Somatosensory and clinical profiles of patients with spine-related and clinical framework-based neck-arm pain

Authors

Camilla Kapitza, PT, MSc, Hochschule Osnabrueck, University of Applied Sciences, Faculty of Business, Management and Social Sciences, Osnabrueck, Germany
Universität zu Lübeck, Institute of Health Sciences, Department of Physiotherapy, Pain and Exercise Research Luebeck (P.E.R.L), Luebeck, Germany

Nikolaus Ballenberger PT, PhD, Hochschule Osnabrueck, University of Applied Sciences, Faculty of Business, Management and Social Sciences, Osnabrueck, Germany

Kerstin Luedtke, PT, PhD, Universität zu Luebeck, Institute of Health Sciences, Department of Physiotherapy, Pain and Exercise Research Luebeck (P.E.R.L), Luebeck, Germany

Annina B Schmid PT, PhD, Nuffield Department of Clinical Neurosciences, Oxford University, John Radcliffe Hospital, Headley Way, Oxford, UK

Brigitte Tampin PT, PhD, Department of Physiotherapy, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia
Curtin School of Allied Health, Curtin University, Perth, Western Australia, Australia
Hochschule Osnabrueck, University of Applied Sciences, Faculty of Business, Management and Social Sciences, Osnabrueck, Germany

Number of pages: 30

Number of tables: 2 (one additional table as supplementary material)

Number of figures: 6

Data availability statement: The original dataset will be made available upon reasonable request

Address all correspondence to Camilla Kapitza:

Blumenthalstr 32, 49076 Osnabrück, Germany

E-Mail: c.kapitza@hs-osnabrueck.de (CK)

+49541 969 3490

+49541 969 3489

Abstract

Spine-related neck-arm pain is heterogeneous and may present on a spectrum between nociceptive and neuropathic pain. A recently developed mechanism-based clinical framework for spine-related pain distinguishes between spinally referred pain without neurological deficits (somatic referred pain, heightened nerve mechanosensitivity, radicular pain), with neurological deficits (radiculopathy) and mixed-pain presentations. This study investigated differences in somatosensory and clinical profiles of patients with unilateral spine-related neck-arm pain grouped according to the clinical framework. Patients (n = 113) underwent a clinical examination, after which they were classified into a subgroup(s). They completed questionnaires to assess function (Neck Disability Index), psychosocial factors (Tampa Scale of Kinesiophobia, Pain Catastrophizing Scale, Depression, anxiety and stress scale), neuropathic pain (Douleur Neuropathique 4) and central sensitization features (Central Sensitization Inventory). Standardized quantitative sensory testing (QST) was performed over the maximal-pain-area and contralateral side. The radiculopathy group showed a significant loss of function on the symptomatic versus asymptomatic side in cold ($p=0.024$) and warm detection ($p=0.004$), thermal sensory limen ($p=0.001$), mechanical detection ($p=0.001$), increased wind-up ratio ($p=0.014$) and cold hyperalgesia ($p=0.049$). No other subgroup showed significant side differences in QST parameters. Symptom descriptors such as burning ($p<0.031$), tingling ($p<0.018$), pins and needles ($p<0.031$), numbness ($p<0.016$), spontaneous pain ($p<0.001$) and electric pain/shock ($p<0.026$) were more common in the radicular/radiculopathy groups compared to the somatic/mechanosensitivity groups. There were no differences in psychosocial parameters between groups. The phenotypic profiles support the construct of the clinical examination and patient classification and its application in clinical practice according to a clinical framework for spine-related pain.

1.0 Introduction

Neck pain is a common musculoskeletal condition[2;62]. In some patients with neck pain, symptoms may also radiate into the arm due to various underlying pain mechanisms[34;55;56]. This is referred to as spine-related neck-arm pain which is an umbrella term for different clinical presentations[51]. Based on the recommended terminology from the Neuropathic Pain Special Interest Group (NeuPSIG)[51], people with spine-related limb pain may present on a spectrum between somatic referred pain, which is referred to as a nociceptive pain, and painful radiculopathy which is considered as dominantly neuropathic pain[47;51]. Nociceptive neck-arm pain is caused by an activation of nociceptors in target tissues such as muscles, joints, ligaments, fascia or tendons[5;51]. Activation of nociceptors in connective tissues surrounding nerves may cause a clinical presentation of heightened nerve mechanosensitivity which is considered to reflect a specific type of somatic referred pain[5;11].

Neuropathic neck-arm pain is defined as pain occurring as a direct consequence of a lesion or disease affecting the somatosensory nervous system in the neck[13;51]. In the context of neuropathic pain, terms such as radiculopathy and radicular pain are frequently used interchangeably but represent distinct concepts[5;51]. Radiculopathy pertains to dermatomal sensory or myotomal motor deficits (loss of function) resulting from a conduction block or conduction slowing caused by a lesion or disease of a nerve root or dorsal root ganglia[5;51]. In contrast, radicular pain is associated with ectopic discharges and hyperexcitability of a dorsal root or it’s ganglion, caused e.g. by inflammation, ischaemia or mechanical deformation[5;51]. Whereas these presentations can occur in isolation, mixed presentations are very common[23;54] (e.g., painful radiculopathy combining radicular pain and radiculopathy). A recently developed clinical framework for spine-related pain distinguishes

between spinally referred pain without neurological deficits (somatic referred pain, heightened nerve mechanosensitivity, radicular pain) and with neurological deficits (radiculopathy) as well as mixed pain presentations[47]. The clinical framework showed substantial inter- and intra-tester reliability in patients with spine-related neck arm pain[23]. Patient subgrouping according to the clinical framework may assist to standardize participant selection in clinical trials and targeted management[29;46]. A recent review emphasized that the use of heterogeneous populations creates conflicting/non-comparable results between trials[29]. In contrast, implementing valid subgroup-based targeted management was shown to be more effective than standard/non-targeted therapies[25;29;45;61].

However, it has not yet been established if the construct of the subgrouping patients in the clinical framework based on clinical examination and decision making is valid in terms of phenotypic profiles that can be determined with objective and valid measures. For example, the radiculopathy group is the only group defined by a loss of function which can be identified clinically, but is this indeed the subgroup demonstrating loss of function, using validated assessments of nerve fiber function, such as quantitative sensory testing (QST)[43]?

Thus, the study aims were:

I) to investigate differences in somatosensory and clinical profiles of patients with spine-related neck arm pain classified according to the clinical framework.

II) to investigate if the clinical subgrouping is substantiated by the phenotypic profiles of each subgroup.

2.0 Methods

This cross-sectional study was conducted from July 2020 until November 2023. The study protocol received approval from the Ethic Committee at the University of Applied Sciences Osnabrueck and adhered to the ethical guidelines of the Declaration of Helsinki[1] and all patients provided informed written consent prior to participating.

2.1 Study population

Patients aged 18-75 years with unilateral spine-related neck-arm pain with pain intensity > 2/10 on a numeric rating scale (NRS) were consecutively recruited from physiotherapy and medical clinics in Osnabrueck (Germany). Each potential patient underwent a screening interview via telephone to assess their eligibility (Figure 1). The neck-arm pain needed to be provoked by movements or static positions of the cervical spine as determined by patients' self-report. Exclusion criteria were previous spinal surgery, current or previous systemic medical conditions (e.g. rheumatoid arthritis, diabetes, thyroid disease), central nervous system disorder, complex regional pain syndrome, peripheral vascular disease, blood clotting disorder, pregnancy, psychiatric disease as well as the presence of non spine-related musculoskeletal shoulder, elbow or hand disorders in the last three months. All patients who met eligibility on screening interview were invited to take part in the study. If any exclusion criteria were revealed during the clinical examination, patients were excluded (Fig.1).

2.2 Clinical examination: classification and clinical profiles

A comprehensive clinical interview was performed by one examiner (CK) who has a Master's degree in Orthopedic Manual Physiotherapy (OMPT) and 22 years work experience in musculoskeletal therapy. The clinical interview included a body chart with patient self-reported symptom descriptors. In addition, patients were asked by the examiner if their pain can occur spontaneously. The pain location, pain intensity measured on a 0-10 NRS (average

during the last 4 weeks), pain behavior (aggravating and easing factors) and symptom history[22] were recorded.

Comorbidities, body mass index (BMI), medications and sleep behavior (numeric rating scale, 0 = good sleep; 10 = poor sleep were documented. The imaging data were not systematically collected and were not relevant for the classification process. The physical examination included musculoskeletal tests e.g. active and passive cervical spine movements, Spurling's test and muscle palpation (supplement S1: clinical examination form), which have shown at least moderate reliability[14;18;30;31;63]. In addition, we performed a bedside neurological examination[48] including reflex testing (absent/ reduced/ normal/ increased), myotomal strength testing[24;48], sensory testing of light touch (cotton wool)[48] and pin prick sensation (neurotip) in dermatomes[42]. Nerve mechanosensitivity was examined with upper limb neurodynamic tests (ULNTs)[48]. The ULNT 1 was performed first, followed by ULNT 2a, 2b and 3. If one test was confirmed as positive, no further ULNT tests were undertaken. ULNTs were interpreted as positive when they at least partially reproduced the person's pain and the pain was altered with structural differentiation[37]. After the clinical examination, patients were categorized by the clinician into the clinical framework's subgroups (Fig. 1). The clinical framework differentiates between (i) somatic referred pain, where tests for neurological integrity and nerve mechanosensitivity are normal, (ii) nerve mechanosensitivity, where the neurological integrity is normal but neurodynamic tests show the presence of heightened nerve mechanosensitivity, (iii) radicular pain where the pain distribution (areas reminiscent of but not necessarily identical to dermatomes) and pain descriptors (burning, pins and needles, shooting pain, electric shock, cold pain etc.) strongly suggest the involvement of a nerve root[51]. Neurological integrity is preserved[51]. The final subgroup (iv) defines radiculopathy, where there is a myotomal and/or dermatomal neuroanatomically plausible neurological deficit[51]. Dermatomal distribution was defined as according to the dermatomes described by Hansen et al.[19], allowing for some slight overlap. Further details

on patient assessment and which test results were used for the classification process are outlined in our previous study[23]. Since radiculopathy is not defined by pain, it had to be grouped with one of the other clinical subgroups, as all patients experienced pain. Patients could present with mixed presentations[23]. For the statistical analysis, people with a mixed presentation had to be classified into one dominant subgroup.

