QST somatosensory profiles in patients with cervical radiculopathy are distinct from those in patients with non-specific neck-arm pain

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Abstract

The aim of this study was to establish the somatosensory profiles of patients with cervical radiculopathy and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP). Sensory profiles were compared to healthy control (HC) subjects and a positive control group, patients with fibromyalgia (FM). Quantitative sensory testing (QST) of thermal and mechanical detection and pain thresholds, pain sensitivity and responsiveness to repetitive noxious mechanical stimulation was performed in the maximal pain area, the corresponding dermatome and foot of 23 patients with painful C6 or C7 cervical radiculopathy, 8 patients with NSNAP in a C6/7 dermatomal pain distribution, 31 HC and 22 patients with FM. For both neck-arm pain groups, all QST parameters were within the 95% confidence interval of HC data. Patients with cervical radiculopathy were characterised by localised loss of function (thermal, mechanical, vibration detection $p < 0.009$) in the maximal pain area and dermatome (thermal detection, vibration detection, pressure pain sensitivity $p < 0.04$), consistent with peripheral neuronal damage. Both neck-arm pain groups demonstrated increased cold sensitivity in their maximal pain area ($p < 0.03$) and the foot ($p < 0.009$), and this was also the dominant sensory characteristic in patients with NSNAP. Both neck-arm pain groups differed from patients with FM, the latter characterised by a widespread gain of function in most nociceptive parameters (thermal, pressure and mechanical pain sensitivity $p < 0.027$). Despite commonalities in pain characteristics between the two neck-arm pain groups, distinct sensory profiles were demonstrated for each group.

1. Introduction

This study focused on two nerve-related spinal neck-arm pain presentations: painful cervical radiculopathy and non-specific (i.e. no clinical signs of the presence of a radiculopathy) neck-arm pain associated with heightened nerve mechanosensitivity (hereafter NSNAP). The latter is characterised in experimental studies [24,21] by peripheral nerve sensitivity to mechanical stimuli and clinically by pain in response to limb movements that cause nerve elongation [25,1,67,13] and local tenderness on nerve trunk palpation. Heightened nerve mechanosensitivity, a feature of nerve trunk pain, is regarded as a nociceptive pain [6,51]. It can coexist with painful cervical radiculopathy [13], but can also occur independently in patients with neck-arm pain [25,67]. The latter applied to our chosen cohort.

While patients with the two above named neck-arm pain conditions can present with similar pain characteristics and sensory symptoms, the pathophysiology, the pain type (nociceptive/neuropathic) and the underlying pain mechanisms do likely differ. Identification of differences between these pain conditions is important for the provision of appropriate best-evidence management. Moreover, the possible dominance of one pain type is of therapeutic relevance [33,3], and may account for individual differences in responsiveness to anti-neuropathic agents, such as pregabalin, as documented in recent clinical trials of patients with lumbar and cervical radiculopathies [4,59].

One approach to assist in the interpretation of pain mechanisms underlying clinical pain presentations is the use of quantitative sensory testing (QST) [36,13,44,50,64]. To our

5

knowledge, no study has profiled patients with unilateral NSNAP comparable to our

cohort, and only one study documented sensory abnormalities in patients with cervical

radiculopathy [13]. However, in the latter, recordings were not taken from the patients'

maximal pain area, as is required for the assessment of NeP components [66,31].

We aimed to establish the somatosensory profiles of patients with painful cervical

radiculopathy and patients with NSNAP in order to explore differences or commonalities

in sensory parameters. For each group, sensory profiles were documented bilaterally in

the area of maximal pain, in the respective dermatome and in one foot as a remote control

site and were compared to healthy control (HC) data. In order to better characterise the

neck-arm pain presentations, a group of patients with fibromyalgia (FM) was included as

a positive control group to allow comparison to a group with widespread pain. We chose

the presentation of FM as this pain disorder is characterised by enhanced sensitivity to a

wide array of somatosensory stimuli and features of central pain processing mechanism

in the absence of demonstrable local somatic abnormality [30,77]. We hypothesised that:

(1) the sensory phenotypes between the two neck-arm pain groups would be different; (2)

in patients with cervical radiculopathy localised sensory abnormalities would be

restricted to the maximal pain area and to the area of dermatomal sensory loss; (3) in

patients with NSNAP sensory abnormalities would be found only in the maximal pain

area; and 4) sensory profiles of the neck-arm pain groups would differ from that of

patients with FM.

2. Materials and methods

The study protocol and recruitment procedures for this cross-sectional study were approved by the local Ethics Committee of all participating institutions and adhered to the ethical guidelines of the Declaration of Helsinki.

2.1 Study population

Patients were recruited from physiotherapy and pain management departments at five local metropolitan hospitals in Perth, Western Australia; a neurosurgery triage clinic and a neurosurgery outpatient department at a large tertiary hospital; general private neurosurgery, medical and physiotherapy practices; from the local community via radio and newspaper advertising and from FM support groups.

Patients with painful C6 or C7 cervical radiculopathy (n = 23; 8 female; mean age 46.3 ± 9.6 years) had to fulfil the following inclusion criteria: unilateral neck pain and arm pain/paraesthesia distribution consistent with radicular distributions; symptom duration of 3 to 18 months; pain intensity ≥ 2 on a visual analogue scale (VAS); signs of C6 or C7 nerve root dysfunction such as motor impairment (either absent or diminished reflex and/or myotomal weakness) and sensory impairment; and a demonstrable clinically relevant abnormality on imaging studies [66,12] indicating compromise of the exiting nerve root at the relevant spinal level. The inclusion criteria for patients with NSNAP (n = 8; 7 female; mean age 45.1 ± 14.9 years) were: unilateral neck pain and arm pain/paraesthesia distribution consistent with C6/C7 distribution; absence of any signs of nerve root dysfunction i.e. absence of radiculopathy, symptom duration of 3 to 18

months; pain intensity ≥ 2 on a VAS; and evidence of increased peripheral nerve sensitivity to mechanical stimuli [25]. The latter included pain in response to a nerve provocation test in the upper limb [25,63,72], a test analogous to the straight leg raise test in the lower limb [20,26]. Exclusion criteria for both patient groups consisted of evidence of metabolic or medical disease; other neurological or psychiatric disease; a history of lumbar surgery and/or sciatica or other musculoskeletal disorders that potentially might affect the sensation in the foot to be tested; a history of cardiovascular disease; and an insufficient level of English.

A comprehensive clinical examination was conducted by one clinician (author BT) on all potential participants in order to confirm that patients satisfied the requirements for inclusion into the study. The consensus of two clinical experts, a Fellowship-trained spinal Neurosurgeon and a Specialist Musculoskeletal Physiotherapist (Fellow of the Australian College of Physiotherapists), was used to verify the diagnosis of cervical radiculopathy, as consistent with a previous study [26]. The classification of NSNAP was verified by the Specialist Musculoskeletal Physiotherapist. Whilst the straight leg raise test is widely used to assess heightened nerve mechanosensitivity in the lower limb [20,26], the upper limb analogue [25] is less widely used in medicine although it has been extensively investigated in musculoskeletal physiotherapy [63,72,14,67]. Therefore the Neurosurgeon in the current study was asked to determine if patients with NSNAP did have a radiculopathy or not. Both experts were blinded to the clinician's patient classification, and independently reviewed the patient notes including the findings of the clinical examination plus the results of any medical investigations. Three patients were

excluded from data analysis as the experts did not make the same diagnosis as the clinical examiner.

Patients with FM (n = 22; 20 female; mean age 46.1 ± 11.5 years) underwent an initial telephone screening examination to verify they met the inclusion and exclusion criteria. Inclusion criteria were the diagnostic guidelines for FM presented by the American College of Rheumatology (ACR) [78] which include widespread pain of at least 3 months duration in combination with tenderness at 11 or more of 18 specific anatomical sites. These guidelines were current at the time of recruitment, however the clinical profile of our FM group appears to also correspond with the new diagnostic criteria [77] (Table 1). The new diagnostic criteria include (i) a symptom duration for at least 3 months, (ii) the patient does not have a disorder that would otherwise explain their pain, (iii) a certain amount of pain areas ($\geq$ 7) and the presence with correlative intensity of symptoms of fatigue, waking unrefreshed, cognitive symptoms and somatic symptoms [77]. Almost all of our patients (n = 21) presented with $\geq$ 7 painful body regions and with symptoms of fatigue and waking unrefreshed (Table 1).

