Sensory Profiles are comparable in Patients with distal and proximal Entrapment Neuropathies, while the Pain experience differs

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Abstract

Objective: Distal and proximal entrapment neuropathies such as carpal tunnel syndrome (CTS) and cervical radiculopathy (CR) share similar aetiologies. Experimental models suggest that despite comparable aetiology, pathomechanisms associated with injuries of the peripheral and central axon branches are distinct. This study therefore compared self-reported and elicited sensory profiles in patients with distal and proximal entrapment neuropathies.

Methods: Patients with electrodiagnostically confirmed CTS ($n = 103$) and patients with CR ($n = 23$) were included in this study. A group of healthy participants served as controls ($n=39$). Symptoms and sensory profiles were evaluated using quantitative sensory testing (QST) and a self-reported neuropathic pain questionnaire (painDETECT).

Results: Both patient groups were characterized by a loss of function in thermal and mechanical detection in the main pain area and dermatome compared to healthy reference data ($p < 0.001$). There was no significant difference between patients with CTS and CR in pain and detection thresholds except for reduced vibration sense in the main pain area ($p < 0.001$) and reduced pressure pain sensitivity in the dermatome in patients with CR ($p < 0.001$). Patients with CR reported however higher pain intensities ($p = 0.008$), more severe pain attacks ($p = 0.009$) and evoked pain by light pressure ($p = 0.002$) compared to patients with CTS.

Conclusion: While QST profiles were similar between patients with CTS and CR, self-reported pain profiles differed and may suggest distinct underlying mechanisms in these patient cohorts.

Keywords: Nerve compression syndromes, carpal tunnel syndrome, radiculopathy, somatosensory profiles, quantitative sensory testing

Short title: somatosensory profiles in distal and proximal entrapment neuropathies

Introduction

Entrapment neuropathies result from compression and/or irritation of peripheral nerves as they travel through narrow anatomical spaces [1]. Peripheral nerves may be affected at different sites: whereas distal entrapment neuropathies affect the peripheral axon branches, proximal entrapment neuropathies affect the central axon branches proximal to the cell body, the spinal nerve or the cell bodies. A typical entrapment neuropathy affecting the distal nerve trunk is carpal tunnel syndrome (CTS), whereas cervical radiculopathy (CR) is an example of a proximal entrapment neuropathy. Entrapment neuropathies are characterised by a plethora of signs and symptoms reflecting both loss (e.g., sensory loss, muscle weakness) and gain of function (e.g., paraesthesia, pain, hyperalgesia) [2, 3, 4, 5]. These signs and symptoms are thought to reflect different pathomechanisms causing either not enough or too many impulses being transmitted within the nervous system.

Despite similar aetiologies, animal models suggest that the pathomechanisms ensuing distal versus proximal nerve injuries differ [6]. For instance, the extent of neuroinflammation in the dorsal root ganglion, which is an important player in the generation of neuropathic pain [7], is more pronounced if the lesion is close to the ganglion (e.g., spinal nerve) compared to injuries affecting more distal parts of the peripheral nerve trunk [8, 9]. In addition, degeneration of peripheral axon branches (e.g., in CTS) reduces normal afferent barrage reaching the peripheral sensory cell bodies, but preserves the continuity between the cell

bodies and the second order spinal neurones. Injury to the dorsal root in contrast (e.g., in CR) deprives second order neurones from both anatomical and physiological input [10]. Such a lack of afferent input on second order neurones has been shown to lead to exaggerated central consequences, and is associated with deafferentation pain [11, 12]. Even though the literature on differential effects of distal and proximal nerve injuries is still sparse, these observations raise the question whether symptoms and signs of loss and gain of function differ in patients with entrapment neuropathies depending on the site of nerve injury.

The aim of this explorative study was therefore to compare the symptoms and sensory profiles of patients with distal (CTS) and proximal nerve entrapment (CR).

Methods

This study compared data from two established patient cohorts, parts of which have previously been published [5, 13, 14, 15, 16]. The study protocols and recruitment procedures were approved by the local and national Ethics Committee of all participating institutions and adhered to the ethical guidelines of the Declaration of Helsinki. All patients gave informed written consent prior to participating.