Clinically, the subgroups further towards the right side of the clinical framework (Fig.1) bear more weight in the clinical decision making. The framework represents the spectrum of spine-related neck arm pain from nociceptive (left side, somatic referred pain) to probable or definite neuropathic pain (right side, radiculopathy). The presence of a radiculopathy potentially requires surgical review (e.g, if there is significant or progressive loss of function). Furthermore, the presence of neuropathic pain (e.g., in radicular pain or radiculopathy) may dictate the use of specific neuropathic pain medications[12]. If a patient had a mixed presentation (including several mechanistic subgroups), we therefore defined the dominant subgroup as the right-most subgroup in the clinical framework. This means that a patient classified with just somatic referred pain does not coexist with any other subgroup, a patient classified with heightened nerve mechanosensitivity coexists with somatic referred pain, a patient classified with radicular pain may coexist with somatic referred pain and/or heightened nerve mechanosensitivity, and a presentation classified as radiculopathy may coexist with one or all other subgroups in different combinations[23].

2.3 Validated questionnaires: clinical profiles and psychosocial parameters

Various questionnaires were used to characterize the symptom descriptor profile and psychosocial parameter of the study population. All questionnaires are well validated and reliable[6;8;15;20;26;33;38;44;60;64] and were completed after clinical examination and classification and before QST testing. The Douleur neuropathique 4 (DN4)[6] is a binary (yes/

no) questionnaire including seven questions for sensory descriptors (burning, painful cold, electric shocks, tingling, pins and needles, numbness, itching) and three tests for sensory examination (hypoesthesia for touch and pinprick and allodynia for brush contact). The cut-off score for likely neuropathic pain is ≥ 4[6].

The Neck Disability Index (NDI)[8;60;65] documented the level of neck related disability. A score of 0-4 indicates no, 5-14 mild, 15-24 moderate, 25-34 severe and ≥ 35 complete disability [21]. The Tampa Scale for Kinesiophobia (TSK-11)[20;44;64] with 11 items evaluated fear of movement and fear of injury or reinjury. Scores range from 11 to 44; a score of ≥ 35 indicates high kinesiophobia[7]. The Depression-Anxiety-Stress-Scale (DASS)[38] examines 21 items, seven for each parameter. The cut-off score for depression is 10, for anxiety 6 and for stress 10. Pain related worrying was determined with the Pain Catastrophizing Scale (PCS)[33]. It contains three subscales: rumination, magnification, and helplessness. A score ≥ 30 represents a clinically significant level of pain related worrying[9;33]. The Central Sensitization Inventory (CSI) [26] is a screening instrument to detect contributions of central pain sensitization, the cut-off score was set at 44 points[26]. However, studies indicated that the CSI seems unsuitable to detect changes in central pain and is rather associated with psychological factors in patients with focal nerve injuries. Therefore, the outcome for central sensitization should be interpreted within this context in this study population[32].

2.4 Quantitative sensory testing (QST): Somatosensory profiles

Standardized QST was performed according to the QST protocol of the German Research Network on Neuropathic Pain (DFNS)[43] by a second examiner who was blinded to the subgroup classification, questionnaire outcomes and medical diagnosis. The examiner had received training in the application of the QST protocol at a DFNS training center. The QST was performed on the same day as the clinical examination. If this was not possible, a second

appointment was made which had to be within 7 days of the clinical examination. QST parameters were taken from the area defined by the tested person as the most painful area and the mirroring asymptomatic contralateral side[17]. The test battery consisted of the following thermal parameters: cold and warm detection thresholds (CDT, WDT), alternating warm and cold stimuli (thermal sensory limen (TSL)) including paradoxical heat sensations (PHS), cold and heat pain thresholds (CPT, HPT). Further parameters were mechanical detection threshold (MDT) and mechanical pain threshold (MPT), mechanical pain sensitivity (MPS) and dynamic mechanical allodynia (DMA), wind-up ratio (WUR), vibration detection threshold (VDT) and pressure pain threshold (PPT).

2.5 Statistical analysis and sample size estimation

We hypothesized to find significant and clinically relevant side differences of QST parameters mainly within the radiculopathy subgroup. Clinical relevance was defined according to effect sizes (cohen's d for paired samples) as follows: 0 to 0.2 no effect, 0.2 to 0.5 small effect, 0.5 to 0.8 moderate effect and > 0.8 large effect[52]. Sample size was calculated for paired t-test with a level of significance of 0,05, a power of 80%. Based on our non-published QST data between sides in 40 persons with spine-related neck-arm pain we assumed an effect size of 0,6 (and correlation of 0,65) between groups. This resulted in a sample size of 24 patients per group to detect differences in QST measures between sides. Sample size was calculated with G-Power (Version: G*Power 3.1.9.4.) Data were analyzed by SPSS Version 27.

All data were analyzed for their normal distribution (Kolmogorov-Smirnov). Not normally distributed QST data were log transformed (expect CPT, HPT and VDT) before statistical analysis[43]. Mean values, mean differences, standard deviations and 95% confidence intervals of the side differences were calculated for the asymptomatic and symptomatic side.

QST data were analyzed between sides within each group using paired t-tests and the related effect sizes. Significance was accepted at $p < 0.05$ for all analyses.

The normally distributed data is shown as mean value and standard deviation, the non-normally distributed data via median and 25^{th} and 75^{th} percentile. The parameters age, sleep quality and NDI were normally distributed and compared via one-way ANOVA including LSD post-hoc test. Pain intensity, TSK-11, symptom duration (weeks), PCS, CSI, DASS, DN4, BMI were not normally distributed and compared with Kruskal Wallis or chi-squared tests. Since a mixed neck-arm pain presentation can include two or up to four subgroups per patient, the mix of pain presentation was determined and the number of patients presenting in a specific mixed presentation was calculated. Data of the mixed pain group was analyzed descriptively and not used for any comparisons. The number of patients and percentage frequency of self-reported symptom descriptors and symptom descriptors reported in the DN4 questionnaire were calculated and the chi-squared test was used to determine significant differences between subgroups.

3.0 Results

3.1 Patient subgroups

One hundred and thirteen people participated in the study. The percentage frequency of dominant subgroup allocation was distributed as follows (Fig. 1): somatic referred pain 22.1%, heightened nerve mechanosensitivity 23.9 %, radicular pain 27.4 % and radiculopathy 26.5 %. A mixed pain presentation was observed in 77.0 % of patients (Table 1). The most frequent mixed pain presentation was somatic referred pain with heightened nerve mechanosensitivity (n = 27). Radicular pain occurred just as frequently with (n = 19) as without radiculopathy (n = 19).

3.2 Patient demographics, psychosocial parameter and clinical profiles

There were significant differences in pain duration between groups (Table 2). The radicular pain and radiculopathy group had significantly shorter pain duration compared to the somatic referred ($p=0.034$) and nerve mechanosensitivity groups ($p<0.001$). In the somatic referred pain group, 88% of patients had pain for longer than three months, as did 92.6 % in the heightened nerve mechanosensitivity group, 66.7% in the radicular pain and 67.7% of patients in the radiculopathy group. There were no statistically significant differences between groups in the measures of pain intensity, sleep quality, pain related worrying, fear avoidance behavior, anxiety, depression and stress scores and CSI. None of these measures achieved a clinically significant cut-off. The NDI was also comparable and represented an average mild disability in all groups. Regarding medication intake, patients in the somatic referred pain group took NSAIDs significantly more often than those in the radicular pain and radiculopathy group ($p=0.007$).

There was no significant difference in the DN4 questionnaire score between the somatic referred pain and heightened nerve mechanosensitivity group ($p=0.707$). Patients in the radicular pain and radiculopathy group had significantly higher scores compared to patients in the other two groups ($p=<0.001$). Patients in the radiculopathy group had a significantly higher score than the radicular pain group ($p=0.011$) and the radiculopathy group was the only group meeting the mean cut-off score of 4 in the DN4, indicating likely neuropathic pain [6]. In the somatic referred pain group three persons out of 25 (12%) had a score ≥ 4, in the heightened nerve mechanosensitivity group two out of 27 (7.4%), in the radicular pain group 14 out of 31 (45.2%) and in the radiculopathy group 20 out of 30 (66.7%).

Patients in the somatic referred pain (76%, $p = 0{,}001$) and nerve mechanosensitivity group (92.6%, $p = 0{,}001$) indicated more frequently the neck as their main pain area, while the arm

was indicated more frequently as the main pain area in patients with radicular pain (58.1%, p=0.001) and radiculopathy (70%, p=0.001) (Figure 2). With regards to pain distribution, a classical dermatomal [19] distribution [19] was documented in 8% of patients in the somatic referred pain group, in none of the patients with heightened nerve mechanosensitivity, in 19.4% of patients with radicular pain and in 16.7% of patients in the radiculopathy group. A positive ULNT was present in 61.3% of patients in the radicular pain group and in 66.7% of patients in the radiculopathy group; there was no significant difference between these two groups (Table 2). Spurling's test was positive in 90% of patients in the radiculopathy group and reproduced significantly more often patients' pain than in all other groups (p=0.001). There were no statistically significant differences between groups in the presence of restricted and painful active and passive movements or pain reproduction with muscle palpation.

3.4 Self-reported symptom descriptors (during interview)

Symptom descriptors such as spontaneous pain (p=0.001), numbness (p<0.018), tingling (p<0.001), electric pain (p<0.002), and pins and needles (p=0.002) were mentioned significantly more frequently in the radicular pain and radiculopathy groups than in the other groups (Figure 3). Pins and needles were significantly more often mentioned in the radicular pain group than in all other groups (p=0.002). Other self-reported symptom descriptors showed no significant differences between subgroups.