Nine patients had been diagnosed with FM by a rheumatologist, 8 patients by their general practitioner by exclusion (negative blood tests) and positive tender point count, 4 patients by a medical specialist (specific specialty unknown to the patient), and in one patient the origin of the diagnosis was not recorded. Prior to participation, tender point count was confirmed using a pressure algometer (probe size 1cm^2) (Somedic AB, Farsta, Sweden), and assessing nine paired points as defined by the ACR Criteria [78] and two

control points (at the centre of the right forearm and the right thumb nail). The exclusion criteria for patients with FM were the same as for the neck-arm pain groups. All patients were requested to refrain from taking non–steroidal anti-inflammatory medications and analgesics on the day of examination.

Thirty-one HC subjects, matched for age to the patient groups (15 female, 45.6 ± 12.5 years), were recruited from the local community. Subjects with a history of current pain, or a chronic pain condition, or any of the additional exclusion criteria described for the patient groups were excluded, including taking medications that influence pain perception.

2.2 Questionnaires

In order to better interpret our data, the establishment of the clinical profiles included multidimensional aspects of pain as proposed by the IMMPACT guidelines [23]. The following questionnaires were used to characterise the patient groups. They were administered before the QST testing was performed.

- Disability was assessed using the Neck Disability Index (NDI) [69], a well validated ten-item questionnaire [68]. Scores of < 4 indicate no disability, 5 – 14 mild disability, 15 – 25 moderate disability, 25 – 34 severe disability, and > 35 complete disability [69].

- Fear avoidance behaviour was quantified using the Tampa Scale of Kinesiophobia [71]. This questionnaire consists of 17 items that relate to fear of movement and fear of (re) injury. A score ≥ 40 is considered to indicate significant kinesiophobia

[16].

- Average pain intensity over the last week was determined with a VAS with the end points 0 cm (no pain) and 10 cm (maximum tolerable pain) [37]. The strongest and average pain intensity over the last four weeks was recorded on a numeric rating scale (NRS) (0 = no pain, 10 = maximum pain).
- Symptom duration was recorded via face-to-face interview.

The following questionnaires were employed to enable clinical characterisation of the patient groups and HC.

- The short form-36 health questionnaire (SF-36v2®) [73] was used to assess health-related quality of life.
- The Hospital Anxiety and Depression Scale is a self-administered questionnaire to screen for the presence of psychological factors [81]. Two independent scores for anxiety and depression are generated with a maximum score of 21 for each parameter. Scores of ≤ 10 for each are considered within normal range.
- Sleep disturbance was determined by asking: "Do you awake tired or non-refreshed?" Fatigue was assessed by asking: "Do you feel fatigued?" [78]. Both sleep and fatigue questions allowed for answers: "never", "seldom", "often or usually", "always". "Never" or "seldom" was scored as negative, and other replies as positive. In addition, all subjects had to rate their sleep quality over the last week on a 100-cm VAS with the end points 0 cm (good sleep) and 10 cm (bad sleep) [34].

2.3 Quantitative sensory testing

Standardised QST was performed according to the QST protocol of the German Research

Network on Neuropathic Pain (DFNS) [57,58] by one investigator (BT) in a laboratory

with a constant room temperature. This protocol comprises all of the somatosensory sub-

modalities that are mediated by different primary afferents (C-, Aδ-, Aβ-) as outlined in

the following sections. Good test/retest- and inter-observer-reliability of this protocol has

been demonstrated for all sub-modalities except wind-up ratio and the number of

paradoxical heat sensations [27]. QST measurements were taken from the maximal pain

area nominated by the patients and their contralateral mirror side for the neck-arm pain

patients and unilaterally from the maximal pain area on the most painful side for patients

with FM (Fig. 1). Given the presence of bilateral pain in patients with FM, if they could

not determine a most painful side, the tested side was determined randomly by the rolling

of a die.

As QST parameters may vary significantly over body areas, comparative HC reference

data have to be obtained for all body regions that are examined in patients

[58,44]. Reference data were obtained in 31 HC. Prior to the commencement of data

collection, and based on our extensive clinical observations over many years, it was

anticipated that while pain areas may vary, a majority of patients nominate the upper

trapezius muscle as their maximal pain area. Consequently early in the data collection

period, QST parameters were measured bilaterally in 26 HC in the upper trapezius

muscle. However, during the course of the study it became apparent that patients

indicated a number of other body regions as their maximal pain area. Although some

studies have calculated patient z-scores using HC reference data from different body regions, this approach has been acknowledged as a study limitation [50,11]. Hence, in order to be able to compare patient data with HC data, unilateral measurements were obtained in all other pain areas in 8 HC, including 3 from the trapezius group. This sample size of 8 subjects is in accordance with established methodology as outlined by DFNS for data standardisation [10]. For patients with radiculopathy, QST was also performed in the dermatomal area of sensory loss (C6 or C7 dermatome) as determined precisely during clinical examination, and for patients with NSNAP in the area of distal paraesthesia or pain (C6 or C7 dermatomal distribution), plus on the contralateral side for both patient groups. Patients with FM were randomly assessed in the C6 dermatome (thenar eminence) (n = 10) or C7 dermatome (dorsum hand) (n = 12) on the most symptomatic side. HC subjects were tested bilaterally in the C6 (n = 13) and C7 (n = 13) dermatome. All patients and 26 HC underwent QST on the dorsum of the foot ipsilateral to the symptomatic side as a remote control site [57,58]. In HC, the 'symptomatic' side was determined randomly by rolling a die.

2.3.1 Thermal detection and pain thresholds and the number of paradoxical heat sensations

Thermal thresholds were measured using the MSA Thermotest system (Somedic AB, Farsta, Sweden) with a 12.5cm^2 probe. The baseline temperature was set at 32˚C; cut-off temperatures were 5˚C and 50˚C. All thresholds were obtained with ramped stimuli (1° C/s) which were terminated when the subject pressed a button. First, cold and warm detection thresholds (CDT, WDT) were assessed, followed by the determination of the

number of paradoxical heat sensations during the thermal sensory limen procedure, and finally the measurement of cold and heat pain thresholds (CPT, HPT). The mean threshold temperature of three consecutive measurements was calculated.

2.3.2 Mechanical detection threshold

The mechanical detection threshold (MDT) was determined using a standardised set of modified von Frey hairs (Optihari2-Set, Marstock Nervtest, Germany) that exert forces upon bending between 0.25 and 512mN. Five ascending and five descending series of stimuli were applied. The final threshold was the geometric mean of these series of ascending and descending stimulus intensities [57].

2.3.3 Mechanical pain threshold

The mechanical pain threshold (MPT) was measured using a set of seven custom-made weighted pinprick stimulators (flat contact area of 0.2 mm diameter) with fixed stimulus intensities (8, 16, 32, 64, 128, 256, and 512 mN) (MRC Systems GmbH, Germany). Five ascending and descending series of stimuli were applied and the subjects were asked to indicate if the sensation was felt as being 'sharp' or 'blunt'. The final threshold was the geometric mean of the five series of ascending and descending stimulus intensities.

2.3.4 Stimulus-response-function: mechanical pain sensitivity for pinprick stimuli and dynamic mechanical allodynia

Mechanical pain sensitivity (MPS) was assessed using the same weighted pinprick stimulators as for MPT. The pinprick stimuli were applied five times. Subjects were

asked to give a pain rating for each stimulus on a NRS (0 = no pain, 100 = most intense pain imaginable). Dynamic mechanical allodynia (DMA) was assessed by light stroking with a cotton wool tip fixed to an elastic strip (100mN), a cotton wisp (3mN), and a brush exerting a force of 200 - 400mN. The stimuli were applied five times and were intermingled with the pinprick stimuli in balanced and standardised order. Subjects were asked to give a rating on the same scale as for pinprick stimuli. MPS was calculated as the geometric mean of all numerical ratings for pinprick stimuli and DMA as the geometric mean of all numerical ratings elicited by light touch stimulators.

