School of Physiotherapy

Clinical and Somatosensory Characteristics of Patients with Nerve-Related Neck-Arm Pain

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis contains no material which has been accepted for the award of any other degree of diploma in any university.

Brigitte Tampin

Signature………………………………….

Date………………………………………

Abstract

Neuropathic pain (NeP), defined as pain caused by a lesion or disease of the somatosensory nervous system, is associated with more severe pain for patients than nociceptive pain and with suffering, disability, impaired health-related quality of life, and increased health care cost. Thus, the early identification of NeP in patients with chronic pain disorders is crucial for targeting appropriate management as NeP conditions require a different therapeutic approach compared to conditions characterised by nociceptive pain. No data exist on the prevalence of NeP in patients with neck-arm pain disorders, but there are indications that NeP is underdiagnosed in musculoskeletal conditions.

Nerve-related neck-arm pain is heterogeneous with differing clinical presentations associated with varying pain types (nociceptive/neuropathic) and pain mechanisms (for example peripheral and central sensitisation). To improve patient outcomes, requires identification of such differences and the appropriate classification of patients with nerve-related neck-arm pain conditions. Specifically, the characterisation of patients with respect to the mix of NeP and nociceptive pain is of therapeutic relevance.

Various clinical tools (clinical classification systems, NeP screening questionnaires) and laboratory tests (quantitative sensory testing (QST)) have been recommended for the assessment of NeP components in patients with chronic pain, however data on assessment of patients with nerve-related neck-arm pain is scarce. The overall aim of this doctoral research was to investigate the clinical characteristics of patients with nerve-related neck-arm pain and to establish the somatosensory profiles of patients with these nerve pain conditions. The thesis explored the characterisation of two specific patient groups: patients with painful cervical radiculopathy and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP). Five studies were conducted.

The first study used specific classification systems to determine: (i) the inter-examiner agreement in classifying patients with cervical radiculopathy and patients with NSNAP; and (ii) the diagnostic accuracy of these clinical examiners, using the

opinion and consensus of two experts as a reference criterion. The results demonstrated high percentage agreement with moderate Kappa coefficients between examiners in classifying both patient groups, supporting the reliability of the classification systems used. Compared to the expert opinion, the examiners were able to accurately classify 80% of cases with these specific clinical neck-arm pain presentations.

The second study investigated the clinical assessment of NeP in a cohort of 152 patients referred to a neurosurgery triage clinic for assessment of their neck/upper limb pain associated with a suspected nerve lesion. The aims of this study were to investigate in this cohort: (i) the clinical application of a newly developed grading system for the assessment of NeP and (ii) to investigate the level of agreement in detecting likely NeP between this model and two NeP questionnaires, the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS) and the painDETECT questionnaire (PD-Q). The proposed diagnostic grading system could readily be applied to this cohort of patients with neck/upper limb pain, however its application required a considerable amount of time and specific expertise due to the complexity of pain presentations. This diagnostic approach might not be feasible in primary care settings. Both questionnaires failed to identify a large number of patients with clinically classified NeP. The diagnostic accuracy of LANSS and PD-Q for the identification of NeP in patients with neck/upper limb pain appears therefore limited.

The third study aimed to establish the somatosensory profile or phenotype of patients with cervical radiculopathy and patients with NSNAP, using the full battery of laboratory QST. QST is a valuable tool for the assessment of sensory alterations and may assist in the interpretation of underlying pain mechanisms. Somatosensory profiles were compared to healthy control subjects and to patients with fibromyalgia. Distinct sensory profiles were demonstrated for each group. Patients with cervical radiculopathy were characterised by localised loss of function in all primary sensory fibers tested (C, Aδ, Aβ), findings consistent with peripheral neuronal damage. These deficits were not present in patients with NSNAP. Both neck-arm pain groups demonstrated a gain of function with the presence of cold hypersensitivity and this was the dominant sensory characteristic in patients with NSNAP. Both neck-arm

pain groups differed from patients with FM, the latter characterised by a widespread gain of function in most nociceptive parameters.

The fourth study was designed to determine the presence of NeP components in the two neck-arm pain groups, using the PD-Q and QST, comparing side-to-side differences of QST parameters in the maximal pain area and corresponding dermatome. A side-to-side difference has been reported to increase the sensitivity to detect sensory abnormalities. Patients with cervical radiculopathy demonstrated a significant difference in mechanical and vibration detection thresholds between the symptomatic and asymptomatic side in both body regions tested, with a loss of function seen on the symptomatic side. The PD-Q score on a group level did not suggest the presence of NeP, but 30% of individuals were identified by PD-Q as having NeP components. Patients with NSNAP did not demonstrate a clinically significant side-to-side difference in any QST parameters of any body region tested and the PD-Q score suggested that nociceptive pain was the dominant pain type in this group.

The aim of the fifth study was to investigate if the self-reported somatosensory profile of patients with cervical radiculopathy and of patients with fibromyalgia, as indicated by responses to verbal sensory descriptors items of PD-Q, corresponded with their sensory phenotype demonstrated by QST, using healthy control QST data as reference criteria. Patients with radiculopathy demonstrated a match between their self-reported sensory phenotype and QST sensory phenotype for all sensory descriptors, except for sensitivity to light touch. The QST sensory phenotype of patients with FM was not consistently reflected by responses to verbal descriptors from the PD-Q. The findings of the study support the use of the PD-Q as a tool to characterise somatosensory profiles in patients with cervical radiculopathy, but not in patients with FM.

This doctoral research demonstrated that clinical classification systems are useful in differentiating the clinical presentations of patients with nerve-related neck-arm pain and in identifying NeP components in the cohorts. Distinct clinical and somatosensory profiles were documented in patients with cervical radiculopathy and patients with NSNAP, suggesting differences in the underlying pain types and

mechanisms. These findings may assist clinicians in better targeting appropriate management for these patient groups.

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List of Abbreviations

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AUS	Australian
BT	Brigitte Tampin
CI	Confidence Interval
CDT	Cold Detection threshold
CPT	Cold Pain Threshold
CT	Computerised Tomography
CxRAD	Cervical Radiculopathy
DFNS	German Research Network on Neuropathic Pain
DMA	Dynamic Mechanical Allodynia
DN4	Douleur Neuropathique en 4 questions
EMG	Electromyography
FM	Fibromyalgia
HADS	Hospital Anxiety and Depression Scale
HC	Healthy Control
HPT	Heat Pain Threshold
IASP	International Association for the Study of Pain
ICC	Intraclass Correlation Coefficient
kPa	Kilopascal
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs pain scale
LSD	Least Significance Difference
MDT	Mechanical Detection Threshold
mN	Millinewton
MPS	Mechanical Pain Sensitivity
MPT	Mechanical Pain Threshold
MRI	Magnetic Resonance Imaging
NCS	Nerve Conduction Study
NDI	Neck Disability Index
NeP	Neuropathic Pain
NeuPSIG	Neuropathic Pain Special Interest Group

NPQ	Neuropathic Pain Questionnaire
NPS	Neuropathic Pain Scale
NPSI	Neuropathic Pain Symptom Inventory
NPT_{MEDIAN}	Nerve Provocation Test with bias to Median Nerve
NRS	Numeric Rating Scale
NSNAP	Non-Specific Neck-Arm Pain associated with heightened nerve mechanosensitivity
PD-Q	painDETECT Questionnaire
PHS	Paradoxical Heat Sensation
PPT	Pressure Pain Threshold
P1	Onset of Pain
P2	Pain Tolerance
QST	Quantitative Sensory Testing
SD	Standard Deviation
SF-36	Short Form-36 Health Questionnaire
TSL	Thermal Sensory Limen
VAS	Visual Analogue Scale
VDT	Vibration Detection Threshold
WDT	Warm Detection Threshold
WUR	Wind Up Ratio

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

Chapter 7   Neuropathic pain components are common in patients with cervical radiculopathy, but not in patients with non-specific neck-arm pain

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

Chapter 1 - Introduction

The traditional approach to musculoskeletal as well as neuropathic pain (NeP), the latter defined as "pain caused by a lesion or disease of the somatosensory nervous system" (Jensen et al. 2011, p2204), involves the classification and management of patients according to the aetiology or location of the lesion (Jensen et al. 2009). This approach has its shortcomings (Baron 2006; Jensen 2002), particularly for the management of patients with non-specific nerve-related neck-arm pain, where the aetiology and pathology of the disorder may remain equivocal and the contribution of pain mechanisms remains largely unexplored. A mechanism-based classification approach has been proposed (Baron 2006; Jensen and Baron 2003; Woolf et al. 1998) that supplements the traditional classification scheme and aims to guide patient management. This approach is based on the hypothesis that different clinical signs and symptoms may reflect different underlying pathophysiological mechanisms of pain generation (Hansson 2002; Jensen and Baron 2003). It is assumed that targeting treatment towards the dominant neurophysiological mechanisms underling the patient's pain may improve clinical outcomes, although this assertion has yet to be substantiated (Cruccu and Truini 2009).