3.5 DN4 neuropathic symptom descriptors

The frequency of chosen sensory descriptors and physical examination findings of the DN4 are shown in Figure 4. The somatic referred pain group and the heightened nerve mechanosensitivity group did not differ in the frequency of their symptom descriptors except for numbness, the latter being more common in the nerve mechanosensitivity group with 25.9% (p=0.038). All symptom descriptors were present in less than 30% of patients in both

groups, except for tingling in the nerve mechanosensitivity group (33.3%). The radicular pain and radiculopathy group did not differ in their reported frequency of burning, tingling, pins and needles and numbness, but electric shock was significantly more common in the radiculopathy group (50%) compared to the radicular group (22.6%) ($p=0.026$) and all others ($p=0.012$). Itching was only reported by patients in the radicular group (9.7%). The radicular group reported more frequently the sensation of burning (45.2%), tingling (64.5%) and numbness (48.4%) compared to the somatic group ($p<0.020$) and more often burning and tingling compared to nerve mechanosensitivity group ($p<0.031$), as well as more frequently the sensation of pins and needles (45.2%) compared to the nerve mechanosensitivity group ($p=0.031$). The radiculopathy group reported tingling (66.6%) and pins and needles (53.3%) significantly more often compared to the somatic ($p<0.027$) and nerve mechanosensitivity group ($p<0.012$). Painful cold sensation was reported in ≤ 20% of patients in each group and the frequency did not differ between groups. Regarding physical sensory examination findings of the DN4, the radiculopathy group demonstrated hypoesthesia to touch (63.3%) and pinprick (53.3%) significantly more often compared to the somatic referred pain group ($p<0.004$), the nerve mechanosensitivity group ($p=0.004$) and the radicular pain group ($p<0.013$). Of those patients who reported numbness on the DN4 (Fig. 3), there was no confirmation of measured hypoesthesia to touch in the physical sensory examination in the somatic referred pain group (0%), but in 3.7% of the nerve mechanosensitivity group, in 9.7% of the radicular pain group and in 36.7% of the radiculopathy group. Painful brushing occurred only in the radiculopathy group (3.3%).

3.6 Somatosensory profiles

There were no differences of QST measurements in the maximal pain area between the symptomatic and asymptomatic sides in the somatic referred pain group, heightened nerve mechanosensitivity and radicular pain group (Figure 5 and 6, Supplement 2). The

radiculopathy group showed significantly reduced cold ($p = 0.024$) and warm detection ($p = 0.004$), TSL ($p = 0.001$), as well as mechanical detection sense ($p = 0.001$) on the symptomatic side compared to the asymptomatic side. Additionally, there was a significant hypersensitivity to cold ($p = 0.049$) and a higher wind-up ratio ($p = 0.014$) on the symptomatic side compared to the asymptomatic side in this group (Figure 5 and 6, Supplement 2). In the somatic referred pain group, PHS was reported by five (20%), in the heightened nerve mechanosensitivity group by three (11.1%), in the radicular pain group by one (3.2%) and in the radiculopathy group by six (20%) patients. DMA was not reported in any group.

4.0 Discussion

This study demonstrated that patients with spine-related neck-arm pain could be classified into different subgroups according to a clinical framework of spine-related pain with most patients presenting as a mixed phenotype and roughly equal distribution into the dominant subgroups. We identified phenotypic plausible differences among the clinically established subgroups in validated measures (QST, DN4). While all groups were comparable in their psychosocial parameters and most physical examinations related to movement, their QST somatosensory and symptom descriptor profiles differed. Only the radiculopathy group showed a significant loss of function on the symptomatic side in thermal and mechanical detection and cold hyperalgesia. All other groups did not show any differences in somatosensory profiles between sides. Neuropathic symptom descriptors measured by DN4, such as burning, tingling, pins and needles, numbness and electric pain/shock were far more common in the radicular/radiculopathy groups compared to the somatic/mechanosensitivity groups. This finding confirms the appropriateness of the self-reported descriptors which were used for classification. Of note, symptom descriptors between the radicular and radiculopathy group differed with more frequent self-report of pins and needles in the radicular group and itching being only present in the radicular group, whereby the radiculopathy group was characterized by more frequent electric shock type pain. These findings highlight differences in somatosensory and symptom descriptor profiles of patients with spine-related neck-arm pain and support the construct of using a clinical examination embedded within a clinical reasoning framework for subgrouping.

Using blinded, validated measures, the radiculopathy subgroup showed increased QST thermal and mechanical detection thresholds in the main pain area, indicating a loss of small and large sensory fiber function and cold hypersensitivity. These findings are consistent with previous findings in patients with cervical[55;56;58] and lumbar radiculopathy[3;16;57]. The

documented loss of function aligns with the definition of radiculopathy[51] and supports the clinical judgement in subgrouping these patients. The DN4 also identified more frequent hypoesthesia to pin prick and touch in radiculopathy compared to all other groups. Our findings support the notion that bedside sensory testing is a valid tool for the assessment of sensory alterations, as shown in numerous studies[27;41;42;66] and endorse the construct of the clinical examination and decision making in classifying patients into the radiculopathy subgroup.

No other groups showed significant somatosensory differences between sides in the maximal pain area. While numerous studies have investigated QST profiles in patients with neck-arm pain[34;35;39;58], only one study applied QST in the patients' main pain area[39] . In the latter study, patients with neck-arm pain and heightened nerve mechanosensitivity and patients with somatic referred pain did show differences in QST profiles compared to healthy controls, however the study did not assess side differences. We specifically chose not to compare our patients to healthy control data, as side comparison within each group is more sensitive to detect loss or gain of function than a comparison with healthy controls[43] especially when adding the challenge of different tests sites as done here. Furthermore, the side-by-side comparison is the usual clinical approach for assessing sensory aberrations, reflecting daily clinical practice, and excluding confounders like sex, age, psychosocial factors etc.

The painful radiculopathy and radicular pain group demonstrated largely comparable symptom descriptors, however some descriptors seemed to differentiate the groups, which has not been reported before. The presence of electric shocks clearly distinguished the radiculopathy group from the radicular pain group and was the most dominant differentiator. The sensation of itching, which is a typical neuropathic symptom descriptor and a sign of gain

of function due to damage of neurons[40], occurred only in the radicular pain group. However, only a minority of patients in this group (9.7%) reported itching, reducing the differentiating value of this descriptor. Self-reported pins and needles occurred more frequently in the radicular pain group which was not observed in the DN4 data or in a previous study in patients with cervical radicular pain/radiculopathy[55]. Also, the frequency of symptom descriptors was generally higher in the DN4 than on self-report. This discrepancy between unprompted self-reported descriptors and descriptors provided by the questionnaire may be explained by the fact that the DN4 prompts patients towards a range of sensations. These findings suggest that prompting of specific symptom descriptors should be added to interview based self-reported descriptors to not miss valuable information. With respect to physical examination tests, only one assessment differentiated the painful radiculopathy group from all others, i.e. the Spurling's test was most often reproducing symptoms in the painful radiculopathy group. Our results suggest that while the neurological identification of loss of function remains the hallmark of painful radiculopathy, specific symptom descriptors and the Spurling's test may heighten clinical suspicion, although these are not perfect discriminators between painful radiculopathy and radicular pain.

Apart from the dominant loss of function phenotype in the painful radiculopathy group, the clinical profiles seemed to show similarities within the somatic/mechanosensitivity groups versus the radicular/radiculopathy groups. Typical descriptors of neuropathic pain (self-reported and DN4) and a more dermatomal pain distribution were reported more frequently in the radicular/radiculopathy groups. However, it should be noted that the majority of patients with radicular pain/painful radiculopathy still presented with extradermatomal symptoms as previously reported[36]. Symptom distribution in isolation is thus not a strong discriminator. Similarly, the majority of patients in these two groups felt the worst pain in their arm rather

than the neck which is a common presentation of radicular pain and painful radiculopathy[28;59].

The dominant heightened nerve mechanosensitivity subgroup presented more similar symptom descriptors and clinical profiles to somatic referred pain than radicular pain/painful radiculopathy. Of note though, heightened nerve mechanosensitivity was a feature of many mixed pain presentations with 61-67% of patients with radicular pain/painful radiculopathy also demonstrating heightened nerve mechanosensitivity. Historically, ULNTs are often part of diagnostic test clusters for radiculopathy[28;49]. However, our results clearly highlight that ULNTs are not selectively positive in painful cervical radiculopathy. Similar observations were reported in patients with carpal tunnel syndrome[4], where 54% of patients had negative ULNTs despite electrodiagnostically confirmed median nerve injury. The reasons for this discrepancy remain elusive, but it was speculated that a more pronounced sensory loss of function found in patients with negative ULNTs may reduce neural mechanosensitivity of nervi nervorum [50].

There were only a few clinical differences between the somatic referred pain group and the nerve mechanosensitivity group. The somatic referred pain group did report electric pain in the subjective examination, but the nerve mechanosensitivity group did not. However, this difference was no longer present in the DN4 when patients were prompted for symptom descriptors. Numbness on DN4 was reported more frequently in the nerve mechanosensitivity group. Interestingly, comparing the percentage of patients documenting hypoesthesia to touch in the physical examination of DN4, the reported numbness was confirmed upon physical testing for only 3.7% of neural tissue mechanosensitive patients and for none in the somatic referred pain group. Maybe some patients reported symptoms in the DN4 that apply to other body regions than the maximal pain area, or there was a discrepancy between experienced and

measured signs or symptoms, as has been documented for numbness in patients with fibromyalgia[53] or for weakness in patients with spine-related leg pain[10]. The DN4 seemed to be able to discriminate between clinically defined nociceptive and neuropathic pain presentations. Only the radiculopathy group achieved the cut-off score of 4, indicating likely neuropathic pain.

Of note, demographic (sex, age, BMI), psychosocial (PCS, TSK-11, DASS, CSI) and several clinical parameters (pain intensity, sleep quality, NDI) were largely comparable among subgroups and of sub-clinical relevance, suggesting that these may not be strong indicators to inform clinicians about patients' classification. Similarly, further clinical parameters like restricted and painful active and passive cervical movements and muscle palpation were comparable and seem not suitable to differentiate between the subgroups. Our patient groups demonstrated only mild disability and moderate pain intensity with a maximum of 6/10 in the nerve mechanosensitivity group. None of the patients took strong analgesic or medication targeting neuropathic pain. While our patient cohort was limited to patients seen in primary care, it is possible that some clinical measures may differentiate between subgroups in a cohort with higher pain and disability.