Study Population

Patients with Cervical Radiculopathy

Patients were recruited from a Neurosurgery Spinal Clinic at a tertiary hospital in Perth, Western Australia; from physiotherapy and pain management departments at metropolitan hospitals; from private neurosurgery, medical and physiotherapy practices and from the local community via radio and newspaper advertising. The inclusion criteria were as follows: unilateral neck pain and arm pain/paraesthesia consistent with C6 or C7 nerve root distributions; symptom duration of 3 to 18 months and pain intensity ≥ 2 on a visual analogue scale (VAS). An emphasis was put on very strict criteria for CR to avoid the inclusion of patients with radicular pain without neurological deficit. As such, clinical signs had to be in line with C6 or C7 radiculopathy with motor deficits (either absent or diminished reflex and/or myotomal weakness) and dermatomal sensory deficits [17]; and a demonstrable clinically relevant abnormality on imaging studies indicating compromise of the exiting nerve root at the relevant spinal level. 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 validate the diagnosis of cervical radiculopathy. Patients with metabolic or systemic disease, other neurological or psychiatric disease, a history of cardiovascular disease and an insufficient level of English were excluded from the study. Out of 464 patients with neck-arm pain clinically examined, 25 patients met the inclusion criteria. Two patients were excluded due to disagreement between the clinical experts and the author, leaving 23 patients (8 female; mean age 46.3 ± 9.6 years) who participated in the study.

Patients with Carpal Tunnel Syndrome

Data from patients with CTS were taken from the Oxford CTS cohort (up to October 2016).

Patients with CTS were recruited through secondary neurophysiology and hand surgery clinics of local public hospitals, local print media and advertisements on public notice boards.

The presence of CTS was determined using clinical [18] and electrodiagnostic criteria [19].

Patients were excluded if electrodiagnostic tests suggested the presence of peripheral neuropathies other than CTS (e.g., ulnar or radial neuropathy), if another medical condition affecting the upper extremity or neck was present (e.g., CR), if a history of previous surgery or significant trauma to the upper limb or neck existed, or if CTS was related to diabetes or pregnancy. Using these criteria, 103 patients with CTS (63 female; mean age 60.2 ± 12.9 years) were included. To prevent selection bias, patients with CTS were deliberately not matched to patients with CR, but statistical analyses were adjusted for baseline differences (see below).

Healthy Control Subjects

Thirteen healthy volunteers (6 female; mean age 45.7 ± 13.4 years) without a history of current or chronic pain or any additional exclusion criteria as described for CR patients were recruited from the general community and served as healthy controls for the CR population.

Another cohort of twenty-six healthy volunteers without any systemic medical condition,

subclinical electrodiagnostic test findings or a history of hand, arm or neck symptoms served to match the CTS group (18 female; mean age 47.7 ± 17.6 years).

Questionnaires

The painDETECT questionnaire was originally developed and validated as a screening tool to identify patients with neuropathic pain [20]. It has also been used as a tool to document self-reported somatosensory profiles in patients with lumbar radiculopathy/radicular pain [21], in patients with diabetic neuropathy and postherpetic neuralgia [22], and in patients with unilateral peripheral nerve injury [23]. The painDETECT consists of one item relating to temporal pain characteristics, one item relating to spatial pain characteristics and seven sensory descriptor items. The descriptor items are weighted from 0 to 5 with 0 indicating the person does not experience the sensation in question, whereas 5 indicates that the person does experience the sensation very strongly. The painDETECT classifies patients into three groups. A score of 0-12 indicates a neuropathic component is unlikely, a score of 13-18 is an unclear or ambiguous result and a score ≥ 19 indicates a likely neuropathic component [20].

Quantitative Sensory Testing

The QST protocol of the German Research Network on Neuropathic Pain (DFNS) [24] was used by both investigators (AS, BT), who had received training in the conduct of this

standardised protocol. A recent analysis of heterogeneity has shown that QST results between centres are comparable if the investigators are well trained [25].