2.3.5 Wind-up ratio to repetitive pinprick stimuli

The perceived magnitude of a single pinprick stimulus (256 mN) was compared with that of a series of 10 pinprick stimuli of the same force repeated at a 1/s rate. The repeated stimuli were given within an area of 1cm^2. Subjects were instructed to give a pain rating for the first stimulus and for the whole series of 10 pinpricks using a 0 – 100 NRS. The mean pain rating of five series of repeated pinprick stimulation divided by the mean pain rating of five single stimuli was calculated as wind-up ratio.

2.3.6 Vibration detection threshold

The vibration detection threshold (VDT) was measured using a Rydel-Seiffer tuning fork (64Hz, 8/8 scale). The threshold was determined as a disappearance threshold with three stimulus repetitions [57]. Measurements were taken over bony prominences unless the maximal pain area did not exhibit a bony surface (n = 13), in which case, measurements were taken over adjacent soft tissue. VDTs were measured over soft tissue in 11 patients

with cervical radiculopathy (paravertebral thoracic spine n = 5; paravertebral cervical spine n = 1; lateral upper arm n = 4; radial extensor group n = 1), in one patient with NSNAP (paravertebral thoracic spine) and in one patient with FM (paravertebral thoracic spine). HC data were obtained for all measurement sites (soft tissues and bony prominences). Measurements in the dermatomal area of patients with cervical radiculopathy and patients with NSNAP were recorded over bony prominences. For patients with FM and HC subjects, VDT of dermatome C6 was measured over the radial styloid and VDT of dermatome C7 was measured over the third 3rd metacarpophalangeal joint. VDT of the foot was recorded over the medial malleolus [57,58] in all patients and HC.

2.3.7 Pressure pain threshold

The assessment of pressure pain thresholds (PPT) is the final test of the QST protocol. The PPT was determined using a pressure algometer with a probe size of 1cm^2 and ramp rate of 50kPa/s ($\approx$ 0.5kg/cm^2) (Somedic AB, Farsta, Sweden). The subjects were asked to push a button when the sensation changed from one of pressure alone to one of pressure and pain. The mean value of triplicate recordings was used for analysis.

2.4 Statistical analysis of demographic data

Age, symptom duration, pain intensity, sleep quality, scores of the NDI and Tampa Scale of Kinesiophobia were compared between groups using a one-way ANOVA. Post hoc comparisons were calculated using LSD-post hoc tests. Differences in frequency of sleep disturbance were determined by means of the Fisher's exact test. Anxiety and depression

scores and the physical and mental component summary scores of the SF-36 were compared between groups using the Kruskal-Wallis Test. Further pairwise analyses were performed using the Mann-Whitney-U Test where differences between groups were evident.

2.5 Statistical analysis of QST data

Data were analysed using the Statistical Package for Social Sciences (SPSS Version 17.0). QST data were log-transformed prior to statistical analysis [58] except HPT and VDT which were normally distributed as raw data. To compare and illustrate patients' QST data profiles with the group mean of age-matched healthy controls patients' data were z-transformed for each single parameter by using the following expression: Z-score = (Mean $_{\text{single proband}}$ − Mean $_{\text{healthy controls}}$)/SD $_{\text{healthy controls}}$ [58]. Z-values were calculated based on the included HC group data (data from trapezius muscle and dermatomes from left and right body side pooled). Patient data for the maximal pain area and dermatome were referenced to multiple matched areas on the HCs and patient's foot data were referenced to foot data of healthy subjects. For clarity of data presentation, the algebraic sign of z-score values for each parameter was adjusted so that it reflects the individual patient's sensitivity for each parameter. Z-values above '0' indicate a gain of function, meaning the patient is more sensitive to the tested stimuli compared with HC, a z-value below '0' indicates as loss of function, meaning a reduced sensitivity of the patient.

Differences of z-score QST data between the 3 patient groups and controls and tested body regions were compared using a two-way analysis of covariance (ANCOVA) with

tested body areas (maximal pain area, dermatome, foot) as the within-subjects factor. Group (patients/controls) and the potential confounding factor gender were entered as between-subjects factors for each variable. Anxiety and depression were entered as covariates to account for potential influence of these factors on pain responses [56]. If individual confounding factors did not demonstrate a significant effect, they were removed from the model. The LSD (LSD; least significant difference) post-hoc test was used to identify differences between body regions for variables that showed a statistical significant difference on ANCOVA. A univariate analysis was conducted for each QST parameter with post-hoc analyses (LSD-post hoc tests) to assess specific group differences within one tested body region. Any confounding factor that was found to be significant in the ANCOVA model was included in the univariate analysis. To investigate body side differences within each neck-arm pain group, paired t-tests were performed for all QST parameters. Significance was accepted at $p < 0.05$ for all analyses.

Frequencies of sensory abnormalities lying outside of the 95% confidence interval (i.e. z-score < -1.96 or > 1.96 standard deviation) of our HC were calculated within each group for each test site on the symptomatic body side. In contrast to group comparison, this analysis allows the identification of individual differences and identification of possible subgroups of patients within a specific diagnostic patient group [40,54,50,11,76]. This documentation can be useful when group mean values may not differ to HC data and therefore present as false-negative [50].

3. Results

3.1 Patient characteristics

A summary of the demographics is presented for each group in Table 1. There were no statistically significant differences between the two neck-arm pain groups in any of the measures including pain intensities, symptom duration, sleep quality, fear avoidance behaviour, anxiety and depression scores, physical and mental component summary score of the SF-36 and NDI scores. The NDI indicated moderate disability for patients with cervical radiculopathy and mild disability for patients with NSNAP. Both neck-arm pain groups differed from HC with significantly poorer sleep quality, lower physical and mental component summary scores of the SF-36 and higher anxiety and depression scores, however over 75% of anxiety and 91% of depression scores fell within the normal range. Compared to patients with FM, both neck-arm pain patient groups demonstrated a significantly shorter symptom duration, lower anxiety scores and higher mental component score of the SF-36. Patients with cervical radiculopathy showed lower average pain intensity during the last week and the last 4 weeks prior to testing and a lower depression score compared to patients with FM. Patients with NSNAP demonstrated a significantly higher physical component score of the SF-36 and lower score on the NDI compared to patients with FM.

In the cervical radiculopathy group, 11 patients presented with a C6 radiculopathy and 12 patients with a C7 radiculopathy. The most common pain descriptors used by patients with radiculopathy for their neck pain were constant pain (n = 17), ache (n = 10), dull (n = 7), burning (n = 6) and sharp (n = 6), and for their arm pain constant pain (n = 11),

burning (n = 7), ache (n = 6) and shooting (n = 5). Eight patients with cervical

radiculopathy indicated their arm pain as the maximal pain area. All patients reported the

presence of paraesthesia (pins and needles, tingling or numb sensation) in their arm.

Seventeen patients reported spontaneous pain. In the patient group with NSNAP, 7

patients presented with pain in a C7 dermatomal distribution and one patient with pain in

a C6 dermatomal distribution. The most common pain descriptors for the neck pain were

constant pain (n = 5), burning (n = 5) and ache (n = 3), and for the arm pain intermittent

pain (n = 5), burning, shooting and nerve pain (n = 2). For all patients in this group, the

maximal pain area was located in the neck/upper thoracic area. All patients reported the

presence of paraesthesia in their arm. Three patients indicated the presence of

spontaneous pain. Two patients had undergone medical imaging (computed tomography)

of their cervical spine, which demonstrated no compromise of the exiting nerve root at

the relevant spinal level. All other patients had no imaging performed.