Nerve-related neck-arm pain disorders are heterogeneous with clinical signs and symptoms and pattern of pain and sensory abnormalities varying widely between individuals. While a neuropathic mechanism is commonly implied in the genesis of some disorders such as painful cervical radiculopathy (Haanpää et al. 2009), patients are likely to present with a mix of nociceptive and NeP, referred to as mixed pain syndrome (Attal and Bouhassira 2004; Baron and Binder 2004; Behrman et al. 2007; Gálvez et al. 2007; Pérez et al. 2009; Portenoy 2006). Both NeP and mixed pain can be intense forms of pain, and patients with these disorders are characterised by impaired physical and mental quality of life and a substantial level of disability, leading to increased health care costs compared to patients with nociceptive pain (Berger et al. 2004; Gálvez et al. 2007; Pérez et al. 2009). Characterisation of these patients with respect to the mix of nociceptive and NeP, and the possible dominance of one pain type in mixed pain syndromes is of therapeutic relevance (Baron and Tölle 2008), as NeP in particular requires targeted management. Heterogeneity of

patients with cervical radiculopathy may partly explain the variability in responsiveness to pharmaceutical intervention in this patient cohort (Saldaña et al. 2010).

This thesis will focus on two sub-groups of patients with nerve-related neck-arm pain: patients with painful cervical radiculopathy and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP). The latter is characterised clinically by pain in response to limb movements that cause nerve elongation (Elvey 1997). The mix of NeP and nociceptive pain has not yet been defined in these groups. While patients with these conditions can present with similar pain characteristics and sensory symptoms, the pathophysiology, the pain type and the underlying pain mechanisms do likely differ. Recognition of differences between these pain conditions is important for targeting appropriate best-evidence management.

Identification of the clinical presentation of cervical radiculopathy and NSNAP as well as the identification of NeP in patients with nerve-related neck-arm pain remains a challenge to clinicians due to a lack of diagnostic gold standards. Clinical classification systems have been proposed for the two specific neck-arm pain disorders (Elvey 1997; Radhakrishnan et al. 1994). Although they have been employed in classifying patients with NSNAP (Allison et al. 2002; van der Heide et al. 2006), their reliability has never been investigated. Similarly, a classification system for the presence of NeP (Treede et al. 2008) and NeP screening tools (Bennett et al. 2007; Bouhassira and Attal 2011) have been recommended by the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) to assist clinicians in recognizing NeP (Haanpää et al. 2011). Whilst their application has been demonstrated in patients with various pain disorders (Attal et al. 2011; Ciaramitaro et al. 2010; Freynhagen et al. 2006; Geber et al. 2009; Guastella et al. 2011; Haanpää et al. 2009; Hallström and Norrbrink 2011), it has not yet been documented in patients with neck/upper limb pain.

The first part of research described in this thesis (Studies 1 and 2) aimed to investigate this gap in knowledge by utilizing these clinical classification systems for the characterisation of patients with nerve-related neck-arm pain. The first study

involved the determination of (i) the inter-examiner agreement in classifying patients with cervical radiculopathy and patients with NSNAP, and (ii) the diagnostic accuracy of the examiners, using the consensus and opinion of clinical experts as the gold standard for comparison.

The second study explored the usefulness of the grading system of NeP (Treede et al. 2008) and the usefulness of two NeP screening tools, the Leeds Assessment of Neuropathic Symptoms and Signs pain scale (LANSS) (Bennett 2001) and the painDETECT questionnaire (PD-Q) (Freynhagen et al. 2006), in the identification of NeP in a cohort of patients with neck-arm pain.

The aim of the second part of the thesis (Studies 3, 4) was to characterise patients with C6 or C7 cervical radiculopathy and patients with NSNAP, using quantitative sensory testing (QST), and to explore the similarities and differences in sensory parameters and underlying pain types. For these studies only patients with NSNAP whose pain mapped to the C6 or C7 dermatome were recruited.

A highly sophisticated QST protocol used to establish the somatosensory profile of patients as precisely as possible, has been developed by the German Research Network on Neuropathic Pain (DFNS) (Rolke et al. 2006a; Rolke et al. 2006b). Using this protocol in patients with diabetic neuropathy and postherpetic neuralgia, sub-groups of patients with distinct somatosensory profiles have been identified (Maier et al. 2010), highlighting the heterogeneity within one aetiology. No study to date has established the complete QST somatosensory profile of patients with cervical radiculopathy and patients with NSNAP, using this DFNS QST protocol. To better characterise the presentation of both patient groups with neck-arm pain, comparison was made to healthy control subjects and to patients with fibromyalgia (FM), a chronic pain disorder characterised by widespread pain, fatigue and sleep disturbance in the absence of evidence of tissue damage (Wolfe et al. 2010) along with sensory alterations that appear to mimic NeP symptoms (Blumenstiel et al. 2011; Klauenberg et al. 2008; Martinez-Lavin et al. 2003; Pfau et al. 2009). A better understanding of different somatosensory phenotypes in these neck-arm pain groups will provide further insight into some of the potential underlying pain mechanisms and potentially assist with guiding therapy.

In the final part of this thesis (Study 5), the value of the PD-Q as a tool for somatosensory profiling was investigated. The PD-Q has been used to characterise somatosensory profiles in patients with painful lumbar radiculopathy/radicular pain (Mahn et al. 2011), diabetic neuropathy, postherpetic neuralgia (Baron et al. 2009) and FM (Rehm et al. 2010). However, the questionnaire assesses self-reported symptoms, but does not measure perceptions elicited in response to predetermined sensory stimuli, as in QST. No study to date has documented if patients' subjective responses to sensory descriptors of the PD-Q corresponded with their sensory phenotype as demonstrated by QST. A

The management of patients with nerve-related neck-arm pain relies upon accurate differential diagnosis/classification and identification of underlying pain types/mix of pain as well as pain mechanisms. The findings of this project will contribute further to the reliability and validity of clinical assessment tools used to identify patients with cervical radiculopathy and patients with NSNAP and to identify NeP in patients with these pain disorders. The studies will also provide an insight into the potential underlying pain types and pain mechanisms in patients with cervical radiculopathy and patients with NSNAP. The enhanced understanding about these pain presentations may assist clinicians in targeting treatment more specifically at the involved pain mechanisms.

1.1   Aims of the PhD project

The aims of the PhD project were:

    i)   To determine the inter-examiner agreement and diagnostic accuracy of two clinical examiners in classifying patients with painful cervical radiculopathy and patients with NSNAP, using specific classification systems.

    ii)   To investigate the application of a clinical classification system of NeP and the diagnostic accuracy of two NeP screening tools in a cohort of patients with neck/upper limb pain.

    iii)   To establish the somatosensory characteristics of patients with painful cervical radiculopathy and patients with NSNAP and to compare these

between groups and compare with healthy control subjects and patients with FM.

iv) To investigate if the self-reported somatosensory profile of patients with cervical radiculopathy and patients with FM, as indicated by responses to verbal sensory descriptors items of the PD-Q, corresponded with the sensory phenotypes demonstrated by QST.

Figure 1.1 illustrates the link between the studies of this thesis.

Study 1
Clinical classification and sub-grouping of patients with neck-arm pain

Study 2
Identification of neuropathic pain in neck/upper limb pain

Clinical and somatosensory characteristics of patients with nerve-related neck-arm pain

Study 3
Characterisation of patients with cervical radiculopathy and patients with NSNAP in comparison to healthy controls and patients with fibromyalgia

Study 4
Neuropathic pain components in patients with cervical radiculopathy and NSNAP

Study 5
Correspondence of self-reported somatosensory profiles with QST profiles in patients with cervical radiculopathy and fibromyalgia

Figure 1.1 Studies of the thesis

1.2 Hypotheses of the PhD

Hypotheses of Study 1

- There would be a high inter-examiner agreement in classifying patients with cervical radiculopathy and patients with NSNAP, using specific classification systems.
- There would be a high agreement in patient classification between two clinical examiners using the specific classification systems and two independent experts.
- The diagnostic accuracy of the clinical examiners would be high, using the opinion and consensus of the experts as a reference criterion.

Hypotheses of Study 2

- The grading system of the NeuPSIG classification model would be applicable in patients with neck/upper limb pain.
- The level of agreement in detecting likely NeP in patients with neck/upper limb pain between the NeuPSIG classification model and the LANSS and PD-Q would be high.

Hypotheses of Study 3

- The sensory phenotypes between patients with cervical radiculopathy and patients with NSNAP would be different.
- In patients with cervical radiculopathy localised sensory abnormalities would be restricted to the maximal pain area and to the area of dermatomal sensory loss.
- In patients with NSNAP sensory abnormalities would be found only in the maximal pain area.
- Sensory profiles of the neck-arm pain groups would differ from that of patients with FM.

Hypotheses of Study 4

- In patients with cervical radiculopathy, there would be a significant side-to-side difference between the symptomatic and asymptomatic side in the previously (Study 3) documented sensory alterations in their maximal pain area and the affected dermatome.

- In patients with NSNAP, there would be a significant side-to-side difference between the symptomatic and asymptomatic side in the previously (Study 3) documented sensory alterations in their maximal pain area.

- Patients with cervical radiculopathy would be more likely to present with NeP components and therefore to score higher on the PD-Q than patients with NSNAP.