Thermal tests were performed with a thermotester at a baseline temperature of 32° Celsius (Somedic, Sweden, thermode size 25x50mm). Cold (CDT) and warm (WDT) detection thresholds were measured in triplicate and the mean used for analysis. The thermal sensory limen (TSL) procedure involved the detection of alternating warm and cold stimuli and the number of paradoxical heat sensations (PHS) during this procedure was recorded. Cold (CPT) and heat pain thresholds (HPT) were measured in triplicate and the average was used for analysis. All thresholds were recorded with ramped stimuli (1° Celsius/second) and thresholds were determined by participants pressing a button. Mechanical detection thresholds (MDT) were measured with von Frey hairs (Optihair, Marstock Nervtest, Germany), using the geometric mean of five series of descending and ascending stimuli. Mechanical pain thresholds (MPT) were examined with weighted pinprick stimulators (MRC Systems, Germany) recording the geometric mean of five series of ascending and descending stimulus intensities. Mechanical pain sensitivity (MPS) was evaluated with the same set of pinprick stimulators applied five times in a balanced order while the patients were asked to rate the evoked pain on a numerical pain rating scale from 0-100 (no pain to most intense pain imaginable). Intermingled with the pinprick stimulations were stimulations with a cotton wisp, a cotton wool tip and a standardised brush (Somedic, Sweden) to determine the presence of mechanical allodynia. Windup ratio (WUR) was determined by the pain rating on

a numerical pain rating scale from 0-100 evoked by a single stimulation with a 256mN pinprick stimulator followed by the pain evoked by a train of 10 stimulations (1/sec, within the same 1 cm²). This was repeated five times and WUR was expressed as the ratio of the mean pain rating of trains divided by the mean pain rating to single stimuli. Vibration detection thresholds (VDT) were measured with a Rydel Seiffer tuning fork (64 Hz, 8/8 scale) using the mean of three measurements. Pressure pain thresholds (PPT) were determined with a manual algometer (Wagner Instruments, USA) or digital algometer (Somedic, Sweden) with a probe area of 1cm² using the mean of three repetitions (ascending ramp of 50kPa/s). Further information about this standardised protocol can be found elsewhere [24]. In order to achieve normal distribution, raw QST values (except for CPT, HPT and VDT) were log-transformed. A small constant of 0.1 was added to the MPS to avoid loss of zero rating values [24]. All values except PHS and DMA were z-transformed, a standardisation method where each individual value is scaled to a healthy control group with a mean = 0 and a standard deviation = 1. Values below zero indicate loss of function (i.e. hypesthesia or hypoalgesia), values above zero indicate gain of function (i.e. hyperesthesia or hyperalgesia).

For patients with CR, QST was performed in the main area of pain as indicated by the patient. VDT was measured over bony prominences unless the main pain area did not exhibit a bony surface. In that case, VDT measures were obtained over soft tissue (n = 11). Patients

indicated eight different body regions as their main pain area [15]. In addition, QST was performed in the dermatomal area of sensory loss as determined during clinical examination (C6 (n = 11) or C7). Age and gender matched DFNS healthy control data were used for the analysis of QST data obtained in the C7 dermatome (dorsum hand) [26] and maximal pain area [27]. Since no normative data is available for the C6 dermatome (thenar eminence), QST reference data from this body region were obtained from the recruited healthy control group.

For patients with CTS and matched controls, QST measurements were taken in the median nerve innervation territory of the hand (palmar side of the distal end of the 2nd metacarpal for VDT, thenar muscle for PPT, palmar side of the index finger for all other parameters). In CTS, this innervation territory also coincided with the most painful area. QST values were z-transformed to matched healthy controls instead of DFNS reference values (currently only available for dorsum of the hand), as it has been shown that significant differences appear between palmar and dorsal hand testing in healthy subjects [28].

Data Analysis

Z-scores of QST parameters were compared between patients with CTS and a) patients with CR in their main pain area and b) patients with CR in their dermatome, applying generalized linear models with the QST parameter as a dependent variable, and CR/CTS as fixed effect,

corrected for the duration of symptoms. Since z-transformation corrects for gender and age differences, these were not taken into account for the model. QST z-values have been shown to be normally distributed [29], thus parametric tests were used. Presence or absence of PHS and DMA were compared using chi-squared tests. Significance level was set at $p < 0.05$.