3.2 Sensory profiles and number of abnormal findings

The QST sensory profiles for each body region (maximal pain area, dermatome and foot

on the symptomatic side) and by group (cervical radiculopathy, NSNAP and FM) shown

as z-scores are illustrated in Figure 2A – 2C. The z-score QST sensory profiles in the

maximal pain area and the dermatome of the symptomatic and asymptomatic arms in

each neck-arm pain group are indicated in Figure 3 (cervical radiculopathy) and Figure 4

(NSNAP).

3.2.1 Patients with cervical radiculopathy

For patients with cervical radiculopathy, the mean values of all QST parameters were within the 95% confidence interval of the reference group (Fig. 2A, Fig. 3). Patients with cervical radiculopathy demonstrated mixed, bi-directional sensory abnormalities, i.e. signs of a loss of function as well as a gain of function. Compared to HC, a loss of function was demonstrated in the maximal pain area for cold and warm detection and mechanical and vibration detection (CDT, WDT, TSL, MDT, VDT: $p \leq 0.008$) (Table 2, Fig. 2A) and for mechanical and vibration detection compared to the contralateral side (MDT: $p = 0.027$, VDT: $p = 0.002$) (Fig. 3, Online Supplemental Table 3). In the symptomatic dermatome, a loss of function was evident for measurements of thermal and vibration detection (CDT, WDT, TSL, VDT: $p < 0.03$) and for pressure pain sensitivity (PPT: $p = 0.048$) compared to HC (Table 2, Fig. 2A). Although mechanical detection was reduced in the dermatome (Fig. 2A), it did not reach statistical significance compared to HC data (MDT: $p = 0.069$), but was significantly different compared to the asymptomatic side (MDT: $p = < 0.001$) (Fig. 3B, Online Supplemental Table 3). Cold detection (CDT: $p = 0.019$), vibration detection (VDT: $p = 0.001$) and pressure pain sensitivity (PPT: $p = 0.011$) were also significantly reduced on the symptomatic side compared to the asymptomatic side (Online Supplemental Table 3, Fig. 3B).

Additional to the preceding documentation of group comparisons between patients with cervical radiculopathy and HC, the number of individual z-score values outside the 95% confidence interval of the HC group are reported in Online Supplemental Table 4. The frequencies of patients presenting with z-scores indicating a loss of function (< -1.95)

were as follows (in order: maximal pain area; dermatome; foot): CDT (39%; 17%; 4%), WDT (26%; 9%; 4%), TSL (39%; 13%; 4%), MDT (26%; 13%; 0%), VDT (22%; 30%; 4%) and PPT (26%; 17%; 0%). To note is the dichotomy of pressure pain sensitivity findings: 26% of patients recorded z-scores < -1.96 in their maximal pain, indicating reduced sensitivity, and 22% of patients recorded z-scores > 1.96 in their pain area, indicating increased pressure pain sensitivity. The mix of lowered and elevated PPTs may have cancelled each other out in a group analysis, hence the group mean may not differ to HC data.

In comparison with HC data, a gain of function was evident for one nociceptive parameter (CPT) (Fig. 2A), data indicating an increased cold sensitivity primarily in the maximal pain area (p = 0.001) and in the foot (p = 0.003) (Table 2). The frequencies of z-scores > 1.95 indicating a gain of function for CPT were: 39%, 30% and 30% for the maximal pain area, dermatome and foot respectively (Online Supplemental Table 4). The cold sensitivity in the maximal pain area was not different compared to the asymptomatic side (Fig 3A, Online Supplemental Table 3). WUR was not consistently present in any of the examined body regions (Table 2, Online Supplemental Table 3). DMA was demonstrated by one patient bilaterally in the maximal pain area and in the dermatome on the symptomatic side. PHS in the maximal pain area was reported once in one patient and by a different patient once on the asymptomatic side. Two patients reported PHS once on the asymptomatic side of the dermatome. PHS in the foot was reported once in three patients and three times in four patients.

3.2.2 Patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity

For patients with NSNAP, the mean values of all QST parameters were within the 95% confidence interval of the reference group (Fig. 2B, Fig. 4). Compared to HC, this group's dominant sensory characteristic was a gain of function for cold pain sensitivity primarily in the maximal pain area (p = 0.024) and in the foot (p = 0.008) (Fig. 2B, Table 2). Twenty-five percent of the 8 patients with NSNAP recorded z-scores for CPT > 1.95 in the maximal pain area indicating a gain of function, and 37% of patients demonstrated this gain in the dermatome and the foot (Online Supplemental Table 4). Cold sensitivity was similar regardless of the side tested (Fig. 4A, Online Supplemental Table 3). There was a tendency for a loss of function in vibration detection in the maximal pain area (Fig. 2B). This finding did not reach statistical significance (p = 0.064) (Table 2) and was not significantly different from the asymptomatic side (Online Supplemental Table 3, Fig. 4A). Twenty-five percent of the 8 patients recorded z-scores of < -1.95 indicating a loss of function for VDT in the maximal pain area (Online Supplemental Table 4). The z-score sensory profiles of the symptomatic and asymptomatic side were nearly identical for the maximal pain area and dermatome, except that the t-test indicated a significant loss of function in the dermatome on the symptomatic side for warm detection (WDT: p = 0.029) (Online Supplemental Table 3, Fig 4). WUR was present in all examined body regions (Table 2, Online Supplemental Table 3). No patients demonstrated DMA in any body region. PHS in the maximal pain area was reported twice by one patient and in the foot on three occasions by another patient.

3.2.3 Patients with fibromyalgia

Patients with FM demonstrated z-scores beyond the 95% confidence interval of the HC

group for cold and pressure pain thresholds in all body regions and for heat pain

thresholds in the maximal pain area and dermatome (Fig. 2C). Their sensory profiles

were characterised predominantly by a gain of function, indicated by increased thermal

and pressure sensitivity in all body regions (CPT, HPT, PPT $p \leq 0.005$) and increased

MPS in the maximal pain area ($p = 0.026$) and foot ($p < 0.001$) (Table 2). The following

frequencies of z-scores were > 1.95 indicating a gain of function (order: maximal pain

area; dermatome; foot) (Online Supplemental Table 4): CPT (95%; 82%; 86%), HPT

(86%; 68%; 45%), MPS (32%; 18%; 36%), WUR (4%; 14%; 4%) and PPT (68%; 64%;

59%). In addition, patients with FM demonstrated signs of a loss of sensory function in

vibration detection in the maximal pain area ($p = 0.013$). Twenty-three percent of patients

with FM recorded z-scores < -1.95 for VDT indicating a loss of function. WUR was

present in all examined body regions (Table 2). Three patients demonstrated DMA in the

maximal pain area and dermatome and five patients demonstrated DMA in the foot. PHS

was reported by one patient in the foot once.

3.3 Comparison of sensory profiles between groups and body regions

Sensory profiles differed between groups and also between body regions. An ANCOVA

of all QST data demonstrated group differences for all variables except MPT (Table 2).

Differences in thermal, mechanical and vibration detection thresholds, were mainly

driven by the loss of function seen in patients with cervical radiculopathy (Fig. 2).

Differences in pain thresholds (CPT, HPT, PPT) and mechanical pain sensitivity were

mainly driven by the increased sensitivity to these stimuli in patients with FM. There were significant differences between tested body regions (Table 2) with greater thermal sensation loss in the maximal pain area compared to the dermatome (CDT p = 0.031; WDT p = 0.049), greater thermal and vibration sensation loss in the maximal pain area compared to the foot (CDT p = 0.002; WDT p = 0.029; VDT p = <0.001) and greater TSL threshold elevation in the maximal pain area compared to the foot (p = 0.017). Vibration detection was lower in the dermatome compared to the foot (p = 0.001). Mechanical pain sensitivity was less dominant in the maximal pain area (p = 0.022) and the dermatome (p = 0.002) compared to the foot. A significant group by region interaction was evident for cold detection (p = 0.003) (Table 2). Patients with cervical radiculopathy demonstrated significantly reduced cold detection in the maximal pain area and the dermatome (Fig. 2A) when compared to HC and patients with NSNAP (Table 2). There was an association between anxiety and HPT in patients with FM, demonstrating higher anxiety scores and increased heat sensitivity. Higher depression scores in patients with FM were correlated with increased mechanical pain sensitivity. Gender only had a significant effect on PPT measurements (group*gender p = 0.041). For comparison of PPT in the maximal pain area the inclusion of gender in the univariate analysis decreased the significance between all 4 groups from significant to non-significant. Further pairwise comparison between groups, including gender adjustment, demonstrated lowered PPT in patients with FM compared to HC (p < 0.001) and compared to patients with NSNAP (p = 0.011). PPT measurements were significantly lower in female than males for all body regions (p < 0.001).