Hypothesis of Study 5

- The self-reported somatosensory profile of patients with painful cervical radiculopathy and of patients with FM, as indicated by responses to verbal sensory descriptors items of PD-Q, would corresponded with their sensory phenotype as demonstrated by QST.

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Chapter 2 –Literature Review

Key factors in developing a targeted holistic approach to management of patients with nerve-related neck-arm pain include the identification of the cause of pain, an appropriate clinical classification system for patients with neck-arm pain, the identification of differences in clinical pain presentations and the recognition of underlying pain types and involved pain mechanisms.

2.1   Heterogeneity of nerve-related neck-arm pain

The diversity of patients with nerve-related spinal neck-arm pain is reflected in the different clinical presentations and underlying pain types (nociceptive/neuropathic) and related pain mechanisms. A conceptual model is proposed with one end of the spectrum comprising pain conditions due to a nerve lesion as seen in cervical radiculopathy, the other end containing clinical presentations with very vague signs of a nerve disorder, characterised by non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) (Allison et al. 2002; Elvey 1997; Hall et al. 1997). Heightened nerve mechanosensitivity is a feature of nerve trunk pain (Dilley et al. 2005) which is regarded as a nociceptive pain (Marchettini et al. 2006) or inflammatory pain (Bennett 2006). It is characterised clinically by pain in response to limb movements that cause nerve elongation and local tenderness on nerve trunk palpation (Allison et al. 2002; Coppieters et al. 2003; Elvey 1997; van der Heide et al. 2006). The condition can present as a discrete disorder without any signs of nerve damage such as sensory or motor loss, abnormalities on imaging or nerve conduction studies (Coppieters et al. 2003; Elvey 1997; van der Heide et al. 2006). Patients with cervical radiculopathy and NSNAP may demonstrate similar clinical characteristics such as pain with or without negative sensory signs and/or positive sensory signs, however the mix of nociceptive and NeP components may vary. Each individual patient's pain might be somewhere on a continuum between "purely nociceptive" and "purely neuropathic" (Horowitz 2007), and the determination of the "pain mix" and possible dominance of one pain type is of therapeutic relevance, as NeP in particular requires targeted management (Baron et al. 2010a; Harden and Cohen 2003).

2.2   Taxonomy of nerve-related neck-arm pain disorders and neuropathic pain

A variety of terminologies are used for the description of peripheral nerve-related neck-arm pain disorders such as cervicobrachial pain (Salt et al. 2011), cervicobrachialgia (Voerman et al. 2000); radicular pain (Bogduk 2009; Merskey and Bogduk 1994), radiculopathy (Bogduk 2009; Merskey and Bogduk 1994), neuralgia, brachialgia, neuropathy, neurogenic pain (Merskey and Bogduk 1994), neuropathic pain (NeP) (Merskey and Bogduk 1994; Treede et al. 2008), and nerve trunk pain (Asbury and Fields 1984; Bennett 2006; Marchettini et al. 2006). One difficulty with various terminologies is a lack of consensus in the definition of some of these terminologies. For example the terms radiculopathy and radicular pain are often used interchangeably in the literature (Bono et al. 2011; Freynhagen et al. 2008; Mahn et al. 2011), but are in fact different entities (Bogduk 2009). Radiculopathy is defined as a neurological state in which conduction is blocked in axons of a spinal nerve or its roots, resulting in a loss of sensory and/or motor function (Bogduk 2009; Merskey and Bogduk 1994), and it may or may not be associated with the presence of pain. Radicular pain is defined as pain perceived in a limb caused by ectopic discharges from a dorsal root or its ganglion (Bogduk 2009). Radiculopathy and radicular pain may exist in isolation or coexist. The two syndromes can be part of a continuum, and radiculopathy may occur subsequent to radicular pain as the underlying disease progresses.

The former definition of NeP according to IASP referred to "pain initiated or caused by a primary lesion or dysfunction of the nervous system" (Merskey and Bogduk 1994). This definition created controversy particularly because of the term "dysfunction", which many authors considered renders the definition too vague (Jensen et al. 2002; Max 2002; Merskey 2002; Rasmussen et al. 2004). A new definition was proposed by NeuPSIG (Treede et al. 2008) and was recently endorsed: "pain caused by a lesion or disease of the somatosensory nervous system" (Jensen et al. 2011). This new definition replaces the term "dysfunction" with "disease" to distinguish NeP from pain such as that caused by neuroplastic changes in response to strong nociceptive stimulation. The term "nervous system" is replaced with the term "somatosensory system" to distinguish NeP from pain caused by lesions in other

parts of the nervous system. Thus, using this definition a motor radiculopathy accompanied by nociceptive neck pain would not be classified as a NeP condition. This distinction is important because the management may require quite different targeted approaches. NeP can be classified into central and peripheral NeP. In the context of this thesis, the term NeP refers to peripheral NeP, unless specified otherwise.

2.3   Epidemiology

Epidemiological data on cervical radiculopathy are scarce. Radhakrishnan et al (1994) performed a large retrospective population based study and reported an annual age-adjusted incidence rate of 83.2 per 100 000 in total, with a mean age at diagnosis 47.9 ± 13.4 years and a male predominance. The male to female ration of the adjusted rates was 1.7. However, it was stated that these data should be considered conservative, as patients with mild symptoms of radiculopathy might not have sought medical attention and therefore might have been under-reported. It is not clearly demonstrated if every patient in the study by Radhakrishnan et al (1994) demonstrated a neurological deficit, meaning that patients with just radicular pain might also have been included in the analysis. A door-to-door survey in Sicily on 7653 individuals found a prevalence of 3.5 per 1000, with similar age distribution (Salemi et al. 1996). Again, these data did not necessarily reflect just the presence of radiculopathy, as they also seemed to include individuals with radicular pain without signs of nerve root damage. A systematic review on the burden and determinants of neck pain in the general population found an incidence rate of 0.055 per 1000 persons per year of disc herniation with radiculopathy (Hogg-Johnson et al. 2008). The course of clinical improvement of patients with cervical radiculopathy is not well documented. While some patients might demonstrate complete recovery with conservative management, others might still present with symptoms after 10 years and/or undergo surgery (Casey 2011).

The prevalence of NSNAP disorders is not known and only anecdotal data exists. Clinical signs of heightened nerve mechanosensitivity was shown in 30 out of 120 patients with cervicobrachial pain syndrome (Allison et al. 2002), however it was not stated if the condition presented as a discrete disorder without any clinical signs of

nerve damage. Clinical signs of heightened nerve mechanosensitivity were also demonstrated in patients with chronic whiplash (Quintner 1989; Sterling et al. 2002b). Out of 40 patients with nerve-related low back and leg pain, 10% demonstrated features of heightened nerve mechanosensitivity as a discrete disorder without any clinically established neurological deficits, and in 57% heightened nerve mechanosensitivity coexisted with clinical signs of nerve root damage such as sensory and strength/reflex deficits (Schäfer et al. 2009).

Data on the prevalence of NeP in chronic neck/upper limb pain conditions are scarce. There are indications that NeP is underdiagnosed in musculoskeletal conditions (Jespersen et al. 2010). In two large cohorts of patients with chronic low back pain (with or without leg pain), the prevalence of NeP components was found to be 37% and 54.7% (Freynhagen et al. 2006a; Kaki et al. 2005). The differences in prevalence may relate to the use of different NeP screening tools (see section 2.9.3) as well as the observation that NeP and nociceptive pain components vary in the back and leg of patients with low back pain (Attal et al. 2011). NeP is typically associated with more severe pain for patients than nociceptive pain (Bouhassira et al. 2008; Freynhagen et al. 2006a; Torrance et al. 2006), and with suffering, disability, impaired health-related quality of life (Berger et al. 2004; Berger et al. 2008; Doth et al. 2010; Freynhagen et al. 2006a; Meyer-Rosberg et al. 2001; O'Connor 2009; Saldaña et al. 2010a; Saldaña et al. 2010b) and increased health care use (Freynhagen et al. 2006a; Saldaña et al. 2010a; Saldaña et al. 2010b).

2.4   Clinical presentation of nerve-related neck-arm pain

2.4.1   Clinical presentation of cervical radiculopathy

The classic clinical picture of cervical radiculopathy includes neck pain with radicular pain radiating down the arm, paraesthesia in arm and hand in conjunction with sensory deficits and/or motor deficits in a dermatomal/myotomal distribution. However, the degrees and frequencies of sensory and motor changes vary as well as the symptoms of paraesthesia and pain (Radhakrishnan et al. 1994). Radicular pain is described as lancinating in quality, shocking and electric, and travels along a narrow band, in the territory supplied by the affected axon (Bogduk 2009; Marchettini et al. 2006; Merskey and Bogduk 1994; van Zundert et al. 2006). However, clinical studies

have shown that segmental origin of radicular pain cannot be determined by its distribution (Bogduk 2009). Slipman et al (Slipman et al. 1998) demonstrated that although the distribution of symptom provocation on cervical nerve root stimulation resembled the classic dermatomal maps for these nerve roots, symptoms were frequently provoked outside of the distribution of these dermatomal maps. Another study demonstrated non-dermatomal pain distribution in patients with cervical nerve root pain in 69.7% of cases (Murphy et al. 2009). Radiculopathy may occur in isolation or in association with radicular pain, somatic referred pain (pain occurring in a region of the body innervated by nerves or branches of nerves other than those that innervate the actual source of pain (Merskey and Bogduk 1994)), nerve trunk pain or local somatic spinal pain.