PainDETECT items were compared between CTS and CR in generalized linear models with the painDETECT item as a dependent variable, and CR/CTS as fixed effect, corrected for gender, age and duration of symptoms. Parametric tests were used, as the painDETECT has been shown to follow nearly normal distributions [30]. Frequency of patients with likely, unlikely or possible neuropathic pain as categorized by the painDETECT score were compared with a chi-squared test.

We also compared the mean QST values of CTS and CR patients to the expected values of a healthy population. Resulting from the definition of z-values, an ideal healthy population has a mean z-value=0 and a standard deviation=1 (z-test). This procedure was applied to all 11 normally distributed QST parameters and for a) patients with CTS, b) patients with CR assessed in their main pain area and c) patients with CR assessed in their affected dermatome. Since testing against ideal populations is prone to producing false positive results, we applied a strictly conservative alpha-level of $p < 0.001$.

We also used our recently developed algorithm [31, 32], that allocates each patient into one of four sensory phenotypes: a) loss of thermal and mechanical detection ('sensory loss'), b) intact sensory function, often combined with thermal hyperalgesia or allodynia ('thermal

hyperalgesia'), c) loss of thermal detection, but not mechanical detection, accompanied by mechanical hyperalgesia or allodynia ('mechanical hyperalgesia'), and d) a mostly normal sensory profile that resembles the profile of healthy subjects ('healthy sensory profile')[31] .

The deterministic version of the algorithm was used, in which each patient is sorted to one phenotype and no mixed phenotypes are possible. Chi-squared tests were used to compare the frequency of each phenotype between CTS and CR dermatome and CTS and CR main pain area.

Results

Demographic and clinical Variables

Patients with CTS were significantly older, more frequently female, had lower baseline pain intensity and longer duration of symptoms compared to patients with CR (Table 1).

Medication intake was similar between groups apart from a slightly more frequent use of antiepileptics and strong opioids in patients with CR.

[Table 1 near here]

QST Profile

Comparison between Patients with CTS and CR

QST profiles of patients with CTS and CR assessed in the main pain area did not differ in pain and detection thresholds except for VDTs, which were significantly lower in CR ($p < 0.001$) (Table 2, Figure 1, Appendix 1). When comparing the QST profiles of patients with CTS to those of patients with CR in the affected dermatome, results were again comparable apart from a significant hypoalgesia to deep pressure pain in patients with CR ($p < 0.001$) (Table 2, Figure 1). Dynamic mechanical allodynia was not frequent in patients with CTS ($n = 0$) and CR ($n = 1$ patient with DMA in both main pain area and dermatome). Similarly, paradoxical heat sensations were rare in patients with CTS ($n = 4$) and CR ($n = 0$ in dermatome, $n = 1$ in maximal pain area).

[Table 2 and Figure 1 near here]

Comparison to healthy control Subjects

Both patients with CTS and CR presented with a significant loss of function in thermal and mechanical detection in the main pain area and dermatome compared to the healthy population ($p < 0.001$), except for CDT in the main pain area in patients with CR (Table 2, Figure 1). Patients with CTS additionally showed significant hypoalgesia to heat ($p < 0.001$), whereas patients with CR demonstrated significant hypoalgesia to painful mechanical stimuli (PPT, MPT, MPS) in the dermatome ($p < 0.001$), and significant hyperalgesia to pinprick stimuli (MPT $p < 0.001$) in the most painful area (Table 2, Figure 1).

Frequency of sensory Phenotypes

The frequency of sensory phenotypes between patients with CTS and patients with CR did not differ in the main pain area ($p = 0.834$, Table 3). In the dermatome, the phenotype ‘sensory loss’ occurred more frequently in patients with CR compared to patients with CTS ($p = 0.029$).