4. Discussion

This study revealed differences in the somatosensory phenotype of patients with cervical radiculopathy and that of patients with NSNAP. Patients with cervical radiculopathy demonstrated a loss of function in their maximal pain area and dermatome, evident by hypoaesthesia to non-nociceptive stimuli and to pressure pain. These deficits were not present in patients with NSNAP. Increased cold sensitivity occurred in both patient groups bilaterally in their maximal pain area and foot, and was the main sensory characteristic in patients with NSNAP. Both neck-arm pain groups differed from patients with FM, the latter demonstrating a widespread gain of function in most nociceptive parameters and a localised loss of vibration sense in their maximal pain area.

Patients with cervical radiculopathy were characterised by sensory alterations in the maximal pain area (reduced thermal, mechanical and vibration detection) and dermatome (reduced thermal and vibration detection and pressure pain sensitivity), indicating a loss of small and large sensory fiber function. The presence of these negative sensory signs is indicative of peripheral neuronal damage and consistent with the presence of NeP components [32,66]. Based on the recently proposed grading system of NeP [66], our patients fulfilled the definition of "definite" NeP. The loss of function occurred in all primary sensory fibers tested (C, Aδ, Aβ), data consistent with previous findings in patients with peripheral nerve injuries [41] and in patients with lumbar radiculopathy [53], although others studies of patients with lumbar radiculopathy reported selective loss of function in Aδ fibers [52] or Aδ and Aβ fibers [26]. In contrast, Chien et al [13] did

26

not find reduced cold detection in tested areas representative of C6/7/8 dermatome, but it is unclear if these areas correlated with each individual patient's area of sensory loss.

The loss of thermal detection did not significantly differ from the asymptomatic side, except for CDT (difference 0.56º) in the dermatome. However, it is unclear what might be considered a clinically significant difference for thermal detection thresholds [57,46,65,44]. An individual side difference of $\geq \pm 1$º for cold and warm detection thresholds has been proposed as pathological [46], while other authors argue a side difference ± 1º is within a normal range [57,65].

The bilateral loss of thermal detection is consistent with other findings for patients with cervical [13] and lumbar radiculopathy [53,26], but contrary to findings of other author [83, 60, 82]. Thermal hypoaesthesia contralateral to the main pain area has been observed in patients with unilateral traumatic partial nerve injury [46] and with unilateral traumatic trigeminal neuropathy [36]. Bilateral hypoaesthesia may be mediated by peripheral nerve damage induced central plasticity [17].

Patients with cervical radiculopathy demonstrated cold hypersensitivity in the maximal pain area, a common sequel of peripheral nerve injury [18,41,44,64]. The clinical significance of our finding is however unclear, as the group mean value for CPT fell within the 95% confidence interval of our HC group and was below the value of defined cold hyperalgesia (CPT $\geq 15°$) [8]. Nevertheless, when evaluating individual results 11 patients demonstrated cold hyperalgesia in their maximal pain area. Cold hypersensitivity

was evident bilaterally, although a trend towards a unilateral differential gain approached significance (p = 0.069). This bilateral cold hypersensitivity was also evident in the NSNAP group.

Cold hypersensitivity also occurred for both neck-arm pain groups in the foot. The clinical significance of this finding remains unclear. Mechanisms underlying cold evoked pain are still not fully understood [5,70] and likely include both peripheral [74,61] and central nervous mechanisms [80,79,15,38]. Further, cold hypersensitivity is not necessarily associated with the presence of pain or with nerve damage as evidenced in patients with painless peripheral nerve injuries [41], by patients with FM [34,9,40,54,11] and by patients with depression without pain [40]. While psychological factors can enhance pain sensitivity [56], our patients with neck-arm pain demonstrated scores within the normal range for anxiety and depression and measurements of cold sensitivity were not affected by adjustments for anxiety or depression.

Contrary to Chien et al [13] who demonstrated widespread increased pressure sensitivity in patients with cervical radiculopathy, this characteristic was not present in our radiculopathy cohort. Apart from differences in body areas assessed, Chien et al's patients demonstrated longer symptom duration (19.7 ± 14.2 months) and higher disability on the NDI compared to our patients. Persistent pain may lead to enhanced pain processing in the central nervous system, resulting in this hypersensitivity. We observed a dichotomy of pressure pain sensitivity in our patients, which is consistent with likely sub-groups of patients with differing somatosensory profiles, as demonstrated recently in

patients with lumbar radiculopathy [49]. These data highlight the need for individual patient assessment in order to determine sensory phenotypes and contribute to management decisions.

Patients with NSNAP did not differ to HC except for the presence of cold hypersensitivity in their maximal pain area and foot. Furthermore, no side differences for QST parameters were found in any body region except for WDT in the dermatome. However, given the modest nature of this difference (WDT < 1º) and the lack of comparative data, the clinical significance is uncertain. If cold hypersensitivity was regarded as a relevant sensory abnormality for the presence of NeP, patients with NSNAP would be classified as having "probable" NeP [66]. Three patients with NSNAP used pain descriptors suggestive of NeP (spontaneous pain, burning) [7,22], and all three demonstrated a loss of function in vibration detection in their maximal pain area. However, mechanical hypoaesthesia does not necessarily indicate neuronal damage as hypoaesthesia to vibration has been documented in patients with FM [42] and chronic low back pain [11], in line with tactile hypoaesthesia documented in non-NeP pain conditions [47,48,28,76].

In our study, patients with FM were characterised by a widespread gain of function in the majority of nociceptive parameters (thermal and pressure pain) and mechanical pain sensitivity in their maximal pain area and foot, pointing to a more generalised sensory discriminative dysfunction in these patients compared with our neck-arm pain groups. Our finding of generalised pressure hyperalgesia is consistent with data from previous

studies [43,40,54,42,11], however findings are not unequivocal. While the thermal

hypersensitivity shown here replicates other studies [43,34,9,11], not all show thermal

sensitivity gains [40,54]. Similarly the increased MPS in our patients with FM

corresponds with some findings [11], but not with others [40,54] and the reduced

vibration sense has been demonstrated by some [42], but not by others [40,54]. These

differing observations may be indicative of the heterogeneity of FM and the possible

existence of various sub-groups [34,29,55]. In the absence of evidence of tissue damage

in FM, aberrations in pain inhibitory [39,35,45] and pain facilitatory mechanisms [45] as

well as central sensitisation/augmentation of sensory input [19,2,62] have been associated

with enhanced pain sensitivity in FM.

Both neck-arm pain groups shared similarities in their demographics and pain

characteristics, except a larger proportion of patients with cervical radiculopathy were on

medication compared to patients with NSNAP. While a possible influence of medication

on pain sensitivity cannot be disregarded, the patient groups were similar in their pain

sensitivity measurements. A distinct difference in somatosensory profiles was shown,

where NeP was likely the dominant pain type in patients with cervical radiculopathy, but

not in patients with NSNAP.

While the identification of differing QST profiles in our patient groups may assist in

targeted treatment such as pharmacological intervention for NeP in patients with cervical

radiculopathy [3], data have to be interpreted in light of a whole person perspective on

pain. The assessment of psychological conditions which were present in our patients, and

to varying degrees, acknowledges the multidimensional nature of pain. The presence of co-morbidities may further explain some of the differences seen in clinical profiles and demand a multidisciplinary management approach in patients with persistent pain, whether neuropathic or not.