For patients with painful cervical radiculopathy, the disorder is associated with disability (Chien et al. 2008; Saldaña et al. 2010a; Saldaña et al. 2010b), impaired physical health and negative impact on mental health with increasing chronicity of the disorder (Daffner et al. 2003; Meyer-Rosberg et al. 2001). Patients presenting with axial neck pain and radicular symptoms are reported to be much more disabled than patients with just neck pain or just radicular pain alone, and the condition has a greater impact on mental health status on younger patients (younger than 40 or 40 – 60 years) compared to patients over 60 years of age (Daffner et al. 2003). Mood disorders such as anxiety and depression (Freynhagen et al. 2006a; Saldaña et al. 2010b; Schmidt et al. 2009) and sleep/fatigue disturbances are frequently reported in patients with radiculopathy (cervical/lumbar) (Freynhagen et al. 2006a; Meyer-Rosberg et al. 2001; Saldaña et al. 2010b; Starkweather), and more frequently compared to patients with nociceptive pain disorders (Freynhagen et al. 2006a; Saldaña et al. 2010b; Schmidt et al. 2009), contributing to impaired mental health. Furthermore, the frequency and severity of these comorbidities in, for example patients with lumbar radiculopathy is similar to that reported in patients with 'typical' NeP conditions such as diabetic neuropathy and postherpetic neuralgia (Mahn et al. 2011).

Radiculopathies related to spinal column diseases are said to be amongst the most common causes of NeP (Haanpää et al. 2009). However, it is not clear if these presentations are always characterised by predominantly NeP components as they are

increasingly referred to as mixed pain syndromes (Attal and Bouhassira 2004; Baron and Binder 2004; Behrman et al. 2007; Freynhagen et al. 2006b; Gálvez et al. 2007; Hansson and Haanpää 2007; Pérez et al. 2009; Portenoy 2006), but can also be classified as a NeP condition (Attal et al. 2008; Bennett 2001; Portenoy 2006; Unal-Cevik et al. 2010). Again, the definition of radiculopathy or diagnostic criteria for radiculopathy varies between publications and this hinders study comparisons and generalisability. No study has yet investigated the predominant underlying pain type in patients with clearly defined painful cervical radiculopathy. This was one of the aims of Studies 3 and 4 (Chapter 6, 7) in this thesis.

2.4.2 Clinical presentation of non-specific neck-arm pain associated with heightened nerve mechanosensitivity

Patients with NSNAP present with pain that is provoked or aggravated by limb movements that cause lengthening/elongation of the affected nerve. Depending on the severity of heightened nerve mechanosensitivity, and compared to the asymptomatic side, such limb movements will be restricted in range due to an evoked pain response (Allison et al. 2002; Coppieters et al. 2003; van der Heide et al. 2006). Shoulder abduction is often limited in range as it has been documented that this movement causes increased tension in the brachial plexus (Elvey 1988; Ginn 1988) and median nerve (Kleinrensink et al. 1995; Wright et al. 1996). Standard clinical neurological examination and electrodiagnostic studies are usually normal unless this clinical presentation exists in concurrence with a nerve lesion, as seen in cervical radiculopathy (Chien et al. 2008).

The concept of heightened nerve mechanosensitivity is not new, with literature on the assessment of heightened nerve mechanosensitivity in the lower and upper limb dating back to 1880 (Supik and Broom 1994) and 1887 respectively (Poore 1887). Whilst the straight leg raise test is widely used in medicine for the examination of patients with heightened nerve mechanosensitivity with lower back and leg pain (Devillé et al. 2000; Freynhagen et al. 2008; Kobayashi et al. 2003; Samuelsson and Lundin 2002), the analogous upper limb tests have not gained much recognition in the medical field and seem to be used predominantly by physiotherapists (Allison et al. 2002; Butler 2000; Coppieters et al. 2006; Coppieters et al. 2003; Elvey 1997;

Sterling et al. 2002b; van der Heide et al. 2006; Wainner et al. 2003). However, their application has been accepted as part of the standard clinical examination of patients with neuromusculoskeletal pain disorders (Petty and Moore 2001), as the presence of heightened nerve mechanosensitivity may have implications for treatment.

2.4.3   Clinical presentation of neuropathic pain

Patients with cervical radiculopathy and patients with NSNAP may present with NeP. Peripheral NeP is generally characterised by pain and sensory abnormalities in the area corresponding to the innervation territory of the damaged nerve structure (Baron 2009; Chong and Bajwa 2003; Hansson 2002; Jensen and Baron 2003). In addition to pain, the core signs include sensory deficits, that is negative sensory symptoms, indicating a loss of function due to the reduction of afferent input caused by the nerve lesion. In addition to these negative sensory signs, various positive sensory symptoms, indicating a gain of function, can be present including paraesthesia or dysaesthesia, spontaneous (not stimulus-induced) ongoing pain, spontaneous electric shock like sensations and evoked pain (hyperalgesia, allodynia) (Baron and Binder 2004; Baron and Tölle 2008; Dworkin 2002). A small percentage of patients with peripheral nerve injury may however present with nearly pure positive sensory signs with no demonstrable sensory deficit (Baron 2009). The quality of NeP is often described as a shooting or burning quality, with tingling or electrical sensations and numbness (Bouhassira and Attal 2011) whereas nociceptive pain is frequently described as an ache (Dworkin et al. 2009; Merskey and Bogduk 1994), dull and throbbing (Rasmussen et al. 2004). While all the above symptoms, signs and pain descriptors are not universally present and no single characteristic is pathognomonic for NeP (Behrman et al. 2007; Hansson et al. 2007), a combination of sensory descriptors can help to discriminate between nociceptive and NeP groups, as demonstrated with the use of various NeP screening tools (see section 2.9.3) (Bennett 2001; Bennett et al. 2005; Bouhassira et al. 2005; Krause and Backonja 2003).

2.5   Aetiology and pathophysiology of nerve-related spinal neck-arm pain

Radicular pain and conduction block in radiculopathy can be caused by lesions that directly compromise the dorsal root ganglion mechanically or indirectly compromise the spinal nerve and its roots by causing ischemia or inflammation of the axons (Merskey and Bogduk 1994). The most common causes for cervical radiculopathy and radicular pain are cervical spondylotic changes such as spurring of the vertebral body, uncovertebral joints, facet joints or a combination of these factors causing foraminal stenosis and cervical disc herniation. These features can act mechanically as a space-occupying lesion affecting the axons (Merskey and Bogduk 1994). The most common level of root compression is C7, followed by C6 (Radhakrishnan et al. 1994). Although degenerative changes of the cervical spine may be very obvious on imaging studies, clinically the disease might not be severe or even symptomatic (Friedenberg and Miller 1963; Kuijper et al. 2011). Myelograms, computed tomographic scans and magnetic resonance images (MRI) have revealed abnormal spinal findings in 20 - 40% of subjects without any history of pain (Boden et al. 1990; Hitselberger and Witten 1968; Matsumoto et al. 1998; Wiesel et al. 1984). In a cohort of 78 symptomatic patients with pain and clinically established unilateral cervical radiculopathy, false-positive results of nerve root compression on MRI were found in 45% of cases, either on the contralateral asymptomatic side or at levels above or below the clinically affected level (Kuijper et al. 2011). Hence, mechanical compression per se is not directly related to pain production.

Compression of a nerve root may induce numbness, but usually does not cause pain (Lindahl 1966; Rydevik et al. 1984; Sunderland 1981). Pain typically becomes part of the compression syndrome when the blood supply to nerve fibres is seriously impaired; when intraneural fibrosis is impairing the nutrition of nerve fibres (Sunderland 1981); or in the presence of inflammation (Ahlgren and Garfin 1996; Garfin et al. 1991; Murphy 1977). The effects of nerve fibre compression and impaired blood supply are supported by the observation that the blood flow in the affected nerve root of patients undergoing discectomy increased in patients who reported pain resolution after surgery compared to patients not reporting any relief of

symptoms, suggesting that in the latter group the experienced symptoms may be partly due to the blood flow restriction (Hida et al. 2003).

The influence of inflammation on pain perception was documented in human experiments in patients with lumbar radicular pain (Greenbarg et al. 1988; Kuslich et al. 1991; Smyth and Wright 1958). In these patients gentle mechanical manipulation of involved or inflamed nerve roots elicited radicular pain but mechanical stimulation of normal nerve roots was pain free. It has been demonstrated in animal experiments that compression and inflammation can induce nerve dysfunction and pain behaviours and that the combination of both may induce more nerve root injury than each factor per se (Rothman and Winkelstein 2007; Takahashi et al. 2003). Furthermore, the magnitude and duration of compression and inflammation are further key factors in modulating nerve function (Takahashi et al. 2003; Winkelstein and DeLeo 2002).