Strengths and limitations

The strength of our study lies in the comprehensive clinical examination, the strict group allocation based on recent recommendations and terminology[51], the blinded QST and DN4 assessment, within group QST side comparisons and a robust statistical method with adequate sample sizes. A limitation is that not all patients were examined clinically and via QST on the same day and therefore there could have been potential changes in health conditions between the two assessments. However, of the 46 patients not examined on the same day, there was an average delay of only 1,4 (SD 2.3) days. The clinical group allocation was only classified by

one examiner (CK) and not confirmed by another clinician, however, we have previously shown substantial reliability for the application of the clinical framework in the same cohort[23]. To avoid confounding of our results, we specifically excluded patients with co-existing non-spine-related musculoskeletal conditions, potentially limiting generalizability of our findings to patients with multiple conditions. It remains be investigated whether the clinical framework can equally be applied in patients with co-existing conditions (e.g., classifying each condition separately).

Conclusion

The clinical framework for spine-related pain could readily be applied in a cohort of patients with spine-related neck-arm pain. The clinical judgement on patient subgrouping was substantiated by validated measures demonstrating the differences in somatosensory and symptom descriptor profiles between subgroups. Future studies would have to explore if targeted management towards these subgroups will results in better outcomes for patients with spine-related neck-arm pain.

Acknowledgement

The project was supported by a scholarship from the Hochschule Osnabrueck, University of Applied Sciences and by a research grant from Physio Deutschland. A.B. Schmid is supported by a Wellcome Trust Clinical Career Development Fellowship (222101/Z/20/Z). The funders played no role in the design, conduct, or reporting of this study. The authors report no conflict of interest. We are very grateful to all participants and for the support from our physiotherapy colleagues, especially Christina Krone, Svenja Hardt and Ellen Loock for blinded QST, Florian Avermann for support in artwork, as well as MVZ Hagen a.T.W. especially Andre Halcour and the medical doctors from FOURBs Osnabrueck with recruitment.

References:

[1] World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama 2013;310(20):2191-2194.

[2] Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392(10159):1789-1858.

[3] Andrasinova T, Kalikova E, Kopacik R, Srotova I, Vlckova E, Dusek L, Bednarik J, Adamova B. Evaluation of the Neuropathic Component of Chronic Low Back Pain. Clin J Pain 2019;35(1):7-17.

[4] Baselgia LT, Bennett DL, Silbiger RM, Schmid AB. Negative Neurodynamic Tests Do Not Exclude Neural Dysfunction in Patients With Entrapment Neuropathies. Arch Phys Med Rehabil 2017;98(3):480-486.

[5] Bogduk N. On the definitions and physiology of back pain, referred pain, and radicular pain. Pain 2009;147(1-3):17-19.

[6] Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lanteri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114(1-2):29-36.

[7] Chimenti RL, Post AA, Silbernagel KG, Hadlandsmyth K, Sluka KA, Moseley GL, Rio E. Kinesiophobia Severity Categories and Clinically Meaningful Symptom Change in Persons With Achilles Tendinopathy in a Cross-Sectional Study: Implications for Assessment and Willingness to Exercise. Front Pain Res (Lausanne) 2021;2:739051.

[8] Cramer H, Lauche R, Langhorst J, Dobos GJ, Michalsen A. Validation of the German version of the Neck Disability Index (NDI). BMC Musculoskelet Disord 2014;15:91.

[9] Crombez G, De Paepe AL, Veirman E, Eccleston C, Verleysen G, Van Ryckeghem DML. Let's talk about pain catastrophizing measures: an item content analysis. PeerJ 2020;8:e8643.

[10] Dove L, Baskozos G, Kelly T, Buchanan E, Schmid AB. Prevalence of weakness and factors mediating discrepancy between reported and observed leg weakness in people with sciatica. Eur Spine J 2024.

[11] Elvey RL. Physical evaluation of the peripheral nervous system in disorders of pain and dysfunction. J Hand Ther 1997;10(2):122-129.

[12] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14(2):162-173.

[13] Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DL, Bouhassira D, Cruccu G, Freeman R, Hansson P, Nurmikko T, Raja SN, Rice AS, Serra J, Smith BH, Treede RD, Jensen TS. Neuropathic pain: an updated grading system for research and clinical practice. Pain 2016;157(8):1599-1606.

[14] Fletcher JP, Bandy WD. Intrarater reliability of CROM measurement of cervical spine active range of motion in persons with and without neck pain. J Orthop Sports Phys Ther 2008;38(10):640-645.

[15] Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22(10):1911-1920.

[16] Freynhagen R, Rolke R, Baron R, Tölle TR, Rutjes AK, Schu S, Treede RD. Pseudoradicular and radicular low-back pain--a disease continuum rather than different entities? Answers from quantitative sensory testing. Pain 2008;135(1-2):65-74.
[17] Haanpää M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, Cruccu G, Hansson P, Haythornthwaite JA, Iannetti GD, Jensen TS, Kauppila T, Nurmikko TJ, Rice ASC, Rowbotham M, Serra J, Sommer C, Smith BH, Treede RD. NeuPSIG guidelines on neuropathic pain assessment. Pain 2011;152(1):14-27.
[18] Hall T, Briffa K, Hopper D, Robinson K. Reliability of manual examination and frequency of symptomatic cervical motion segment dysfunction in cervicogenic headache. Man Ther 2010;15(6):542-546.
[19] Hansen JT, Netter FH, Machado CAG. Netter's Clinical Anatomy: Elsevier, 2019.
[20] Hapidou EG, O'Brien MA, Pierrynowski MR, de Las Heras E, Patel M, Patla T. Fear and Avoidance of Movement in People with Chronic Pain: Psychometric Properties of the 11-Item Tampa Scale for Kinesiophobia (TSK-11). Physiother Can 2012;64(3):235-241.
[21] Irmak R. Relatively short term test re-test reliability of Neck Disability Index by long term test re-retest reliability method of Oswestry Disability Index in healthy office workers. Work 2019;64(3):635-640.
[22] Kapitza C, Lüdtke K, Tampin B, Ballenberger N. Application and utility of a clinical framework for spinally referred neck-arm pain: A cross-sectional and longitudinal study protocol. PLoS One 2020;15(12):e0244137.
[23] Kapitza C. Luedtke K, Komenda M., Kiefhaber M., Schmid A.B., Ballenberger N., Tampin B. Inter- and intra-rater-reliability of a clinical framework for spine-related neck-arm pain. Musculoakeletal Science and Practice 2023;67.
[24] Kendall FP, McCreary EK, Provance PG. Muscles Testing and Function 4th edition Baltimore: Williams and Wilkins 1993.
[25] Kent P, Mjosund HL, Petersen DH. Does targeting manual therapy and/or exercise improve patient outcomes in nonspecific low back pain? A systematic review. BMC Med 2010;8:22.
[26] Klute M, Laekeman M, Kuss K, Petzke F, Dieterich A, Leha A, Neblett R, Ehrhardt S, Ulma J, Schäfer A. Cross-cultural adaptation and validation of the German Central Sensitization Inventory (CSI-GE). BMC Musculoskelet Disord 2021;22(1):708.
[27] Koulouris AE, Edwards RR, Dorado K, Schreiber KL, Lazaridou A, Rajan S, White J, Garcia J, Gibbons C, Freeman R. Reliability and Validity of the Boston Bedside Quantitative Sensory Testing Battery for Neuropathic Pain. Pain Med 2020;21(10):2336-2347.
[28] Lam KN, Heneghan NR, Mistry J, Ojoawo AO, Peolsson A, Verhagen AP, Tampin B, Thoomes E, Jull G, Scholten-Peeters GGM, Slater H, Moloney N, Hall T, Dedering Å, Rushton A, Falla D. Classification criteria for cervical radiculopathy: An international e-Delphi study. Musculoskelet Sci Pract 2022;61:102596.
[29] Lascurain-Aguirrebeña I, Dominguez L, Villanueva-Ruiz I, Ballesteros J, Rueda-Etxeberria M, Rueda JR, Casado-Zumeta X, Araolaza-Arrieta M, Arbillaga-Etxarri A, Tampin B. Effectiveness of neural mobilisation for the treatment of nerve-related cervicobrachial pain: a systematic review with subgroup meta-analysis. Pain 2024;165(3):537-549.
[30] Lemeunier N, da Silva-Oolup S, Chow N, Southerst D, Carroll L, Wong JJ, Shearer H, Mastragostino P, Cox J, Côté E, Murnaghan K, Sutton D, Côté P. Reliability and validity of clinical tests to assess the anatomical integrity of the cervical spine in adults with neck pain and its associated disorders: Part 1-A systematic review from the