The group of patients with NSNAP was comparatively small and the risk of a type II error cannot be excluded. However, the recruitment of these patients proved to be extremely difficult with only 8 fulfilling the inclusion criteria out of 464 clinically examined patients with neck-arm pain, suggesting the prevalence of this pain condition may be overestimated.

Numerous researchers have reported limitations due to unavailability of HC reference data for assessed pain regions [75,50,11]. Whilst we were able to obtain age matched HC data for all assessed body regions, we were not able to gender match these data, however our results were controlled for gender. Further, the size of some HC reference groups was small (n = 8), thus these reference data should not be referred to as 'normative' data.

While similarities in pain characteristics and sensory signs were evident between patients with cervical radiculopathy and NSNAP, distinct somatosensory profiles were demonstrated for each group. These distinct phenotypes may reflect differences in the underlying pathophysiology, pain types and pain mechanisms, a suggestion strengthened by the presence of sub-groups with differing somatosensory profiles within these neck-

arm pain groups. The findings of this study may assist clinicians in more appropriate
targeting of management for patients in these sub-groups.

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Table 1

Demographics and profiles of healthy control (HC) subjects, patients with cervical radiculopathy (CxRAD), patients with neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) and patients with fibromyalgia (FM)

	HC (n = 31)	CxRAD (n = 23)	NSNAP (n = 8)	FM (n = 22)	p-value ANOVA
Age (years)*	45.6 (12.5)	46.3 (9.6)	45.1 (14.9)	46.1 (11.5)	0.992
Gender (female, n)	15 (48%)	8 (35%)	7 (87%)	20 (91%)	
Symptom duration (months)*		7.6 (4.1)	8.1 (3.0)	124.9 (83.1)[c, e]	<0.001
Average pain intensity during last week (VAS)*		5.2 (2.0)	6.0 (1.5)	7.3 (1.2)[c]	<0.001
Maximal pain intensity during last 4 weeks (NRS 0-10)*		7.2 (2.2)	7.6 (0.6)	8.3 (1.2)	0.116
Average pain intensity during last 4 weeks (NRS 0-10)*		5.0 (2.1)	5.1 (0.6)	6.2 (1.3)[d]	0.043
Sleep quality during last week (VAS)*	2.9 (2.6)	5.3 (2.7)[b]	5.9 (2.2)[b]	6.8 (2.3)[a]	<0.001
Sleep disturbance (n)					<0.001[###]
Negative	26	11	1	1	

Positive	5 (16%)	12 (52%)	7 (87%)	21 (95%)	
Fatigue (n)					<0.001[###]
Negative	25	9	4	2	
Positive	6 (19%)	14 (61%)	4 (50%)	20 (91%)	
Hospital Anxiety and Depression Scale					
Anxiety score (HADS)[#]	3.0 (5.0)	6.0 (5.0)[b]	8.0 (4.2)[b]	12.0 (6.2)[a, c, f]	<0.001[##]
Within normal range (≤ 10), n	29 (93%)	21(91%)	6 (75%)	7 (32%)	
Depression score (HADS)[#]	1.0 (1.0)	3.0 (4.0)[a]	3.5 (5.5)[b]	6.0 (4.2)[a, d]	<0.001[##]
Within normal range (≤ 10), n	31 (100%)	21 (91%)	8 (100%)	19 (86%)	
SF-36					
Physical Component[#]	57.7 (3.7)	40.6 (12.6)[a]	46.4 (12.0)[b]	36.4 (11.9)[a, f]	<0.001[##]
Mental Component[#]	56.0 (7.6)	52.3 (17.4)[b]	48.4 (20.5)[b]	30.8 (21.5)[a, d, f]	<0.001[##]
Neck Disability Index*		16.2 (7.7)	13.4 (5.9)	19.7 (4.0)[f]	0.032
Tampa Scale of Kinesiophobia*		40.9 (8.1)	36.7 (7.5)	38.4 (5.4)	0.281

Patients with medication, n	15 (65.2%)	3 (37.5%)	12 (54.5%)
Current medication$^\diamond$			
Selective serotonin reuptake inhibitor, n	1 (4.3%)	1 (12.5%)	7 (31.8%)
Serotonin-norepinephrine reuptake inhibitor, n	2 (8.7%)		2 (9.1%)
Tricyclic antidepressant, n	1 (4.3%)		3 (13.(%)
Tetracyclic antidepressant, n			1 (4.5%)
Antiepileptics, n	2 (8.7%)		
Opioids, n	4 (17.4%)		1 (4.5%)
Benzodiazepine, n	2 (8.7%)		
Analgesics, n	7 (30.4%)	1 (12.5%)	3 (13.(%)
Non-steroidal anti-inflammatories, n	7 (30.4%)	2 (25%)	

*Data are mean (SD); #Data are median (IQR); ##Kruskal –Wallis Test; ###Fisher's Exact Test

[a]Significantly different to HC (p < 0.001); [b]Significantly different to HC (p < 0.05); [c]Significantly different to CxRAD (p < 0.001); [d]Significantly different to CxRAD (p < 0.05) ; [e]Significantly different to NSNAP (p < 0.001); [f]Significantly different to NSNAP (p < 0.05); $^\diamond$Multiple answers possible

Table 2

QST parameters are shown of healthy controls (HC), patients with cervical radiculopathy (CxRAD)

patients with neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP)

and patients with fibromyalgia (FM) in the maximal pain area (MPA), dermatome (DERM) and

foot (FOOT). Data are shown as mean for untransformed data (HPT, VDT) ± standard deviation

and retransformed mean for log-normally distributed data.

QST Parameter	HC n = 31	CxRAD n = 23	NSNAP n = 8	FM n = 22	*p-* Group/ region	*p-* Group	*p-* Body region
CDT (°C)					0.003	0.003	0.003
MPA	1.31	1.89[d, e]	1.16	1.57			
DERM[a]	1.57	2.68[c, e, f]	1.55	1.56			
FOOT[a]	3.42	3.06	3.86	3.02			
WDT (°C)					0.529	<0.001	0.037
MPA	2.65	3.83[d, e, f]	2.64	2.79			
DERM[a]	2.94	4.17[c, f]	3.14	2.56			
FOOT[a]	4.70	6.30[c, f]	4.42	3.95			
TSL (°C)					0.302	<0.001	0.028
MPA	4.26	6.22[d, e, g]	4.17	4.11			
DERM	4.71	6.87[c, f]	5.11	4.03			
FOOT[a]	9.39	11.78[f]	8.84	6.69[c]			
CPT (°C)					0.050	<0.001	0.095
MPA	7.1	11.16[c, g]	12.16[c, f]	24.2[d]			
DERM	6.11	8.08[g]	7.80[g]	18.03[d]			
FOOT	5.76	9.39[c, g]	10.59[c, f]	18.73[d]			

HPT (°C)					0.183^h	$<0.001^h$	0.949^h
MPA	46.6±1.9	45.4±4.4[g]	45.1±2.2[f]	39.5±3.3[d]			
DERM	47.3±2.1	46.1±3.8[f]	46.4±2.2[f]	40.8±5.3[c]			
FOOT	46.3±2.6	46.4±2.8[g]	44.0±2.5	41.8±4.0[c]			
MDT (mN)					0.193	0.014	0.112
MPA	2.11	3.79[c, e]	1.37	3.08			
DERM	2.24	4.53[f]	2.65	1.50			
FOOT	6.34	10.15	6.67	5.50			
MPT (mN)					0.241^h	0.512^h	0.282^h
MPA	66.24	29.85	28.10	31.60			
DERM	72.81	84.45	34.90	54.68			
FOOT	58.45	34.92	31.72	42.23			
MPS (rating 0-100)					0.097^i	0.009^i	0.034^i
MPA	0.45	0.45[f]	0.77	1.90[c]			
DERM	0.36	0.34[f]	0.74	1.38			
FOOT[a, b]	0.41	0.66[f]	1.04	2.10[c]			
WUR (ratio)					0.050	0.029	0.236
MPA	3.80	2.81	2.98	4.36			
	(n = 16)	(n = 18)	(n = 8	n = 22)			
DERM	2.77	2.45[f]	2.15[f]	4.34[c]			
	(n = 17)	(n = 15)	(n = 8)	(n = 22)			
FOOT	3.30	2.86	2.24	4.04			
	(n = 21)	(n = 21)	(n = 8)	(n = 22)			
VDT (x/8)					0.106	0.027	0.001
MPA	6.1±0.8	5.4±1.1[c]	5.2±1.0	5.5±1.1[c]			

DERM	7.1±0.7	6.2±1.0[c]	6.6±1.4	6.7±1.0			
FOOT[a, b]	5.9±1.1	5.7±1.0	5.5±2.0	5.4±1.1			
PPT (kPa)					0.161[j]	0.004	0.792[j]
MPA	428	403	390	183			
DERM	471	572[c, e, g]	417[f]	249[d]			
FOOT	584	573[g]	522[g]	299[d]			

CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold.

