

[16] de Vet HC, Terwee CB, Mokkink LB, Knol DL. Validity. Measurement in Medicine. Cambridge: Cambridge University Press; 2011. p. 150-201.

[17] Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: A comprehensive protocol for clinical trials. European Journal of Pain. 2006;10(1):77-88.

[18] Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states. Pain. 2007 Jun;129(3):256-9.

[19] Maier C, Baron R, Tolle TR, Binder A, Birbaumer N, Birklein F, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain. 2010 Sep;150(3):439-50.

[20] Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain. 2006 Aug;123(3):231-43.

[21] Geber C, Klein T, Azad S, Birklein F, Gierthmuhlen J, Huge V, et al. Test-retest and interobserver reliability of quantitative sensory testing according to the protocol of the German Research Network on Neuropathic Pain (DFNS): A multi-centre study. Pain. 2011 Mar;152(3):548-56.

[22] Felix ER, Widerstrom-Noga EG. Reliability and validity of quantitative sensory testing in persons with spinal cord injury and neuropathic pain. J Rehabil Res Dev. 2009;46(1):69-83.

[23] Scherens A, Maier C, Haussleiter IS, Schwenkreis P, Vlckova-Moravcova E, Baron R, et al. Painful or painless lower limb dysesthesias are highly predictive of peripheral neuropathy: Comparison of different diagnostic modalities. Eur J Pain. 2008 Sep 11.

[24] Selim MM, Wendelschafer-Crabb G, Hodges JS, Simone DA, Foster SX, Vanhove GF, et al. Variation in quantitative sensory testing and epidermal nerve fiber density in repeated measurements. Pain. 2010 Dec;151(3):575-81.

[25] Freynhagen R, Rolke R, Baron R, Tölle TR, Rutjes AK, Schu S, et al. Pseudoradicular and radicular low-back pain - A disease continuum rather than different entities? Answers from quantitative sensory testing. Pain. 2008 Jun 13;135(1-2):65-74. [26] Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. Pain. 2003 Aug;104(3):509-17.

[27] Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain. 2001 May;92(1-2):147-57.

[28] Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet. 1999 Jun 5;353(9168):1959-64.

[29] Magerl W, Fuchs PN, Meyer RA, Treede RD. Roles of capsaicin-insensitive nociceptors in cutaneous pain and secondary hyperalgesia. Brain. 2001 Sep;124(Pt 9):1754-64.

[30] Treede RD, Handwerker HO, Baumgärtner U, Meyer RA, Magerl W. Hyperalgesia and Allodynia: Taxonomy, Assessment, and Mechanisms. In: Brune K, Handwerker HO, editors. Hyperalgesia: Molecular mechanisms and Clinical implications. Seattle: IASP Press; 2004. p. 3-15.

[31] Hall TM, Elvey RL. Management of mechanosensitivity of the nervous system in spinal pain syndromes. In: Boyling JD, Jull G, editors. Grieves Modern Manual Therapy. 3rd ed. Edinburgh: Churchill Livingstone; 2004. p. 413-33.

[32] Chen C, Cavanaugh JM, Song Z, Takebayashi T, Kallakuri S, Wooley PH. Effects of nucleus pulposus on nerve root neural activity, mechanosensitivity, axonal morphology, and sodium channel expression. Spine. 2004 Jan 1;29(1):17-25.

[33] Bove GM, Ransil BJ, Lin HC, Leem JG. Inflammation induces ectopic mechanical sensitivity in axons of nociceptors innervating deep tissues. J Neurophysiol. 2003 Sep;90(3):1949-55.

[34] Dilley A, Lynn B, Pang SJ. Pressure and stretch mechanosensitivity of peripheral nerve fibres following local inflammation of the nerve trunk. Pain. 2005 Oct;117(3):462-72.

[35] Allison GT, Nagy BM, Hall T. A randomized clinical trial of manual therapy for cervico-brachial pain syndrome -- a pilot study. Man Ther. 2002 May;7(2):95-102.