Cervical Assessment and Diagnosis Research Evaluation (CADRE) Collaboration. Eur Spine J 2017;26(9):2225-2241.
[31] Lemeunier N, Jeoun EB, Suri M, Tuff T, Shearer H, Mior S, Wong JJ, da Silva-Oolup S, Torres P, D'Silva C, Stern P, Yu H, Millan M, Sutton D, Murnaghan K, Côté P. Reliability and validity of clinical tests to assess posture, pain location, and cervical spine mobility in adults with neck pain and its associated disorders: Part 4. A systematic review from the cervical assessment and diagnosis research evaluation (CADRE) collaboration. Musculoskelet Sci Pract 2018;38:128-147.
[32] Matesanz-García L, Cuenca-Martínez F, Simón AI, Cecilia D, Goicoechea-García C, Fernández-Carnero J, Schmid AB. Signs Indicative of Central Sensitization Are Present but Not Associated with the Central Sensitization Inventory in Patients with Focal Nerve Injury. J Clin Med 2022;11(4).
[33] Meyer K, Sprott H, Mannion AF. Cross-cultural adaptation, reliability, and validity of the German version of the Pain Catastrophizing Scale. J Psychosom Res 2008;64(5):469-478.
[34] Moloney N, Hall T, Doody C. Sensory hyperalgesia is characteristic of nonspecific arm pain: a comparison with cervical radiculopathy and pain-free controls. Clin J Pain 2013;29(11):948-956.
[35] Moloney N, Hall T, Doody C. Divergent sensory phenotypes in nonspecific arm pain: comparisons with cervical radiculopathy. Arch Phys Med Rehabil 2015;96(2):269-275.
[36] Murphy DR, Hurwitz EL, Gerrard JK, Clary R. Pain patterns and descriptions in patients with radicular pain: does the pain necessarily follow a specific dermatome? Chiropr Osteopat 2009;17:9.
[37] Nee RJ, Jull GA, Vicenzino B, Coppieters MW. The validity of upper-limb neurodynamic tests for detecting peripheral neuropathic pain. J Orthop Sports Phys Ther 2012;42(5):413-424.
[38] Nilges P, Essau C. [Depression, anxiety and stress scales: DASS--A screening procedure not only for pain patients]. Schmerz 2015;29(6):649-657.
[39] Ottiger-Boettger K, Ballenberger N, Landmann G, Stockinger L, Tampin B, Schmid A. Somatosensory profiles in patients with non-specific neck-arm pain with and without positive neurodynamic tests. Musculoskelet Sci Pract 2020;50:102261.
[40] Pereira MP, Wiegmann H, Agelopoulos K, Ständer S. Neuropathic Itch: Routes to Clinical Diagnosis. Front Med (Lausanne) 2021;8:641746.
[41] Reimer M, Forstenpointner J, Hartmann A, Otto JC, Vollert J, Gierthmühlen J, Klein T, Hüllemann P, Baron R. Sensory bedside testing: a simple stratification approach for sensory phenotyping. Pain Rep 2020;5(3):e820.
[42] Ridehalgh C, Sandy-Hindmarch OP, Schmid AB. Validity of Clinical Small-Fiber Sensory Testing to Detect Small-Nerve Fiber Degeneration. J Orthop Sports Phys Ther 2018;48(10):767-774.
[43] Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006;123(3):231-243.
[44] Rusu AC, Kreddig N, Hallner D, Hulsebusch J, Hasenbring MI. Fear of movement/(Re)injury in low back pain: confirmatory validation of a German version of the Tampa Scale for Kinesiophobia. BMC Musculoskelet Disord 2014;15:280.

[45] Schäfer A, Hall T, Muller 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;20(3):482-490.
[46] 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;20(3):482-490.
[47] Schmid A, Tampin B. . Spinally referred back and leg pain. Scott D. Boden (Ed): Online book of The International Society for the Study of the Lumbar Spine, 2018.
[48] Schmid AB, Brunner F, Luomajoki H, Held U, Bachmann LM, Kunzer S, Coppieters MW. Reliability of clinical tests to evaluate nerve function and mechanosensitivity of the upper limb peripheral nervous system. BMC Musculoskelet Disord 2009;10:11.
[49] Schmid AB, Fundaun J, Tampin B. Entrapment neuropathies: a contemporary approach to pathophysiology, clinical assessment, and management. Pain Rep 2020;5(4):e829.
[50] Schmid AB, Hailey L, Tampin B. Entrapment Neuropathies: Challenging Common Beliefs With Novel Evidence. J Orthop Sports Phys Ther 2018;48(2):58-62.
[51] Schmid AB, Tampin B, Baron R, Finnerup NB, Hansson P, Hietaharju A, Konstantinou K, Lin CC, Markman J, Price C, Smith BH, Slater H. Recommendations for terminology and the identification of neuropathic pain in people with spine-related leg pain. Outcomes from the NeuPSIG working group. Pain 2023;164(8):1693-1704.
[52] Sullivan GM, Feinn R. Using Effect Size-or Why the P Value Is Not Enough. J Grad Med Educ 2012;4(3):279-282.
[53] Tampin B, Briffa NK, Slater H. Self-reported sensory descriptors are associated with quantitative sensory testing parameters in patients with cervical radiculopathy, but not in patients with fibromyalgia. Eur J Pain 2013;17(4):621-633.
[54] Tampin B, Lind C, Jacques A, Slater H. Disentangling 'sciatica' to understand and characterise somatosensory profiles and potential pain mechanisms. Scand J Pain 2022;22(1):48-58.
[55] Tampin B, Slater H, Briffa NK. Neuropathic pain components are common in patients with painful cervical radiculopathy, but not in patients with nonspecific neck-arm pain. Clin J Pain 2013;29(10):846-856.
[56] Tampin B, Slater H, Hall T, Lee G, Briffa NK. Quantitative sensory testing somatosensory profiles in patients with cervical radiculopathy are distinct from those in patients with nonspecific neck-arm pain. Pain 2012;153(12):2403-2414.
[57] Tampin B, Slater H, Jacques A, Lind CRP. Association of quantitative sensory testing parameters with clinical outcome in patients with lumbar radiculopathy undergoing microdiscectomy. Eur J Pain 2020;24(7):1377-1392.
[58] Tanıgör G, Hepgüler S, Köken İ, Uyar M. Quantitative sensory test findings in cervical radicular pain and their relationship with the symptoms. Agri 2022;34(4):235-244.
[59] Thoomes EJ, Scholten-Peeters GG, de Boer AJ, Olsthoorn RA, Verkerk K, Lin C, Verhagen AP. Lack of uniform diagnostic criteria for cervical radiculopathy in conservative intervention studies: a systematic review. Eur Spine J 2012;21(8):1459-1470.
[60] Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. J Manipulative Physiol Ther 1991;14(7):409-415.
[61] Vibe Fersum K, O'Sullivan P, Skouen JS, Smith A, Kvale A. Efficacy of classification-based cognitive functional therapy in patients with non-specific chronic low back pain: a randomized controlled trial. Eur J Pain 2013;17(6):916-928.
[62] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basanez MG, Baxter A, Bell

ML, Benjamin EJ, Bennett D, Bernabe E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fevre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gosselin R, Grainger R, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Ma J, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA, 3rd, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De Leon FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2163-2196.

[63] Williams MA, McCarthy CJ, Chorti A, Cooke MW, Gates S. A systematic review of reliability and validity studies of methods for measuring active and passive cervical range of motion. J Manipulative Physiol Ther 2010;33(2):138-155.
[64] Woby SR, Roach NK, Urmston M, Watson PJ. Psychometric properties of the TSK-11: a shortened version of the Tampa Scale for Kinesiophobia. Pain 2005;117(1-2):137-144.
[65] Young IA, Cleland JA, Michener LA, Brown C. Reliability, construct validity, and responsiveness of the neck disability index, patient-specific functional scale, and numeric pain rating scale in patients with cervical radiculopathy. Am J Phys Med Rehabil 2010;89(10):831-839.
[66] Zhu GC, Böttger K, Slater H, Cook C, Farrell SF, Hailey L, Tampin B, Schmid AB. Concurrent validity of a low-cost and time-efficient clinical sensory test battery to evaluate somatosensory dysfunction. Eur J Pain 2019;23(10):1826-1838.

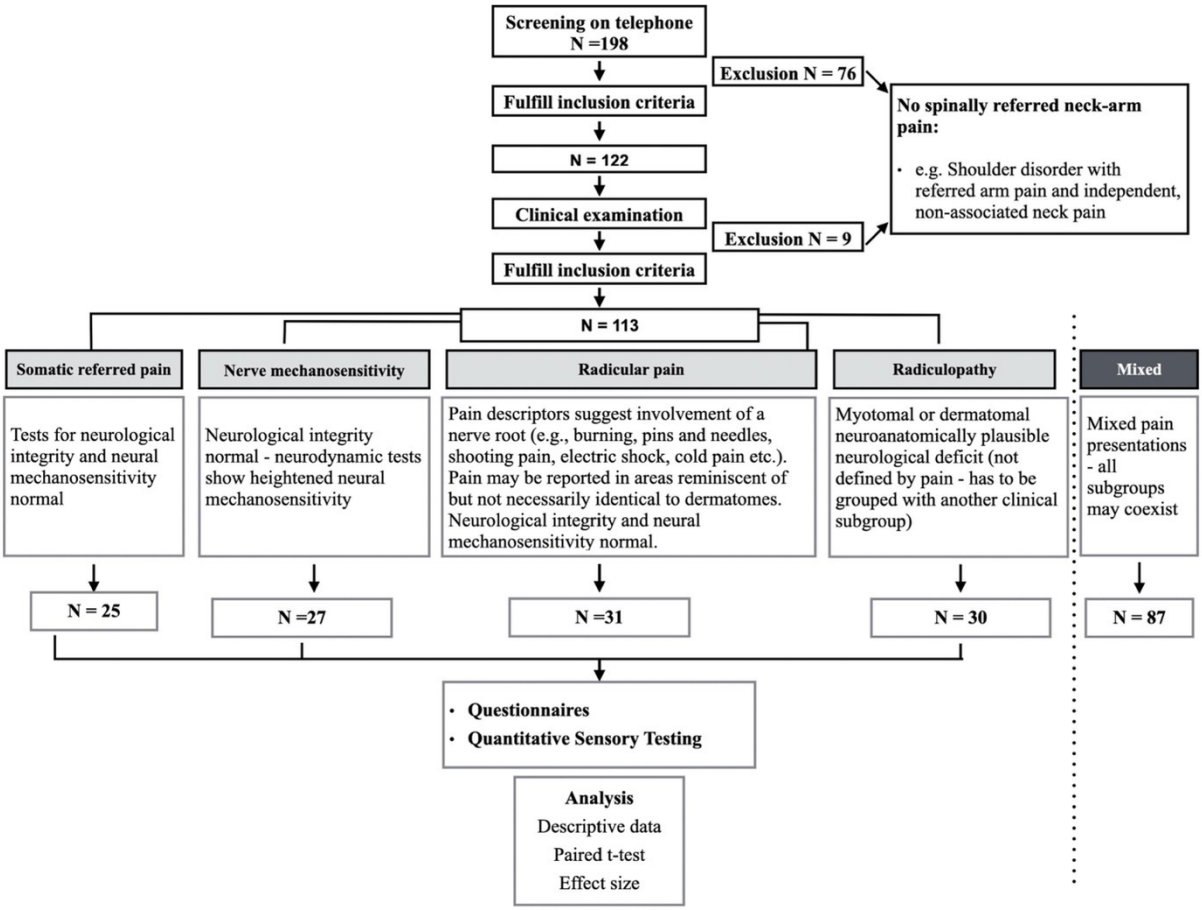


Fig. 1) Flowchart and classification. Please note that N-numbers are not exclusive presentations, but one patient could be classified into more than 1 group, at which point they would also be part of the mixed group.