[Table 3 near here]

Pain-detect Profile

The majority of patients with CTS (66%) reported a score of <13 on painDETECT, indicating that the presence of neuropathic pain was unlikely (Table 4). For 24% of patients with CTS, a neuropathic pain component was unclear and 10% were classified as having a likely neuropathic pain component. In contrast, only two patients with CR (9%) were classified as having unlikely neuropathic pain; for 61% the classification was unclear and 30% were classified as having likely neuropathic pain. Patients with CR reported significantly more severe pain attacks ($p = 0.009$) and pain evoked by slight pressure ($p = 0.002$) compared to patients with CTS (Figure 2, Table 4).

[Table 4 and Figure 2 near here]

Discussion

The study was set out to explore differences in sensory profiles and self-reported symptoms between patients with a distal (CTS) and proximal entrapment neuropathy (CR). QST findings revealed largely comparable phenotypes between proximal and distal entrapment neuropathies, apart from a greater loss of vibration sense in the maximal pain area and decreased pressure sensitivity in the dermatome in patients with CR. Sensory profile clustering demonstrated that a higher proportion of patients with CR have ‘sensory loss’. In contrast, the self-reported pain profile differed between groups with patients with CR reporting more severe pain attacks and pain evoked by light pressure. Patients with CR also had a higher prevalence of likely neuropathic pain as determined with the painDETECT.

Loss of function was largely comparable between the two entrapment neuropathies, as apparent for most QST parameters as well as the self-reported numbness. The greater loss of vibration sense in the main pain area of patients with CR may be attributed to the more frequent measurement over soft tissues rather than bone (48% vs 0% in CTS) [15].

Differences in mechanical impedance of these tissues [33] likely explain the inflated VDT measurements in CR. Interestingly, the cluster analysis revealed a higher prevalence of ‘sensory loss’ in patients with CR than CTS. These findings are consistent with a predominant ‘sensory loss’ phenotype found in patients with lumbar radiculopathy [32].

While no major differences were apparent for individual detection thresholds between the two entrapment neuropathies, both groups had significant loss of function compared to

healthy controls as previously reported [5, 15, 34, 35]. The dominant characteristic of ‘sensory loss’ and numbness in both patient groups is in line with patient and experimental studies identifying demyelination and axon degeneration in both distal and more proximal entrapment neuropathies [5, 36, 37].

Despite comparable pain thresholds in QST, patients with CR reported higher pain intensities and more patients were classified by painDETECT as having neuropathic pain. In addition, patients with CR experienced more severe pain attacks and pain evoked by slight pressure.

Previous studies using cluster analyses revealed a similar self-assessed sensory profile of severe painful attacks and pressure-induced pain in patients with lumbar radiculopathy [21, 22]. It is difficult to draw firm conclusions about potential pathomechanisms responsible for this pattern that seems more pronounced in patients with proximal entrapment neuropathies.

It is however consistent with a previously reported potentiated neuroinflammation at the level of the dorsal root ganglia following proximal nerve injury [8, 9]. Neuroinflammation has been strongly implicated with axonal ectopic activity and neuropathic pain behaviour in rodents [38], and may explain the heightened pain experience in patients with CR. Another likely explanation is the presence of deafferentation pain caused by a lack of peripheral input on second order spinal neurons [12]. The disrupted connection between the primary afferent cell body and the second order neuron in CR may lead to substantial adaptations within the spinal sensory circuitries [12]. Deafferentation pain is often resistant to peripherally acting pain medications such as topical lidocaine or non-steroidal anti-inflammatories [39], but may

be influenced by centrally acting drugs such as antidepressants or opioids, which are not usually prescribed in patients with CTS, but have shown benefit in patients with CR [39]. As such, deafferentation pain might explain the higher levels of spontaneous pain associated with a predominant loss of function phenotype in patients with CR. Alternatively, an increased expression of voltage-gated sodium channels at demyelinated sites with subsequent axonal hyperexcitability has also been suggested to underlie painful attacks [40]. Whether such changes are more likely to happen in peripheral rather than centrally projecting axons remains to be investigated. Of note, more patients with CR were prescribed antiepileptics, which produce a frequency-dependent voltage-gated sodium channel block.