[a]Significantly different to maximal pain area ($p < 0.05$); [b]Significantly different to dermatome ($p < 0.05$); [c]Significantly different to HC ($p < 0.05$); [d]Significantly different to HC ($p < 0.001$); [e]Significantly different to NSNAP ($p < 0.05$); [f]Significantly different to FM ($p < 0.05$); [g]Significantly different to FM ($p < 0.001$); [h]adjusted for anxiety; [i]adjusted for depression, [j]adjusted for gender

Online Supplement: Table 3

QST parameters[a] of patients with cervical radiculopathy (CxRAD) and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivit

(NSNAP) in the asymptomatic (asymp) and symptomatic (symp) arm.

QST Parameter	MAXIMAL PAIN AREA						DERMATOME					
	CxRAD			NSNAP			CxRAD			NSNAP		
	Asymp	Sympt	*p*	Asymp	Sympt	*p*	Asymp	Sympt	*p*	Asymp	Sympt	*p*
CDT (°C)	1.86	1.89	0.767	1.12	1.16	0.803	2.12	2.68	**0.019**	1.43	1.55	0.405
WDT (°C)	3.45	3.83	0.209	2.28	2.64	0.536	3.43	4.17	0.118	2.25	3.14	**0.029**
TSL (°C)	5.51	6.22	0.132	3.94	4.17	0.664	6.15	6.87	0.269	4.20	5.11	0.121
CPT (°C)	9.10	11.16	0.069	10.50	12.16	0.294	7.56	8.08	0.625	8.40	7.80	0.709
HPT (°C)	45.9±3.7	45.4±4.4	0.386	45.3±2.3	45.1±2.2	0.736	45.6±3.5	46.1±3.8	0.586	46.2±3.1	46.4±2.2	0.720
MDT (mN)	2.10	3.79	**0.027**	1.57	1.37	0.555	1.18	4.53	**<0.001**	2.26	2.65	0.683

MPT (mN)	23.75	29.85	0.376	19.87	28.10	0.352	70.91	84.45	0.465	36.13	34.90	0.867
MPS (NRS$_{100}$)	0.53	0.45	0.328	1.01	0.77	0.166	0.39	0.34	0.399	0.84	0.74	0.519
WUR (ratio)	2.68[b]	2.81[a]	0.579	2.49	2.98	0.548	2.01[c]	2.45[b]	0.358	2.04	2.15	0.620
VDT (x/8)	5.9±0.9	5.4±1.1	**0.002**	5.2±0.4	5.2±0.1	0.867	7.0±0.8	6.2±1.0	**0.001**	6.6±1.2	6.6±1.4	0.829
PPT (kPa)	434	403	0.249	366	390	0.288	492	572	**0.011**	405	417	0.208

CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold.

[a]Data are shown as mean for untransformed data (HPT, VDT) ± standard deviation and retransformed mean for log-normally distributed data.

[b]n = 18, [c]n = 14

Online Supplement: Table 4

Number of individuals within each group with z-score values outside the 95% confidence interval of healthy control subjects

(+/- 1.96 standard deviation)

QST Parameter	Maximal pain area HC n = 31 +	-	CxRAD n = 23 +	-	NSNAP n = 8 +	-	FM n = 22 +	-	Dermatome HC n = 26 +	-	CxRAD n = 23 +	-	NSNAP n = 8 +	-	FM n = 22 +	-	Foot HC n = 26 +	-	CxRAD n = 23 +	-	NSNAP n = 8 +	-	FM n = 22 +	-
CDT	1	0	1	9	0	0	1	8	0	0	0	4	0	0	0	1	0	2	1	1	0	0	0	0
WDT	1	0	0	6	0	0	1	1	0	3	0	2	0	0	0	2	0	0	0	1	0	0	0	0
TSL	0	0	0	9	0	1	1	1	0	0	0	3	0	0	0	1	0	2	1	1	0	0	1	0
CPT	1	0	9	0	2	0	21	0	0	0	7	0	3	0	18	0	1	0	8	0	3	0	19	0
HPT	2	0	5	0	1	0	19	0	2	0	6	0	0	0	15	0	0	0	1	0	1	0	10	0
MDT	0	0	0	6	1	1	1	3	0	0	0	3	0	2	3	1	1	0	0	0	0	0	0	0
MPT	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
MPS	1	0	2	0	0	0	7	0	0	0	2	0	0	0	4	0	1	0	1	0	1	0	8	0
WUR	0	0	0	2	0	0	1	0	0	1	1	2	0	1	3	0	1	0	0	0	0	0	1	0
VDT	0	0	0	5	0	2	0	5	0	1	0	7	0	3	0	5	0	1	0	1	0	2	0	1
PPT	0	1	5	6	1	0	15	1	1	0	2	4	0	1	14	0	1	0	0	0	0	0	13	0
DMA*	0	0	1	0	0	0	3	0	0	0	1	0	0	0	3	0	0	0	0	0	0	0	5	0

HC: healthy control subjects; CxRAD: cervical radiculopathy; NSNAP: non-specific neck-arm pain associated with heightened nerve mechanosensitivity; FM: fibromyalgia;

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

+: Number of patients with positive individual z-score values, indicating an increased sensitivity compared to normative data ($> + 1.96$ standard deviation).

−: Number of patients with negative individual z-score values, indicating a decreased sensitivity compared to normative data ($> - 1.96$ standard deviation).

* As no DMA occurred in healthy control subjects, z-score values could not be calculated. Data are shown as absolute number of subjects showing DMA.

CxRAD	NSNAP	FM
Upper trapezius (n=4) Paravertebral thoracic spine (n=7) Upper arm lateral (n=5) Paravertebral cervical spine (n=2) Forearm (n=2) Above spine scapula (n=1) Below spine scapula (n=1) Lateral just above elbow (n=1)	Upper trapezius (n=6) Paravertebral thoracic spine (n=2)	Upper trapezius (n=14) Paravertebral thoracic spine (n=4) Paravertebral cervical spine (n=2) Upper arm lateral (n=1) Above spine scapula (n=1)