A further mechanism for compression linking with pain provocation, lies in the involvement of the dorsal root ganglia. Animal studies have shown that minimal stimulation/compression of intact dorsal root ganglia induced prolonged repetitive firing in sensory axons (Howe et al. 1977; Wall and Devor 1983). It therefore seems likely that compression of the dorsal root ganglia can play a role in the generation of radicular pain (Bogduk 2009; Howe et al. 1977). Furthermore, in vivo studies on rats demonstrated a significant correlation between the duration of nerve root compression and mechanical allodynia, defined as pain in response to non-noxious mechanical stimulus, and microglial activation in the dorsal horn; the longer the sustained compression, the greater the pain sensitivity and spinal glial reactivity (Rothman et al. 2010). Similarly, a correlation was observed in rats between increased severity of nerve root injury elicited by nerve root ligation, and mechanical allodynia and greater spinal glial activation (Winkelstein and DeLeo 2002). Spinal glia cells release neurotransmitters and pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL) – 1 and IL-6, suggesting these have a direct influence on neuronal activity in the spinal cord and on pain modulation (Watkins et al. 2001).

Nerve root dysfunction and pain can also be induced by inflammation and chemical irritation without any mechanical compression of nerve tissue (Marshall and Trethewie 1977; Olmarker et al. 1993; Peng et al. 2007; Smyth and Wright 1958; Yabuki et al. 1998). Inflammation can be caused by injury or by an autoimmune reaction from exposure to disc tissues resulting in release of cytokines (TNF-α) (Bobechko and Hirsch 1965; Gertzbein et al. 1975; Rothman et al. 2009). Breakdown products from a degenerating nucleus pulposus might leak out and induce a chemical radiculitis along the nerve root (Marshall and Trethewie 1977). A clinical study by Peng et al (Peng et al. 2007) demonstrated a significant correlation between the site of annular tear and the side of radiating leg pain in patients with discogenic low back pain with no disc herniation. In this study, abnormalities of electromyogram (EMG) and reduced motor nerve conduction velocity were found on the side of radiating leg pain, consistent with nerve injury in the absence of nerve compression (Peng et al. 2007). Other causes of radicular pain such as malignancy (Kuijper et al. 2009), infection (De Burca 2009; Feinberg et al. 2007; Kuijper et al. 2009; Polston 2007) and vascular causes (Benney et al. 2011) have also been reported.

Sensitisation of nerve tissue by mechanical, chemical or inflammatory means (Kuslich et al. 1991; Owen et al. 1994; Smyth and Wright 1958) can increase the affected nerve's sensitivity to mechanical stimuli. Preliminary data from animal studies have documented that with induced inflammation, intact nerve fibres can become mechanosensitive to pressure at the lesion site and mechanosensitive to stretch in the absence of any concurrent signs of axonal damage (Bove et al. 2003; Dilley et al. 2005; Eliav et al. 2001). The majority of responsive fibres responded to less than 5% stretch, which is within the range of human in vivo nerve stretch seen during normal limb movements (Dilley et al. 2003). This model of heightened nerve mechanosensitivity may account for pain provoked in patients with NSNAP with upper limb movements that induce lengthening of the affected nerve.

A further proposed mechanism for heightened nerve mechanosensitivity is the activation of the nervi nervorum which are located in peripheral nerve sheaths (Amir et al. 2006; Eliav et al. 1999; Marchettini et al. 2006; Quintner and Bove 2001). Electrophysiological studies demonstrated that at least some of the nervi nervorum

function as nociceptors, as they responded to noxious mechanical, chemical and thermal stimuli (Bove and Light 1995; Bove and Light 1997). Further, it has been shown that the nervi nervorum contain neuropeptides including substance P and calcitonin gene-related peptide. Release of these neuropeptide may assist in initiating neurogenic inflammation, hence contributing to nociception and pain perception (Bove and Light 1997; Sauer et al. 1999).

2.6   Pain mechanisms

Distinct subtypes of pain exist: nociceptive, inflammatory, neuropathic and functional pain (Woolf 2004b). Nociceptive pain is defined as a transient pain in response to a noxious stimulus/ stimulation of nociceptive primary afferents. The initiating event is impending or actual tissue damage. Strictly speaking, in the absence of tissue damage, nociceptive pain is a physiological pain rather than a clinical pain (Backonja 2003). However, the term nociceptive pain is commonly used for pain in response to damage to non-neuronal tissues with the nociceptive system being intact (Baron and Tölle 2008), such as in osteoarthritis or inflammatory pain (Campbell and Meyer 2006). In the context of this thesis, the latter definition of nociceptive pain will be used. In contrast, NeP is initiated by structural damage to the nociceptive nervous pathway accompanied by a loss or gain in sensitivity. Functional pain is characterised by hypersensitivity to pain resulting from abnormal central processing of normal input in the absence of any peripheral abnormality or tissue damage such as in patients with FM (Woolf 2004b). Despite the different causes of nociceptive, neuropathic and functional pain, they do present with similar characteristics, such as spontaneous pain in the absence of any stimulus, an exaggerated pain response to noxious input (hyperalgesia) or evoked pain such as pain in response to light touch (allodynia). There may be commonalities, but also differences in the underlying mechanisms between the pain types. For example peripheral sensitisation of nociceptors due to changes to the chemical environment after tissue damage is not a prerequisite for functional pain.

Nociception and associated pain are normally elicited by activity in C-fiber nociceptors with slowly conducting unmyelinated axons and Aδ nociceptors with thinly myelinated axons. The receptive properties of these afferent neurons are

determined by their expression of transducing ion-channel receptors (Woolf 2004b). When tissue damage occurs, inflammatory mediators activate and sensitise sensory afferents by producing changes in the expression of membrane ion-channels, resulting in ongoing nociceptive input and spontaneous neuronal discharge. Compared to nociceptive pain, and as an example, the increased expression of voltage-gated sodium channels is suggested to play a key role in the pathogenesis of NeP (Amir et al. 2006; Baron 2006). Higher sodium channel density not only occurs at the site of a nerve lesion, but also in the nerve root and intact dorsal root ganglion with subsequent increased ectopic discharges and higher mechanosensitivity (Chen et al. 2004; Dilley et al. 2005). This ectopic excitability is suggested to be a contributor to spontaneous NeP such as spontaneous burning pain and electric-shock-like sensations (Baron 2006; Woolf 2004a).

Peripheral inflammation may induce upregulation of temperature-sensitive ion channels (Knowlton et al. 2010; Obata et al. 2005), leading to peripheral sensitisation of C-nociceptors and associated symptoms of cold or heat hyperalgesia (Baron 2006) in inflammatory and NeP disorders. Peripheral nerve injury may also cause changes in neighbouring uninjured nerve fibers, contributing to pain signalling (Baron 2006; Woolf 2004a). Release of nerve growth factors may trigger the release of TNF-α and channel and receptor expression, potentially altering the excitability of uninjured afferents (Baron 2006; Wu et al. 2002). Furthermore, a switch in the phenotype of neurons has been reported (Woolf and Salter 2000), thus that brain-derived-neurotrophic-factors and substance P, that are normally expressed in C-fibers, can be expressed in A-fibers (Woolf 2004a). Hence, these A-fibers may be able to produce central changes such as mechanical allodynia that are normally induced by C-fibers input.

As a consequence of peripheral nociceptor hyperactivity, secondary changes can occur in second-order neurons in the spinal cord dorsal horn, contributing to central sensitisation. A cascade of events takes place that is induced by the release of transmitters from nociceptive terminals, leading to synaptic plasticity, facilitating nociceptive input. For example, prolonged firing of C-fibre nociceptors causes release of substance P and glutamate which acts on postsynaptic N-methyl-D-aspartate (NMDA) receptors in the spinal cord. Activation of NMDA receptors

causes second order spinal cord neurons to become hyperresponsive, so that normally undetected inputs provoke an expansion of neuronal receptive fields. Innocuous stimuli such as light touch may elicit pain such as dynamic mechanical allodynia and areas outside an injured site develop secondary hyperalgesia presenting as tenderness (Baron 2006). Peripheral nerve injury also activates spinal cord glial cells which further enhances excitability of wide dynamic range neurons by releasing cytokines and growth factors and increasing glutamate formation (Rothman et al. 2010). One mechanism of increased dorsal horn excitability that is associated with sensation and nerve fibre loss applies only to NeP (Baumgärtner et al. 2002). It is proposed that the loss of afferent input from large myelinated fibres leads to hypoactivity of the inhibitory interneurons and may facilitate spontaneous activity in nociceptive neurons (Baumgärtner et al. 2002).

Peripheral and central sensitisation are physiological processes occurring with any kind of tissue injury and represent temporary plasticity of the nociceptive system, and is typically associated with a reversible modulation of the nociceptive system (Woolf and Salter 2000). Disinhibition may also contribute to enhanced pain processing. As indicated previously, within the spinal cord, inhibition is mediated by inhibitory interneurons. Cell death of these interneurons, as seen after nerve injury, may diminish the tight inhibitory control on dorsal horn neurons (Woolf and Mannion 1999). In addition, descending inhibitory inputs from the brain stem may be altered, with a loss of the normal inhibitory restraint of CNS excitability, and descending facilitatory mechanisms may play a role in increased sensory transmission after inflammation and peripheral nerve injury (Woolf 2004b). Furthermore, psychosocial factors such as emotions, cognition and attention cause changes in cortical and subcortical areas, hence playing an integral role in pain perception (Neugebauer et al. 2009).