Treatment stratification using QST and self-reported sensory profiling has shown promising results in the pharmacological management of neuropathic pain [41, 42, 43, 44, 45, 46]. The here identified differences in self-reported sensory profiling in patients with distal and proximal entrapment neuropathies suggest the need for distinct pharmacological treatment approaches. Future research is required to evaluate the benefit of treatment stratification using sensory profiling in patients with different entrapment neuropathies.

Responses to the painDETECT matched the QST findings in patients with CTS. This was however not the case for patients with CR with respect to the item ‘pain evoked by slight pressure’, which aims to reflect similar mechanisms as the PPT. This discordance might be

attributed to several factors. Firstly, the increased pain medication in patients with CR may have concealed a potential hyperalgesia. Secondly, the heterogeneity of pressure pain sensitivity [15] may have washed out any effects at a group level. Thirdly, QST is limited both spatially and temporally. The increased severity of pain attacks in patients with CR may point towards spontaneous pain, which cannot easily be depicted with QST.

Study Limitations

The QST data were collected in different centers, which may have influenced the results.

Given that both investigators (AS and BT) were trained by the DFNS and strictly followed the standardised QST protocol, differences in data quality should be minimal. The comparability of QST collected in different locations is further supported by homogenous results amongst different centres [47].

Antiepileptic and strong opioid use was slightly more frequent in patients with CR and could have influenced painDETECT and QST measurements. However, only a minority of patients took these medications (~20%) and medication has not been associated with relevant differences in sensory phenotypes in previous studies [23, 32].

The incidence of cervical radiculopathy is low [48], which makes sampling a large population highly challenging (464 patients clinically examined to include 23 with CR).

Rather than relaxing the inclusion criteria and risking to include patients with radicular pain in the absence of radiculopathy, we decided to include a smaller but homogenous group of

patients. Our study is a post-hoc analysis of two published cohorts of exploratory character.

This makes any form of sample size or power analysis either unethical (post-hoc justification of existing sample sizes) or bad statistical practice (post-hoc power analyses) [49].

Conclusions

This study demonstrates similarities in QST profiles in patients with distal and proximal entrapment neuropathies, which are dominated by loss of function in both patient populations. However, self-reported pain experience differed, as apparent by an increased severity of pain attacks and pressure pain sensitivity in patients with CR. In addition, patients with CR are more often categorized as having ‘neuropathic pain’. These differences in patients with proximal and distal entrapment neuropathies may point towards some differences in underlying pain mechanisms that may require targeted pharmacological treatment.

Transparency section

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Table 1: Demographics of patients with carpal tunnel syndrome and cervical radiculopathy

Variable	CTS	CR	P
Number of participants	103	23	
Age (years) (SD)	60.2 (12.9)	46.3 (9.6)	< 0.001 [*]
Female sex	63 (61%)	8 (35%)	0.021 [°]
Symptom duration (months)	59.4 (80.3)	7.4 (4.1)	0.002 [*]
Current pain intensity (NRS)	1.4 (2.1)	3.7 (1.2)	< 0.001 [*]
Maximum pain intensity during past 4 weeks (NRS)	5.2 (3.4)	7.2 (2.1)	0.008 [*]
Average pain intensity during past 4 weeks (NRS)	3.4 (2.7)	5.0 (2.0)	0.008 [*]
Participants reporting analgesic drug use [°]	42 (40.8)	14 (60.9)	0.080 [°]
Analgesics (e.g, Paracetamol)	26 (25.2)	4 (17.4)	0.424 [°]
Nonsteroidal anti-inflammatory drugs (NSAIDS)	18 (17.5)	8 (34.8)	0.064 [°]
Topical NSAIDS	4 (3.9)	0	1.000 [*]
Antidepressants			
Tricyclic antidepressants	3 (2.9)	1 (4.4)	0.558 [*]

Serotonin/norepinephrine reuptake inhibitors	5 (4.9)	2 (8.7)	0.467°
Selective Serotonin reuptake inhibitors	0	1 (4.4)	0.183*
Antiepileptics	6 (5.8)	5 (21.8)	0.015°
Opioids			
weak	12 (11.7)	6 (26.1)	0.074°
strong	1 (1.0)	4 (17.4)	0.004*

CTS, Carpal Tunnel Syndrome; CR, Cervical Radiculopathy; NRS, numeric rating scale

Data are presented as n (%), mean (SD). °unpaired t-test, °chi-squared test, *Fisher's exact test, °multiple answers possible.