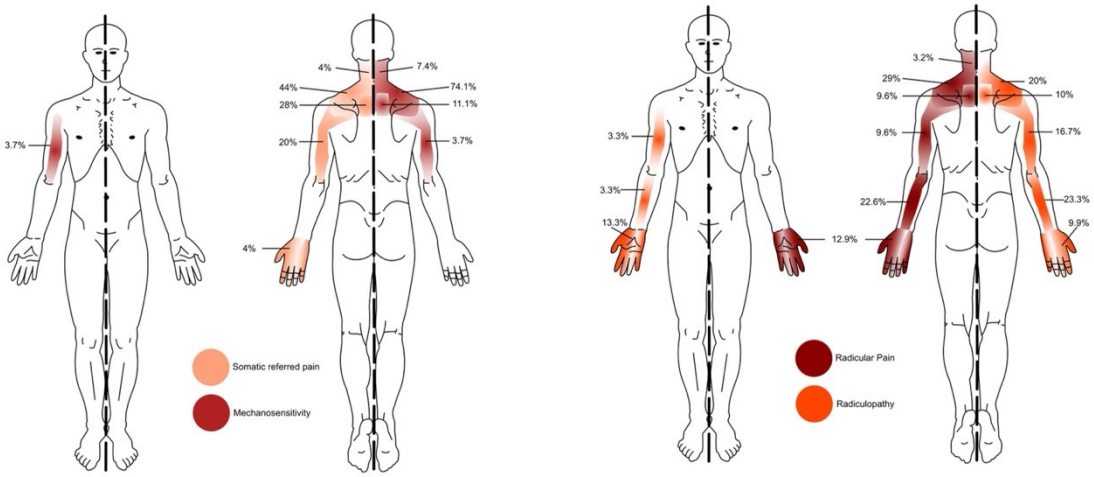


Fig. 2) Percentage frequencies of maximal pain areas in each subgroup.

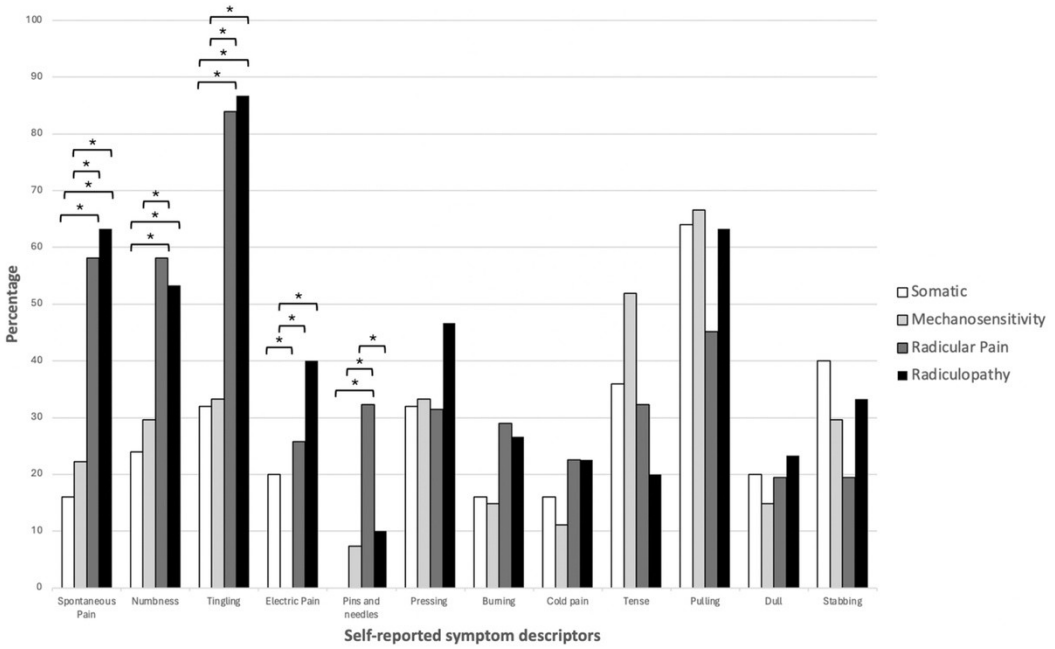


Fig. 3) Percentage frequencies of self-reported pain descriptors based on the subjective examination.

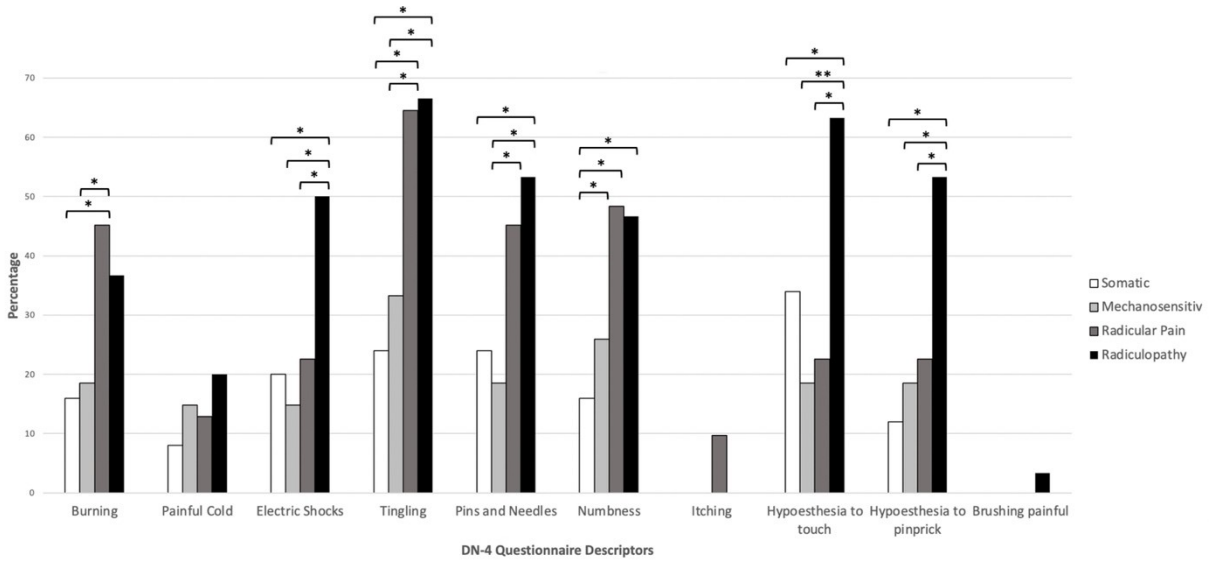


Fig. 4) Percentage frequencies of pain descriptors based on the DN-4 Questionnaire.

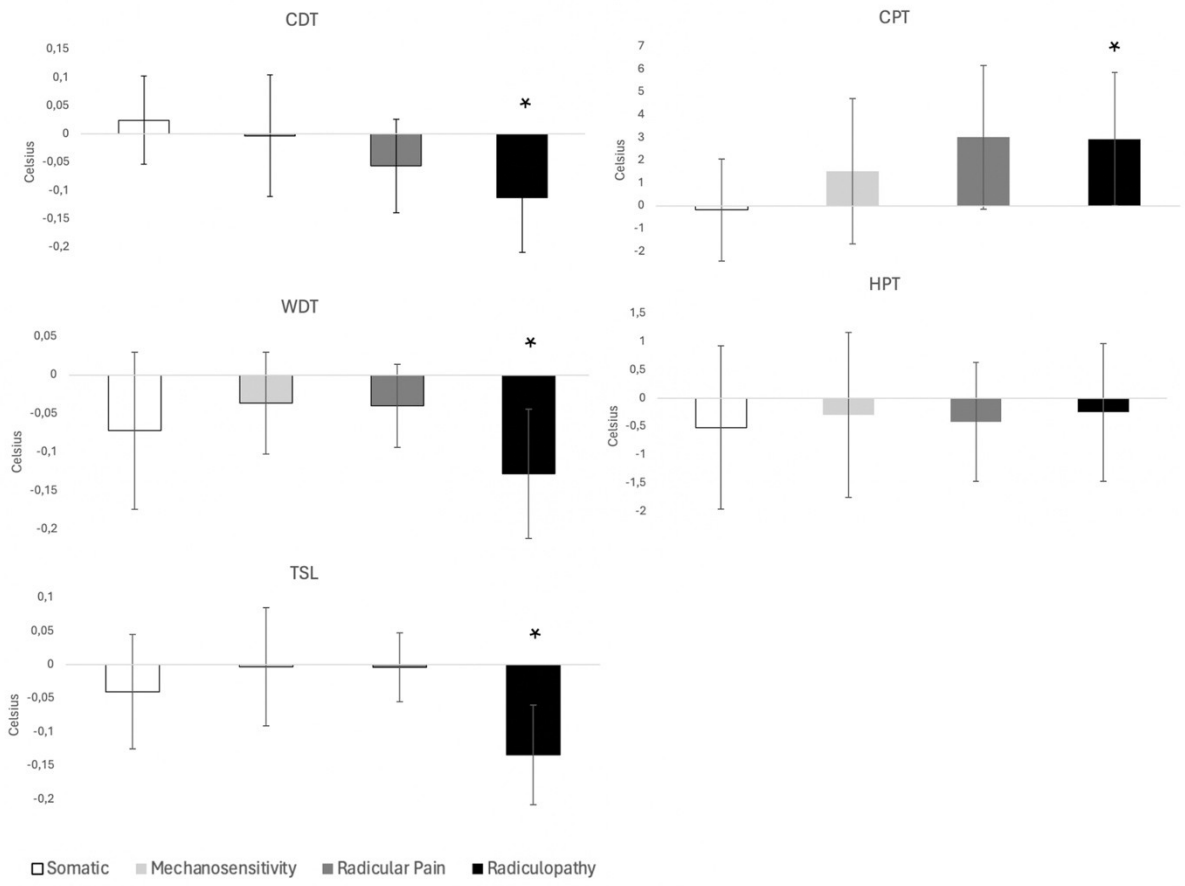


Fig. 5) Side difference of QST parameters in each subgroup. CDT (cold detection threshold), WDT (warm detection threshold), TSL (thermal sensory limen), CPT (cold pain threshold) and HPT (heat pain threshold). Log- transformed mean value difference (except for CPT, HPT) between sides is shown. Error bars indicate the 95% CI (confidence interval).