Fig. 1 Areas of maximal pain nominated by patients with cervical radiculopathy (CxRAD), patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) and patients with fibromyalgia (FM).
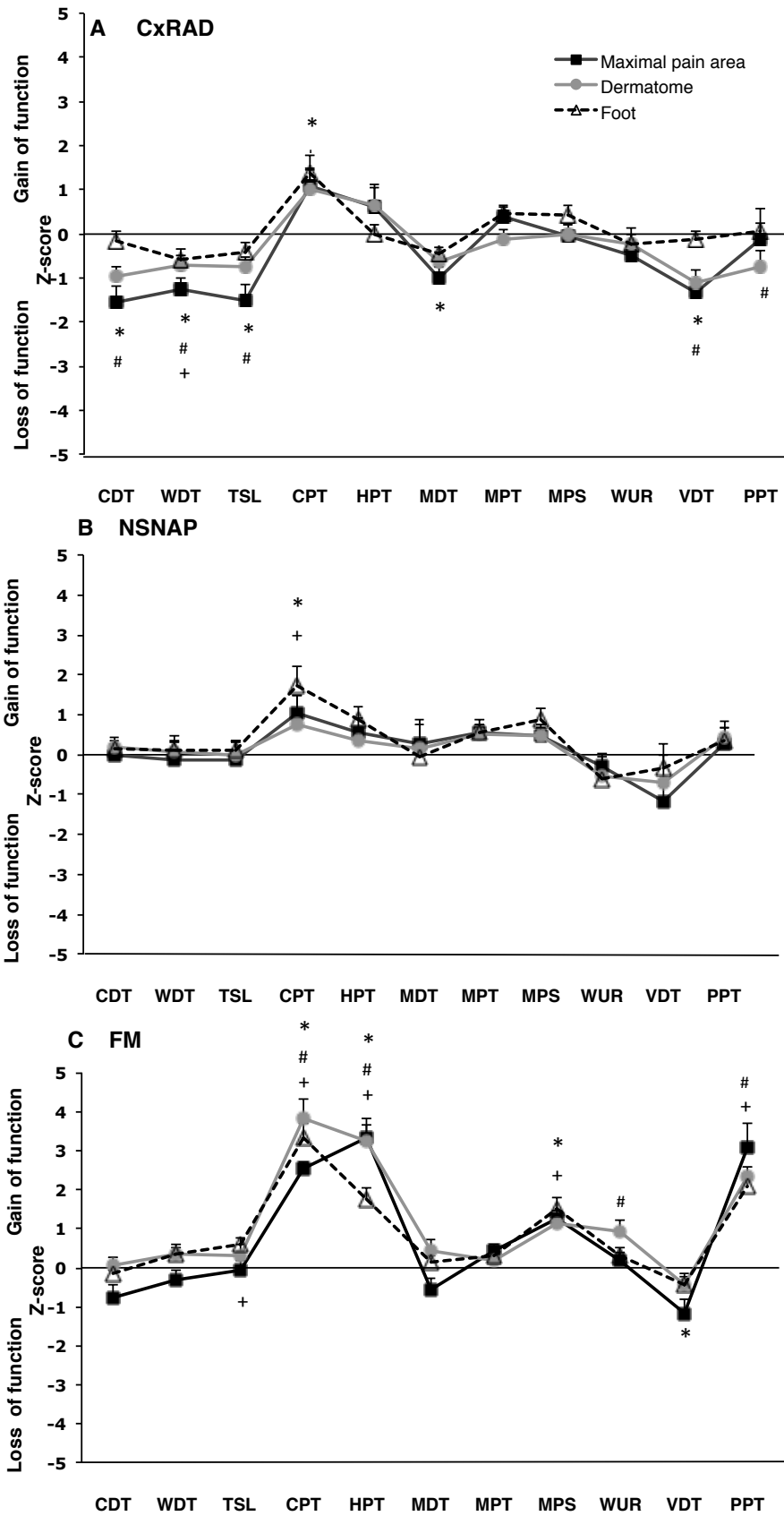
Fig. 2 Sensory profiling. The z-score sensory profiles are shown of patients with

cervical radiculopathy (CxRAD) (A), patients with non-specific neck-arm pain

associated with heightened nerve mechanosensitivity (NSNAP) (B) and patients with

fibromyalgia (FM) (C) in the maximal pain area (filled square), dermatome (filled

circle) and foot (empty triangle). Error bars indicate the standard error of

measurement. CDT: cold detection threshold; WDT: warm detection threshold; TSL:

thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT:

mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical

pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT:

pressure pain threshold.

* Significantly different in maximal pain area compared to HC

Significantly different in dermatome compared to HC

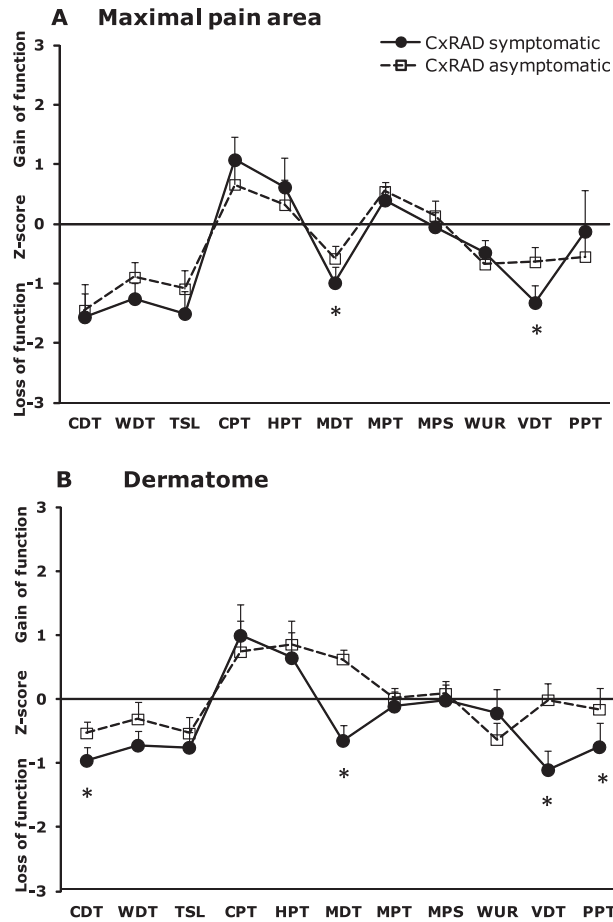+ Significantly different in foot compared to HC

Fig. 3 Z-score sensory profiles of the symptomatic (filled circle symbol) and asymptomatic (empty square symbol) side in patients with cervical radiculopathy (CxRAD) in the maximal pain area (A) and dermatome (B). Error bars indicate the standard error of measurement. CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold.
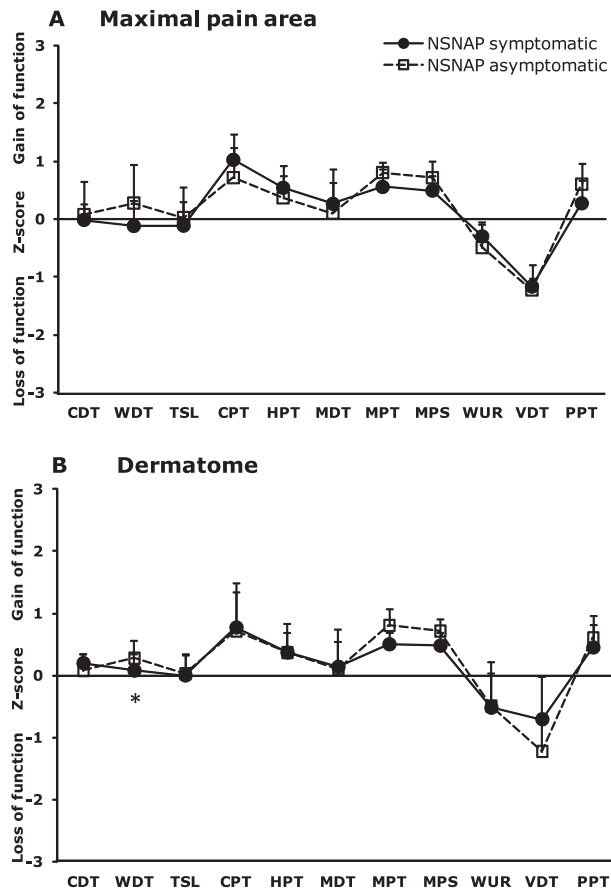
*p < 0.05

Fig. 4. Z-score sensory profiles of the symptomatic (filled circle symbol) and asymptomatic (empty square symbol) side in patients with NSNAP in the maximal pain area (A) and dermatome (B). Error bars indicate the standard error of measurement. CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold.

$*p < 0.05$