[36] Cleland JA, Childs JD, Palmer JA, Eberhart S. Slump stretching in the management of non-radicular low back pain: a pilot clinical trial. Man Ther. 2006 Nov;11(4):279-86.

[37] Jinkins JR. The anatomic and physiologic basis of local, referred and radiating lumbosacral pain syndromes related to disease of the spine. J Neuroradiol. 2004 Jun;31(3):163-80.

[38] Gardell LR, Vanderah TW, Gardell SE, Wang R, Ossipov MH, Lai J, et al. Enhanced evoked excitatory transmitter release in experimental neuropathy requires descending facilitation. J Neurosci. 2003 Sep 10;23(23):8370-9.

[39] Ren K, Dubner R. Descending modulation in persistent pain: an update. Pain. 2002 Nov;100(1-2):1-6.

[40] Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain. 2005 Aug;9(4):463-84.

[41] Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, et al. Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci. 2002 Apr 1;22(7):2748-52.

[42] Baumgärtner U, Magerl W, Klein T, Hopf HC, Treede RD. Neurogenic hyperalgesia versus painful hypoalgesia: two distinct mechanisms of neuropathic pain. Pain. 2002 Mar;96(1-2):141-51.

[43] Chien A, Eliav E, Sterling M. Hypoaesthesia occurs with sensory hypersensitivity in chronic whiplash - Further evidence of a neuropathic condition. Manual Therapy. 2009;14(2):138.

[44] Lewis C, Souvlis T, Sterling M. Sensory characteristics of tender points in the lower back. Manual Therapy. 2010;In Press, Corrected Proof.

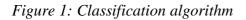
[45] Staud R, Robinson ME, Price DD. Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. Pain. 2005 Nov;118(1-2):176-84.

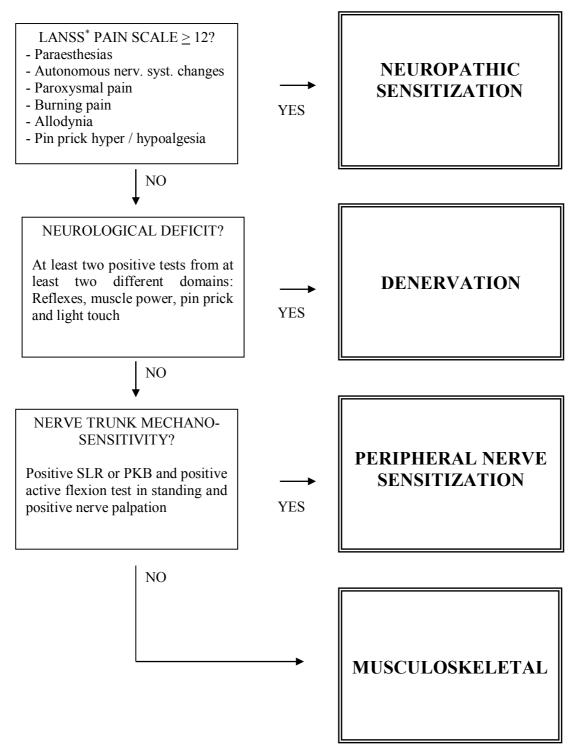
[46] Dickenson AH, Bee LA. Neurobiological mechanisms of neuropathic pain and its treatment. In: Castro-Lopes J, Raja S, Schmelz M, editors. Pain 2008 An updated review. Seattle: IASP press; 2008. p. 277-86.

[47] Kobayashi S, Baba H, Uchida K, Kokubo Y, Kubota C, Yamada S, et al. Effect of mechanical compression on the lumbar nerve root: localization and changes of intraradicular inflammatory cytokines, nitric oxide, and cyclooxygenase. Spine. 2005 Aug 1;30(15):1699-705.