Table 2: Comparison of QST parameters between patients with carpal tunnel syndrome, patients with cervical radiculopathy and health controls in the main pain area and dermatome

	MPA	Dermatome	MPA	MPA	Dermatome
	CTS / CR	CTS / CR	CTS / healthy	CR / healthy	CR / healthy
	P-value	P-value	P-value	P-value	P-value
CDT	0.055	0.323	<0.001	0.021	<0.001
WDT	0.687	0.563	<0.001	<0.001	<0.001
TSL	0.981	0.710	<0.001	<0.001	<0.001
CPT	0.532	0.800	0.513	0.194	0.015
HPT	0.781	0.979	<0.001	0.128	0.024
PPT	0.058	0.016	0.712	0.002	<0.001
MPT	0.667	0.268	0.302	<0.001	<0.001
MPS	0.274	0.454	0.074	0.113	<0.001
WUR	0.137	0.594	0.540	0.077	0.244
MDT	0.250	0.893	<0.001	<0.001	<0.001
VDT	<0.001	0.065	<0.001	<0.001	<0.001
PHS *	1.000	1.000			
DMA *	0.186	0.186			

CTS, Carpal Tunnel Syndrome; CR, Cervical Radiculopathy; MPA, main pain area. 'z-test (considered significant only if $p < 0.001$), *Fisher's exact test, °chi-squared test, remaining p-values derived from generalized linear models, controlled for duration of symptoms.

Table 3: Frequency of sensory phenotypes in patients with carpal tunnel syndrome and patients with cervical radiculopathy

	CTS	CR MPA	CR dermatome
‘Sensory loss’	25 (24.3%)	5 (21.7%)	12 (52.2%)
‘Thermal hyperalgesia’	21 (20.4%)	6 (26.1%)	5 (21.7%)
‘Mechanical hyperalgesia’	33 (32.0%)	7 (30.4%)	2 (8.7%)
Healthy sensory profile	24 (23.3%)	5 (21.7%)	4 (17.4%)

CTS, Carpal Tunnel Syndrome; CR, Cervical Radiculopathy. MPA, main pain area; chi-squared test CTS/CR main pain area $p = 0.834$, CTS/CR dermatome $p = 0.029$

Table 4. painDETECT profiles of patients with carpal tunnel syndrome and patients with cervical radiculopathy. Data are presented as mean (SD) or n (%) as indicated.

	CTS	CR	
	(n = 103)	(n = 23)	<i>P</i>
painDETECT score	11.3 ($\pm$ 4.8)	17.2 ($\pm$ 5.2)	0.001
Neuropathic pain unlikely (n)	68 (66%)	2 (9%)	
Unclear (n)	24 (24%)	14 (61%)	
Neuropathic pain likely (n)	10 (10%)	7 (30%)	
Burning quality	1.1 (1.7)	2.5 (1.5)	
Tingling quality	3.1 (1.2)	3.3 (1.2)	
Pain attacks	1.3 (1.9)	3.0 (1.5)	0.009
Numbness	3.0 (1.5)	3.3 (1.1)	
Evoked pain: light touch	0.2 (0.8)	1.0 (1.1)	
Evoked pain: cold / heat	0.3 (1.0)	1.0 (1.3)	
Evoked pain: pressure	0.5 (1.1)	2.0 (1.4)	0.002
CTS, Carpal Tunnel Syndrome; CR, Cervical Radiculopathy			

Figure legends:

Fig. 1 Sensory profiles of patients with carpal tunnel syndrome and patients with cervical radiculopathy. Data are presented as z-scores and standard errors.

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; DMA: dynamic mechanical allodynia; PHS: paradoxical heat sensation.

Fig. 2 Self-reported sensory profiles of patients with carpal tunnel syndrome and patients with cervical radiculopathy, based on responses to the painDETECT. Data are presented as mean and standard error.