* Significant difference between sides

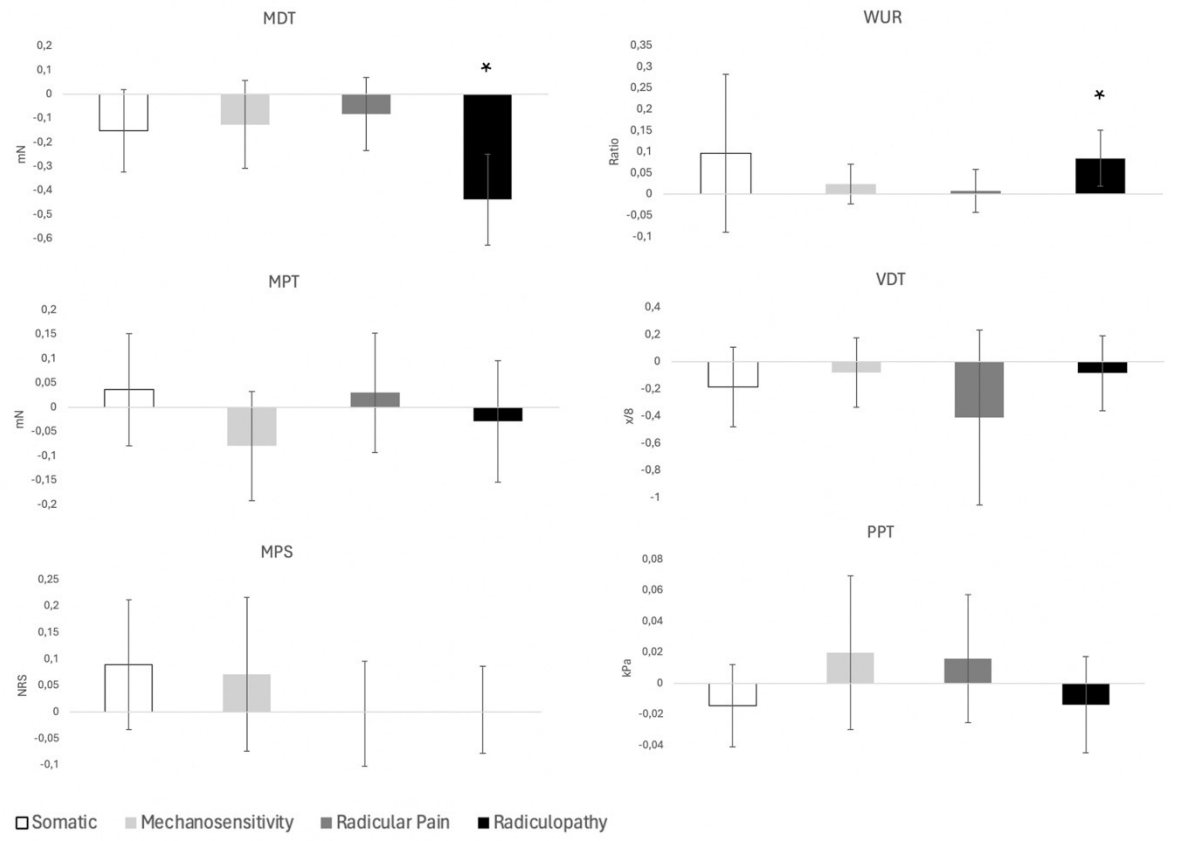


Fig. 6) Side difference of QST parameters in each subgroup. MDT (mechanical detection threshold), MPT (mechanical pain threshold), MPS (mechanical pain sensitivity), VDT (vibration detection threshold), WUR (wind-up ratio pain threshold) and PPT (pressure pain threshold), mN (milliNewton), NRS (numeric rating scale), kPa (kilopascal). Log-transformed mean value difference (except for VDT) between sides is shown. Error bars indicate the 95% CI (confidence interval).

* Significant difference between sides

Table 1) (Mixed) subgroup classification of study population

Somatic	**Mechanosensitivity**	**Radicular pain**	**Radiculopathy**	**Number of participants**
x				25
x	x			27
x	x	x		19
x		x		10
		x		1
	x	x		1
x		x	x	10
x	x		x	1
x	x	x	x	19
Total				113

Table 2) Demographic and clinical data of study population classified into the dominant subgroups

Variable	Somatic referred pain	Mechanosensitivity	Radicular Pain	Radiculopathy	P-value
N = 113	N = 25	N = 27	N = 31	N = 30	/
Sex female	18	19	17	17	0.417
Age years *	43.8 (10.9)	46.2 (13.4)	49.5 (9.6)	47.8 (11.9)	0.135
Sleep quality (NRS)*	3.6 (2.3)	4.7 (2,6)	4.6 (1.8)	3.9 (2.5)	0.213
NDI*	12.4 (4.5)	13.5 (4.7)	13.4 (7.4)	11.1 (6.0)	0.373
BMI	25.2 (21.5; 27.6)	24.1 (20.3; 27.7)	24.5 (22.3; 27.5)	23.9 (22.2; 26.6)	0.930
Pain intensity	5 (4; 7)	6 (5; 6)	5 (4; 7)	4 (3; 6)	0.357
Pain duration (weeks)*	80 (18; 260) [c, d]	156 (44; 312) [c, d]	24 (8; 78) [a, b]	22 (8; 84.5) [a, b]	**<0.001**
PCS	11 (5; 26)	14 (8; 21)	9 (3; 25)	12,5 (5; 22)	0.816
CSI	32 (23.5; 43.5)	31 (25; 44)	25 (18; 36)	27,5 (16; 40.5)	0.228

Data are presented as number of patients (n) and frequency (%), mean (SD)*, or median (25^{th} and 75^{th} percentile). Bold numbers indicate significant difference between groups. Significant differences are marked as follows: [a] Significantly different to somatic referred pain; [b] Significantly different to mechanosensitivity; [c] Significantly different to radicular pain; [d] Significantly different to radiculopathy. NRS: Numeric rating scale, NDI: Neck Disability Index, PCS: Pain Catastrophizing Scale, CSI: Central Sensitization Inventory, TSK-11: Tampa Scale for Kinesiophobia, DASS Depressions- anxiety- stress- scale; DN-4: Douleur neuropathique 4, BMI: body mass index, ULNT: Upper limb neurodynamic tests.

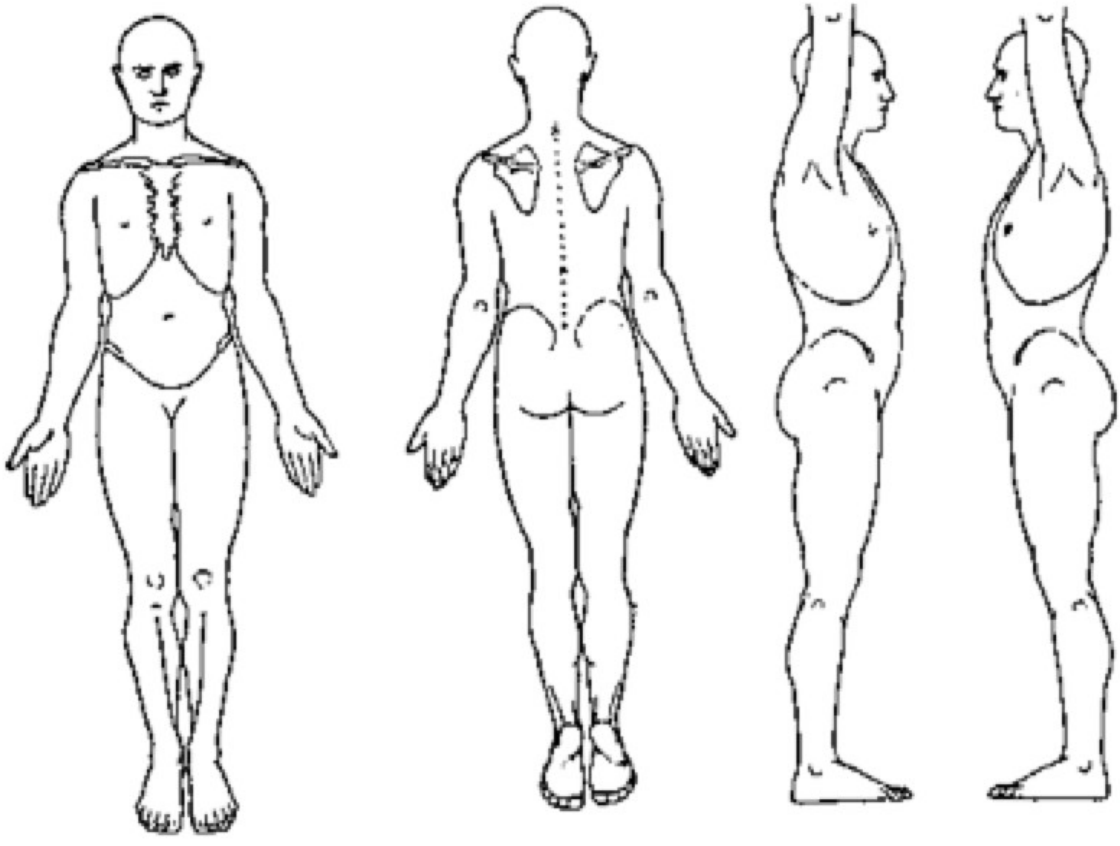
Supplement 1

CLINICAL EXAMINATION FORM

ID:
DOB:

Date:	**Age:**	**Sex:**	**Profession:**
Dominant side:	**Height:**	**Body Weight:**	**BMI:**

Main Problem:



Current Hx:

Past Hx:

Pain behaviour:

Aggravating factors:

Ease factors:

Mechanical pain behaviour:

Spontaneous pain behaviour:

Painful cold:

24h:

N:

Do you wake up tired and not recovered? ‘Never’ ‘seldom’ ‘often or usual’ ‘always’

Sleep quality:

0 10
Good sleep Poor sleep

AM:

During the day:

End of day:

General health:

Comorbidities/fracture/Trauma/Op:

Fatigue: Are you generally tired over the day? ‘Never’ ‘seldom’ ‘often or usual’ ‘always’

Diabetes:
Thyroid disease:
Rheumatoid arthritis:
B12:
Handling or working with toxins:

X-Ray, MRI etc.:

Weight loss:

Spinal cord symptoms:

Vertebral artery signs:

Reaction to coughing/sneezing:

Medication:

Name	Dosage	Duration of intake	Effect

PHYSICAL EXAMINATION

pp (NRS):

Inspection:

Functional demonstration:

Active movements:

Cervical spine	**Range, Symptom, Quality of movement**	**Shoulders**	**Range, Symptom, Quality of movement**
Flexion:		Flexion:	
Extension:		Abduction:	
Rotation right:		Abduction + cervical contralateral Lateral flexion:	
Rotation left:		Abduction + hand dorsal extension:	
Lateral flexion right:			
Lateral flexion left:			

Spurling's Test (Lateral Flexion, Rotation, Compression.):

Right:

Left:

Neurological examination

Strength **Rating 5/5=√**	**Left**	**Right**
Scapula Elev. (C4)		
Shoulder ABD (C5)		
Elb. Flex. (C5/6)		
Elb. Ext. (C6/7)		
Hand Ext. (C7)		
Thumb Ext. (C8) Finger Flex.		
Interossei (T1)		
others		

Reflex	**Hyperreflexia/Clonus: ++++** **Increased: +++** **Normal: ++** **Reduced: +** **Absent: -**	
	Left	**Right**
BICEPS		
TRICEPS		
BRACHIORADIAL		
PRONATOR QUA.		

Sensation	**Intensity** **N** = normal **Less** = Hypoaesthesia **Loss** = Analgesia **Increased** = Hyperaesthesia	**Quality** **N** = Normal **C = Changed** (Paraesthesia, Dysaesthesia (unpleasant), Allodynia)

	Dermotome C4 – T1			
	Left		**Right**	
	Intensity	Quality	Intensity	Quality
Soft touch (cotton wool)				
Pin Prick				

Maximal pain area:

	Left		Right	
	Intensity	Quality	Intensity	Quality
Soft touch (cotton wool)				
Pin Prick				
Cold (Coin)				
Warm (Coin)				
Ice cube test				
Vibration				
Second pain area:				
Soft touch (cotton wool)				
Pin Prick				
Cold (Coin)				
Warm (Coin)				
Ice cube test				
Vibration				

Others	**Left**	**Right**
BABINSKI		
CLONUS		
Gait		
BALANCE Single leg stance Romberg Test		
COORDINATION Tandem walk		

Upper Limb Neurodynamic Tests:

Nerve palpation:

Right **Left**

Median nerve:
Radial nerve:
Ulnar nerve:

Passive movements cervical spine

Passive Physiological Intervertebral Movements cervical spine:

Passive Accessory Intervertebral Movements cervical spine:
Central, unilateral (with angulations) Cervical 1 - 7

Palpation (Triggerpoints):

Scalenus muscle	**right:**	**left:**
Pectoralis minor muscle	**right:**	**left:**
Subclavius muscle	**right:**	**left**
Infraspinatus muscle	**right:**	**left:**
M. levator scap	**right:**	**left:**
Upper trapezius	**right:**	**left:**

Supplement 2: Table 1) QST parameters (mean +/- SD and effect size) on the asymptomatic and symptomatic side for each subgroup

QST parameter	**Subgroup**	**Asymptomatic Side**	**Symptomatic Side**	**Difference**	**P - Value**	**Effect size**
CDT (°C)	Somatic	1.66 (1.20)	1.45 (1.43)	0.21 (1.17)	0.524	0.129
	Mechanosensitivity	1.62 (0.98)	1.62 (1.31)	0.00 (1.38)	0.951	0.012
	Radicular Pain	1.93 (1.64)	2.03 (1.57)	0.10 (1.21)	0.152	0.260
	Radiculopathy	**1.86 (1.70)**	**2.30 (1.63)**	**0.44 (1.80)**	**0.024**	**0.435**
WDT (°C)	Somatic	3.42 (1.79)	3.80 (1.32)	0.38 (2.30)	0.157	0.293
	Mechanosensitivity	2.69 (1.10)	2.95 (1.89)	0.26 (1.23)	0.268	0.218

	Radicular Pain	3.46 (3.32)	3.56 (2.41)	0.10 (1.45)	0.091	0.309
	Radiculopathy	**2.99 (2.02)**	**3.90 (1.71)**	**0.91 (2.66)**	**0.004**	**0.570**
TSL (°C)	Somatic	5.85 (2.83)	6.21 (2.74)	0.35 (2.63)	0.336	0.196
	Mechanosensitivity	5.08 (3.81)	5.43 (2.16)	0.35 (4.02)	0.939	0.015
	Radicular Pain	6.25 (4.11)	6.13 (3.38)	0.12 (1.87)	0.740	0.059
	Radiculopathy	**5.53 (2.96)**	**7.51 (4.44)**	**1.98 (3.96)**	**0.001**	**0.676**
CPT (°C)	Somatic	17.63 (9.45)	17.44 (9.22)	0.18 (5.42)	0.868	0.034
	Mechanosensitivity	13.92 (8.13)	15.43 (7.90)	1.51 (8.09)	0.340	0.187

	Radicular Pain	12.89 (8.28)	15.90 (8.92)	3.01 (8.60)	0.062	0.343
	Radiculopathy	**13.40 (8.59)**	**16.33 (9.47)**	**2.93 (7.82)**	**0.049**	**0.375**
HPT (°C)	Somatic	43.28 (4.32)	43.80 (3.16)	0.52 (3.51)	0.465	0.149
	Mechanosensitivity	43.56 (9.21)	43.86 (8.46)	0.30 (3.69)	0.675	0.081
	Radicular Pain	44.22 (4.33)	44.64 (4.04)	0.42 (2.87)	0.445	0.137
	Radiculopathy	44.20 (3.29)	44.45 (3.76)	0.25 (3.27)	0.676	0.077
MDT (mN)	Somatic	2.68 (3.42)	3.19 (3.32)	0.51 (2.84)	0.081	0.364
	Mechanosensitivity	3.32 (6.94)	10.13 (34.64)	6.81 (28.19)	0.170	0.271

	Radicular Pain	2.28 (3.26)	2.71 (4.29)	0.43 (1.75)	0.216	0.223
	Radiculopathy	**1.75 (2.04)**	**5.12 (7.71)**	**3.37 (7.62)**	**0.001**	**0.867**
MPT (mN)	Somatic	46.09 (94.94)	33.18 (47.78)	12.91 (56.46)	0.524	0.129
	Mechanosensitivity	34.11 (96.25)	37.70 (79.71)	3.59 (30.18)	0.157	0.280
	Radicular Pain	41.68 (48.02)	37.87 (37.54)	3.81 (37.79)	0.500	0.121
	Radiculopathy	66.43 (83.44)	90.49 (143.37)	24.06 (77.43)	0.636	0.087
MPS (NRS 0-100)	Somatic	6.31(6.99)	5.43 (6.21)	0.88 (5.36)	0.419	0.164
	Mechanosensitivity	5.03 (5.76)	3.61 (4.51)	1.42 (3.07)	0.322	0.194

	Radicular Pain	4.19 (5.07)	3.93 (4.70)	0.26 (2.14)	0.989	0.002
	Radiculopathy	3.75 (6.10)	3.81 (6.12)	0.06 (3.63)	0.910	0.021
WUR (ratio)	Somatic	3.95 (3.54)	4.54 (3.92)	0.59 (3.33)	0.387	0.176
	Mechanosensitivity	3.91 (3.38)	4.27 (4.04)	0.36 (1.89)	0.309	0.200
	Radicular Pain	3.79 (4.31)	3.79 (4.34)	0.01 (1.23)	0.302	0.186
	Radiculopathy	**2.59 (1.77)**	**3.20 (1.94)**	**0.60 (1.35)**	**0.014**	**0.479**
VDT (x/8)	Somatic	4.79 (1.08)	4.61 (1.19)	0.19 (0.71)	0.204	0.261
	Mechanosensitivity	4.86 (1.33)	4.78 (1.14)	0.08 (0.65)	0.529	0.123

	Radicular Pain	5.40 (2.09)	5.00 (1.25)	0.40 (1.76)	0.230	0.217
	Radiculopathy	5.17 (1.25)	5.08 (1.15)	0.08 (0.74)	0.542	0.113
PPT (kPa)	Somatic	282.44 (117.0)	290.32 (290.32)	7.88 (83.16)	0.596	0.107
	Mechanosensitivity	334.44 (124.69)	333.41 (155.89)	1.03 (89.35)	0.421	0.157
	Radicular Pain	392.58 (208.70)	377.39 (194.91)	15.19 (100.81)	0.623	0.088
	Radiculopathy	396.96 (182.03)	412.60 (187.19)	15.64 (66.82)	0.370	0.166

Mean and standard deviation (± SD) of untransformed QST raw data are shown. P- values and effect size calculated with log-transformed QST data (expect normal distributed data CPT, HPT, VDT). Bold numbers indicate significant difference between sides. QST: quantitative sensory testing; CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold;

MDT: mechanical detection threshold; MPS: mechanical pain sensitivity; MPT: mechanical pain threshold; VDT: vibration detection threshold; WUR, wind-up ratio pain threshold; PPT: pressure pain threshold, mN: milliNewton, NRS: numeric rating scale; kPa: kilopascal.