Hyperalgesia is a common sensory symptom in nociceptive as well as NeP and is based on the facilitation of the nociceptive system, either due to peripheral sensitisation of nociceptors and central sensitisation of spinal cord neurons or reduced descending inhibition of increased facilitation, or a mixture of all (Treede and Magerl 2000). It is suggested that in NeP states, hyperalgesia due to central sensitisation occurs predominantly in the close vicinity of the affected peripheral

nerve, whereby a deficit in descending inhibition typically has remote effects in other body areas (Magerl and Klein 2006).

2.7 Assessment and classification of patients with painful cervical radiculopathy

2.7.1 Clinical assessment of patients with painful cervical radiculopathy

Numerous musculoskeletal disorders such as myofascial pain syndromes, lateral epicondylitis, and de Quervain's tenosynovitis may mimic radicular symptomatology (Ahlgren and Garfin 1996; Cannon et al. 2007; Dalton and Jull 1989; Dillin et al. 1986; Lauder 2002). Therefore specific diagnostic criteria are required in order to distinguish cervical radiculopathy from other pathologies. Due to a lack of diagnostic gold standards the diagnosis of painful cervical radiculopathy is largely clinical. The clinical diagnosis is based on the findings of a comprehensive clinical examination (Kuijper et al. 2009; Wainner and Gill 2000) incorporating the medical history, an assessment of both musculoskeletal and related neural tissues and a neurological bedside examination of somatosensory and motor function (Cruccu et al. 2010; Hansson 2002; Jepsen et al. 2006; Wainner et al. 2003). Moderate to substantial inter-examiner reliability (Landis and Koch 1977) has been documented for clinical tests of nerve function (sensory testing, reflexes and manual muscle testing) in the upper limb (Jepsen et al. 2006; Jepsen et al. 2004; Schmid et al. 2009) and for clinical nerve root provocative tests such as the Spurling's test (Spurling and Scoville 1944), the Valsalva manoeuvre and neck distraction test (Wainner et al. 2003). Generally, the existing literature appears to indicate high specificity and low sensitivity for the latter three tests (Tong et al. 2002; Viikari-Juntura et al. 1989; Wainner et al. 2003), indicating the need for better discriminative tools to identify patients with cervical radiculopathy.

Results of medical investigations (e.g. imaging, electrodiagnostic tests) may aid in the diagnostic work-up of painful cervical radiculopathy (Bono et al. 2011; Kuijper et al. 2009; Treede et al. 2008), however, as already outlined, sometimes clinical findings do not correlate with radiological findings. MRI is the method of choice to confirm correlative nerve compression, particular to detect disc protrusion, whereas computerised tomography (CT) is possibly superior in showing foraminal stenosis by

bony prominence (Kuijper et al. 2009). The diagnostic value of electromyography (EMG) is still a matter of debate (Bono et al. 2011; Kuijper et al. 2009; Plastaras and Joshi 2011; Tsao 2007). The sensitivity of EMG in detecting radiculopathy is limited by several factors (Plastaras and Joshi 2011) that can lead to false-negative results. Firstly, radiculopathies that are predominantly sensory cannot be confirmed by EMG (Dillingham 2002; Dillingham and Lauder 2005; Plastaras and Joshi 2011), as the EMG investigates myotomal pattern of abnormalities. Secondly, a myotomal pattern of abnormalities may not be identified if axonal compromise is not severe enough; and thirdly, the appearance of abnormalities is time-dependent and may not appear until some weeks after axonal damage (Plastaras and Joshi 2011; Tsao 2007). Nerve conduction studies (NCS) are useful to rule out other conditions like median or ulnar neuropathies or polyneuropathies, but have little value in confirming radiculopathy (Dillingham 2002; Kuijper et al. 2009). Sensory NCS typically are normal in patients with radiculopathy because the location of the nerve root lesion is proximal to the dorsal root ganglion (Dillingham 2002; Plastaras and Joshi 2011; Tsao 2007). Motor NCS are only abnormal if substantial motor axon loss (up to 50%) has occurred. Furthermore routine motor NCS performed in the upper limb assess muscles predominantly subserved by the C8 and T1 nerve roots, hence these NCS may be insensitive for the most common C6 and C7 radiculopathies (Plastaras and Joshi 2011; Tsao 2007).

2.7.2   Classification of patients with cervical radiculopathy

No single examination item (clinical or medical investigation) on its own is diagnostic. Therefore the diagnosis of cervical radiculopathy should be based on a combination of items. Wainner et al (Wainner et al. 2003) identified a test item cluster of 4 clinical items for the identification of cervical radiculopathy, using electrophysiological examination as reference criterion for radiculopathy. The proposed cluster included a median nerve-biased nerve provocation test (NPT) (NPT$_{MEDIAN}$) (Elvey 1997), cervical rotation less than 60º, the neck distraction test and the Spurling's test (Spurling and Scoville 1944). If all four items were present, the probability of the presence of cervical radiculopathy increased to 90%. However, the analysis included only 16 patients with cervical radiculopathy, limiting generalisability of the findings. Interestingly, this prediction rule did not include any

clinical signs of nerve root dysfunction such as loss of sensory or motor function which are the characteristic of defined radiculopathy (Bogduk 2009). The clinical items rather relate to pain provocation tests. Thus, these test items are likely to be positive in patients with radicular pain, but this may not be associated with nerve root damage.

Radhakrishnan et al (Radhakrishnan et al. 1994) proposed certain sets of diagnostic criteria to confirm the presence of definite radiculopathy (see Study 1, Chapter 4, Table 4.1). Although this classification system is 16 years old, it is still recommended (Rubinstein et al. 2007), however the reliability has never been assessed. The first set of diagnostic criteria relates to electromyographic evidence of acute denervation or identification of an affected cervical root at surgery. The second set includes clinical signs of sensory and motor nerve root impairment and the third set incorporates clinical findings such as the presence of pain with positive sensory symptoms or motor impairment as well abnormalities on myelography, computer-assisted myelography, or magnetic resonance imaging at the clinically relevant level correlating with cervical radiculopathy. The system has some shortcomings, as the first two sets of criteria do not make any reference to pain, and the last set does not include computed-tomography scans which are recognised as a confirmatory tests for nerve root compression (Bono et al. 2011; Treede et al. 2008). Additionally, as defined in the last set of diagnostic criteria, the presence of neck pain with paraesthesia and a demonstrable abnormality on imaging does not necessarily implicate the presence of radiculopathy. However, including appropriate amendments to these sets of diagnostic criteria, the classification system may be feasible for the identification of painful radiculopathy. This was investigated in Study 1 (Chapter 4).

2.8   Assessment and classification of patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity

2.8.1   Clinical assessment of patients with NSNAP

Analogue the straight leg raise test, examination procedures (Neurodynamic Tests or NPT) have been developed to examine heightened nerve mechanosensitivity in the upper limb (Bragard 1929; Butler 1991; Elvey and Hall 1997; Poore 1887; Shacklock 2005). Moderate to substantial inter-examiner reliability has been documented for these NPTs in the upper limb (Jepsen et al. 2006; Schmid et al. 2009; Vanti et al. 2010; Wainner et al. 2003). Anatomical experiments have verified that the NPT_{MEDIAN}, which will be used in this thesis, has the highest specificity amongst the upper limb tests (Kleinrensink et al. 2000; Kleinrensink et al. 1995), that is it did not cause significant tension in other nerves.

An abnormal response to a NPT is defined as the reproduction of the patient's symptoms together with reduced range of motion in the symptomatic limb compared to the asymptomatic side (Elvey 1997; Hall and Elvey 1999). A second condition for a positive test is that the symptoms can be influenced by changing the amount of nerve provocation by alteration of proximal or distal joint positions. This clinical evaluation is used to differentiate symptoms of neural origin from local musculoskeletal pathology. Many structures are stressed during the NPT (McLellan and Swash 1976; Moses and Carman 1996; Wilson et al. 1994) any of which can contribute to a painful response to the test (Di Fabio 2001). However, using a combination of limb and spine movements it is possible to move and bias mechanical stress to neural structures (Kleinrensink et al. 1995; Wilson et al. 1994; Zorn et al. 1995). The NPT_{MEDIAN} has been shown to discriminate between referred and local sources of upper limb pain (Selvaratnam et al. 1994). Furthermore, the application of an experimental in vivo human pain model provided indirect support for the validity of the testing procedure. Hypertonic saline-induced pain in the thenar muscles of healthy volunteers did not alter the responses to the NPT_{MEDIAN} (Coppieters et al. 2006), suggesting that the NPT_{MEDIAN} did not provoke predominant strain on the thenar muscles, but may be on neural tissues.