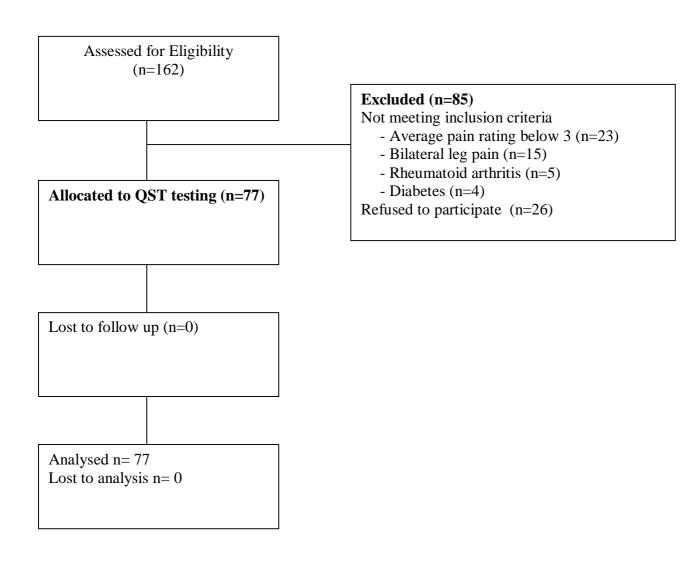
[48] Tachihara H, Kikuchi S, Konno S, Sekiguchi M. Does facet joint inflammation induce radiculopathy?: an investigation using a rat model of lumbar facet joint inflammation. Spine. 2007 Feb 15;32(4):406-12.

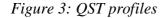
[49] Olmarker K, Larsson K. Tumor necrosis factor alpha and nucleus-pulposusinduced nerve root injury. Spine. 1998 Dec 1;23(23):2538-44.

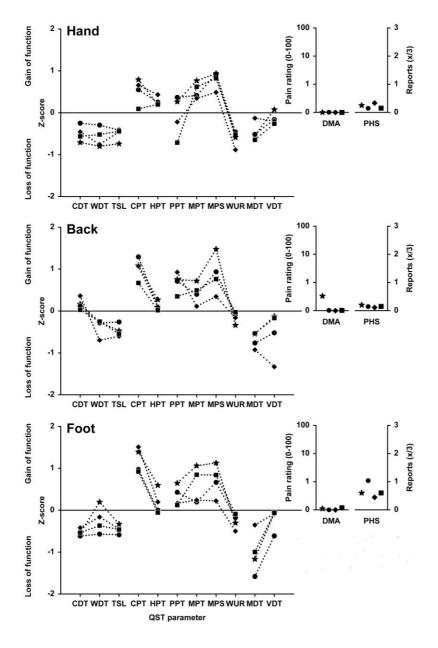




*LANSS: Leeds Assessment of Neuropathic Symptoms and Signs [27]







- ★ 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.

	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)	.83ª
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°

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

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

QST parameter	Group main effects		Tukey HSD post hoc for group main effects				Body region main effects		Inter- action region by group	
	<i>F</i> -	<i>p</i> -	Mean	<i>p</i> -	95%		<i>F</i> -	<i>p</i> -	<i>F</i> -	<i>p</i> -
	value	value	difference (z-score)	value	Confidence Interval		value	value	value	value
			(2-score)		upper	lower				
					bound	bound				
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	0.5	0.001	-0.56	0.495	-1.53	0.41	0.6	0.045	0.0	0.501
HPT	0.5	0.891					0.6	0.845	0.9	0.531
MDT C-NS	3.7	0.007	0.7509	0.058	-0.012	1.52	4.1	0.02	1.6	0.354
C-NS C-D			.9543	0.038	-0.012 0.24	1.52				
C-D 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	0.7100	0.070	0.02	11.19	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	0.4	0.402	-0.8075	0.267	-1.92	0.31	4.0	0.001	0.0	0.010
WUR	0.4	0.493					4.9	0.001	0.9	0.910
VDT PPT	1.3 2.0	0.260 0.287					2.6 8.7	.083 0.001	1.6 1.8	0.131 0.405
DMA	2.0	0.287					8.7 1.5	0.001	1.8 .7	0.405
PHS	1.0	0.743					1.5	0.754	.7 .9	0.820
1115	1.0	0.341					1.2	0.010	.)	0.090

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

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