Nerve trunk palpation may further aid in the assessment of mechanical nerve sensitivity (Bragard 1929; Butler 2000; Elvey 1997; Elvey and Hall 1997; Jepsen et al. 2006; Poore 1887; Quintner and Bove 2001; Shacklock 2005). Mechanical hyperalgesia of peripheral nerve trunks has been demonstrated in the symptomatic arm of patients with painful cervical radiculopathy (Chien et al. 2008; Hall and Quintner 1996) suggesting peripheral nerve sensitisation. However, the diagnostic value of nerve trunk palpation for the evaluation of patients with neck-arm pain is not known, and one has to keep in mind that palpation over a nerve trunk may simultaneously stimulate other tissue in close vicinity such as fascia and muscles that may provoke a pain response. Furthermore, a heightened pain response to nerve trunk palpation or to a NPT is not necessarily a corollary of peripheral nerve sensitisation. Patients with whiplash associated disorders demonstrated decreased pressure pain thresholds over upper limb peripheral nerve trunks in both the symptomatic and asymptomatic arm (Sterling et al. 2002a), and similarly abnormal responses to the NPT$_{MEDIAN}$ were observed in both arms (Sterling et al. 2002b). This bilateral increased sensitivity of neural structures to pressure and movement suggests a more global generalised hypersensitivity. So the NPT is really just another clinical sign, which taken alone is not diagnostic for any specific syndrome.

2.8.2   Classification of patients with NSNAP

The response of a patient to a single NPT is of limited value for the identification of nerve trunk pain and associated heightened nerve mechanosensitivity. Test responses must be interpreted within the clinical context of a number of other assessment procedures before a classification of heightened nerve mechanosensitivity as a clinical sign, can be made. A set of classification criteria has been proposed (Elvey 1997) and this includes: (i) an abnormal response to a NPT, (ii) a correlating active movement dysfunction (e.g. limitation of range of motion of shoulder abduction and/or pain on shoulder abduction, and which increases with addition of cervical contralateral flexion and/or with wrist extension as loading manoeuvres) and (iii) an abnormal response on clinically relevant nerve trunk palpation (hypersensitivity compared to the asymptomatic side). This classification system has been applied in various studies (Allison et al. 2002; Hall et al. 1997; van der Heide et al. 2006) and

while reliability has been established in patients with low back and leg pain (Schäfer et al. 2009), the reliability has not yet been established in patients with neck-arm pain.

In summary, patients with painful cervical radiculopathy and patients with NSNAP may demonstrate similar clinical pain patterns, but their clinical presentations typically differ. Identification of such differences and the appropriate classification of patients with these neck-arm pain conditions is important, to enable clinicians to provide appropriate best-evidence management. The classification of these patients is largely clinical, and while specific classification systems have been proposed for both pain conditions, their reliability has never been established. This was the focus of Study 1 presented in Chapter 4.

2.9 Assessment and classification of patients with neuropathic pain

2.9.1 Clinical assessment of patients with neuropathic pain

The diagnosis of NeP is based on findings of clinical examination and diagnostic tests (Cruccu et al. 2010; Haanpää et al. 2011; Haanpää et al. 2009). The clinical examination comprises the patient's medical history, pain drawings including location, description and intensity of pain, pain behaviours, and a neurological examination, including sensory testing. Pain distribution in the innervation territory of the affected nerve structure and a history indicative of a nerve injury or disease provide hints for the possible presence of NeP (Treede et al. 2008). For the assessment of somatosensory functions, sensory testing of touch, vibration, cold, warmth and pinprick is recommended (Haanpää et al. 2011). However, no consensus is evident for which type of sensory testing is obligatory for the assessment of NeP, as for example the two NeP screening tools that contain physical examination items do not include the assessment of vibration and thermal stimuli (Bennett 2001; Bouhassira et al. 2005).

Furthermore, sensory abnormalities found in the patient's area of pain do not necessarily indicate the presence of NeP. Sensory aberrations have been reported in patients with nociceptive pain, in experimental pain models on humans and in

patients with no identifiable underlying pathology such as FM (Blumenstiel et al. 2011; Geber et al. 2008; Leffler et al. 2000; Magerl and Treede 2004; Pfau et al. 2009; Westermann et al. 2011). In addition, cold hypersensitivity, a common sequel of nerve injuries (Landerholm et al. 2010; Taylor et al. 2010), has also been documented in patients with depression but without pain (Klauenberg et al. 2008).

Currently it is recommended that sensory testing in patients with unilateral pain should be compared to the contralateral mirror side (Haanpää et al. 2011; Haanpää et al. 2009) however, there is evidence the asymptomatic side may be misleading as a true control (Baron 2006). Bilateral sensory changes have been documented in patients with trigeminal neuropathy (Jääskeläinen et al. 2005; Leffler and Hansson 2008), cervical radiculopathy (Chien et al. 2008), and non-NeP (Leffler et al. 2003). Bilateral sensory alterations may suggest neuronal plasticity in the mediation of sensory input from the contralateral side (Davis et al. 2011) and activation of inhibitory mechanism interacting bilaterally (Leffler et al. 2003). Despite the complexity of sensory alterations, studies have shown that sensory examination can discriminate patients with NeP from patients with nociceptive pain (Bennett 2001; Bouhassira et al. 2005; Dworkin et al. 2007; Rasmussen et al. 2004; Scholz et al. 2009).

Findings of diagnostics tests such as imaging techniques, neurophysiological tests and skin biopsies complement the diagnostic work-up for the presence of NeP (Baron and Tölle 2008; Cruccu et al. 2010; Haanpää et al. 2011). While these diagnostic tests do not distinguish between painful and painless nerve lesions, they do supplement the differential diagnosis of a peripheral nerve lesion or disease.

2.9.2   Classification of patients with neuropathic pain

The identification of NeP in patients with 'typical' NeP conditions such as postherpetic neuralgia is reported to be much easier compared to the identification of NeP in conditions with mixed nociceptive and neuropathic pain characteristics such as radiculopathy (Attal and Bouhassira 2004; Behrman et al. 2007; Rasmussen et al. 2004). There may be various degrees of neuropathic components, also referred to as pain 'being more or less neuropathic' (Attal and Bouhassira 2004; Bennett et al.

2006). In order to address this spectrum of NeP, two previous studies in patients with chronic pain of various aetiologies grouped patients according to the 'increased suspicion' of NeP (e.g.'definite', 'possible' or 'unlikely') (Bennett et al. 2006; Rasmussen et al. 2004). This concept was also adopted by the NeuPSIG and a grading system with different levels of certainty about the presence of NeP (no, possible, probable, definite) was developed (Treede et al. 2008). This new diagnostic approach is based on a stepwise process that requires a history-derived working hypothesis, based on pain distribution and history suggesting a relevant lesion, and confirmatory evidence from a neurological examination and diagnostic tests (e.g. neuroimaging, neurophysiological methods). The application of this grading system has been recommended for use in primary care (Haanpää et al. 2009) and its use has been reported in some case studies (Geber et al. 2009; Haanpää et al. 2009), and more recently in a prospective study following thoracotomy (Guastella et al. 2011). However, the applicability of this grading system in identifying NeP in patients with neck-arm pain has not yet been investigated. This was the aim of Study 2 (Chapter 5) in this thesis.

2.9.3   Neuropathic pain screening tools

NeP screening tools have been developed in order to assist clinicians and non-specialists in identifying NeP. Several screening tools were developed for the identification of NeP in general; the LANSS (Bennett 2001), the self-reported version of LANSS (S-LANSS) (Bennett et al. 2005), the PD-Q (Freynhagen et al. 2006a), the Douleur Neuropathique en 4 questions (DN4) (Bouhassira et al. 2005), the Neuropathic Pain Questionnaire (NPQ) (Krause and Backonja 2003) and the ID-Pain (Portenoy 2006). These questionnaires are based on verbal pain descriptors, with or without items relating to a physical sensory examination. There are differences between the tools in the methodology of their developmental and validation studies. Some studies used the consensus of two experts as reference criterion (Bouhassira et al. 2005; Freynhagen et al. 2006a), while others used only the opinion of one expert clinician (Bennett 2001; Bennett et al. 2005; Portenoy 2006). Furthermore, the populations studied varied in their proportion of patients with peripheral NeP due to a specific aetiology. The DN4 was the only one to include patients with central NeP syndromes. In addition, the type of sensory

descriptors used and the different weighting in the total scores varies between the questionnaires, making comparisons difficult. These variations may also explain the observed differences in performance between questionnaires when applied in the same patient population (Hallström and Norrbrink 2011). However, despite the methodological differences, certain items seem to overlap and have been considered as the 'core symptoms' for NeP, including tingling, numbness, burning, electric shock and touch-evoked pain (Bouhassira and Attal 2011). The sensitivity of the screening tools reported in their original validation studies ranges from 66% (NPQ) to 85% (LANSS, PD-Q) and specificity from 74% (NPQ) to 90% (DN4). For the ID-Pain, sensitivity and specificity were not reported. The questionnaires and their translated versions have been widely used for the identification of NeP in patients with various pain disorders (Bouhassira and Attal 2011) and in epidemiological studies (Baron et al. 2009; Bouhassira et al. 2008; Freynhagen et al. 2006a; Rehm et al. 2010; Torrance et al. 2006), although they have not yet been validated for the latter purpose (Cruccu et al. 2010; Haanpää et al. 2011).

NeP screening tools should not replace clinical judgement (Bouhassira and Attal 2011; Haanpää et al. 2011; Hansson and Haanpää 2007) given that patients with non-NeP such as patients with FM or hip osteoarthritis also use sensory descriptors common to NeP, as demonstrated by their responses to the LANSS (Giske et al. 2009; Martinez-Lavin et al. 2003) and PD-Q (Amris et al. 2010; Gwilym et al. 2009; Rehm et al. 2010). However, a high score on these questionnaires is not sufficient to conclude that these pain conditions are neuropathic.

All NeP screening tools except the ID-Pain (Portenoy 2006) were developed based on dichotomous groups: patients with NeP and patients with nociceptive pain. Patients with mixed pain presentations were excluded in the developmental studies and this approach limits the generalisability of the results to a typical clinical population presenting with mixed pain presentations (Behrman et al. 2007; Bennett 2001). None of the screening tools have been validated in patients with nerve-related neck-arm pain of mixed pain. Based on the observation that pain qualities in patients with mixed pain presentations may differ from those obtained in patients with NeP (Behrman et al. 2007; Rasmussen et al. 2004), further questionnaires were developed, such as the expanded version of the Short-form McGill Pain

Questionnaire (SF-MPQ-2) (Dworkin et al. 2009) and the Pain Quality Assessment Scale (Jensen et al. 2006; Victor et al. 2008). While these questionnaires may assist in characterisation of the symptoms of patients with both neuropathic and non-NeP, they are not designed as NeP screening tools.

Two NeP screening tools, the LANSS and PD-Q, were applied in this thesis, primarily because both questionnaires have been validated in patient cohorts including patients with low back and leg pain (Freynhagen et al. 2006a; Unal-Cevik et al. 2010). Hence, the questionnaires might be transferable to patients with neck-arm pain, although no study has yet investigated their usefulness in detecting NeP in patients with nerve-related neck-arm pain. This was one of the aims of Study 2 (Chapter 5). Furthermore, both questionnaires appeared to demonstrate the same level of diagnostic accuracy in identifying NeP in their original validation study cohorts. However, it is unknown if they show similar performance when applied to an identical patient cohort as in Study 2 (Chapter 5). If this were the case, the use of the PD-Q would be preferable in primary care, as it would save valuable practitioner time.

The LANSS (Bennett 2001) (Appendix 4), was developed utilising a total of 60 patients, 30 patients with distinct clinical diagnostic categories of NeP (including 5 patients with lumbar and 2 patients with cervical radiculopathy) and 30 patients with non-NeP. The questionnaire demonstrated a sensitivity of 83% and specificity of 87% and was further validated in another cohort of 40 patients (sensitivity 85%, specificity of 80%) (Bennett 2001). The questionnaire is applied in an interview format and contains five sensory descriptor items and two clinical examination items. The validity and reliability of LANSS has been well established in numerous studies in patients with peripheral NeP (Bennett 2001; Pérez et al. 2006; Rejas et al. 2006; Unal-Cevik et al. 2010; Yucel et al. 2004), demonstrating sensitivity between 70.2% - 89.9% and specificity between 90.3% and 96.6% (Rejas et al. 2006; Unal-Cevik et al. 2010; Yucel et al. 2004). The study by Rejas et al (Rejas et al. 2006) included 156 patients. Although the aetiology of all patients was not specified, 22 patients had been clinically classified as having mixed pain. Sensitivity and specificity values were 81.8% and 89.4% respectively for the whole patient sample, and 85.9% and 90.3% respectively when patients with mixed pain were excluded from the analysis.

Hence, sensitivity reduced slightly with the presence of mixed pain presentations, but the proportion of mixed pain presentations was small (14%). The sensitivity of LANSS was also substantially lower (29.5%) in a cohort of 168 patients with cancer which is considered a mixed pain presentation (Baron and Tölle 2008; Mercadante et al. 2009), however these results need to be interpreted with caution given the different pathology involved. To date, there are no reports on the discriminative ability of LANSS in large cohorts of patients with musculoskeletal mixed pain.

The PD-Q (Freynhagen et al. 2006a) is a self–reported tool consisting of seven weighted sensory descriptor items, plus one item relating to temporal pain characteristics and one item relating to spatial pain characteristics (Appendix 4). The questionnaire was designed to identify NeP components specifically in low back pain patients with and without referred pain (Freynhagen et al. 2006a). The PD-Q was developed and validated in 392 German patients with clinically diagnosed pain of predominantly either nociceptive or neuropathic origin and demonstrated a sensitivity of 85% and specificity of 80%. However, the proportion of patients with clinical diagnosis of neuropathic back and/or leg pain was not stated in the publication. The NeP population used in the study included: "patients with postherpetic neuralgia, painful polyneuropathy, nerve trauma and low back pain (solely of the lumbar vertebrae, sacrum and coccyx)" (Freynhagen et al. 2006a). The presence of lumbar radiculopathy/radicular pain was not mentioned. Hence it remains unclear if the identification of NeP in this cohort related to NeP back pain or NeP leg pain as neuropathic and nociceptive components of patients with LBP do vary in the back and leg (Attal et al. 2011).

The PD-Q is easy to implement in clinical practice, is available in various languages including English (Amris et al. 2010; Morsø et al. 2011; Steegers et al. 2008), and the translated versions have been used for the identification of NeP in patients with low back pain (Beith et al. 2011; Morsø et al. 2011), patients with thoracic surgery (Steegers et al. 2008) and patients with chronic musculoskeletal pain (Jespersen et al. 2010). However, its reliability and revalidation of translated versions have been reported in only one study in Swedish patients with central NeP due to spinal cord injury (Hallström and Norrbrink 2011). In that group of patients reliability was

moderate and diagnostic accuracy was lower than that reported in the original study (sensitivity 67.9%, specificity 83%).

NeP screening tools fail to identify 10 - to 20% of patients with clinically diagnosed NeP (Bennett et al. 2007) and do not provide any information on the underlying cause of the pain condition. A study by Attal et al (Attal et al. 2008) demonstrated that symptoms of pain were very similar for patients with various NeP aetiologies, thus symptoms alone were not discriminant enough to indicate the underlying pathology (Attal et al. 2008). Therefore the clinical assessment, as outlined under sections 2.7 and 2.9.1 is argued as crucial in order to establish the presence of a nerve lesion/disease and the presence of NeP in patients with nerve-related neck-arm pain. Furthermore, Scholz et al (Scholz et al. 2009) documented that in patients with low back and leg pain sensory symptoms obtained from patients using an interview format were less sensitive for the distinction between NeP and non-NeP than physical examination items. Hence, the physical examination of sensory signs, using clinical examination or QST, is an important aspect of clinical examination when discriminating the underlying pain types.

2.9.4 Quantitative sensory testing

Commonly used QST measures are thermal, pressure and pinprick sensation exploring the function of small unmyelinated C-fibres and small myelinated Aδ fibres as well as touch and vibration threshold assessing the function of large myelinated Aβ fibres (Hansson et al. 2007). For the assessment of NeP, QST is complementary to bedside examination as the site of measurement is determined on the basis of prior clinical examination (Backonja et al. 2009; Hansson et al. 2007). Compared to bedside assessment, QST allows a more precise and reliable assessment of the magnitude of sensory loss and quantification of thermal and mechanical hyperalgesia/allodynia (Chong and Cros 2004; Eliav et al. 2004; Hansson et al. 2007; Rolke et al. 2006b; Shy et al. 2003). In contrast to nerve conduction studies which can assess only a loss of function in myelinated nerve fibers, QST can also assess small nerve fiber function and a gain of function (Krumova et al. 2010). Thus, in the context of NeP, while QST can be used to support a hypothesis as to whether or not a nerve lesion is present, it cannot indicate the location of the lesion. Sensory

aberrations may be due to a dysfunction anywhere along the sensory pathway between the peripheral sensory receptor apparatus and the brain (Chong and Cros 2004; Shy et al. 2003). Sensory aberrations have also been documented in patients with non-NeP (Blumenstiel et al. 2011; Geber et al. 2008; Klauenberg et al. 2008; Leffler et al. 2000; Leffler et al. 2003; Pfau et al. 2009; Westermann et al. 2011).

QST is not an objective assessment of pain or sensibility. It is a psychophysical assessment in which an objective stimulus is applied and a subjective response from a participant recorded. Hence, participant's responses are influenced by cognitive factors (Backonja et al. 2009) and psychosocial and psychological components (Rhudy and Meagher 2000; Shy et al. 2003). Furthermore, factors such as age, gender and site of stimulation, the environment of a test laboratory and instructions given to the participants do have an impact on QST measures. Therefore standardisation of testing protocols is important to facilitate reliability and comparison of QST data between studies. The DFNS (Rolke et al. 2006a; Rolke et al. 2006b) has developed such a standardised QST protocol that was employed in this thesis (see Chapter 3, section 3.6.1).

The DFNS protocol has been applied in numerous studies (Blumenstiel et al. 2011; Freynhagen et al. 2008; Klauenberg et al. 2008; Koroschetz et al. 2010; Maier et al. 2010; Pfau et al. 2009; Westermann et al. 2011) and 117 investigators in 15 different countries have been trained in this method (Magerl et al. 2010). Reference data have been obtained in Germany from 180 healthy control subjects which were stratified for 5 age groups. To compare a patient's QST data profile with control data independent of the different units of measurement across QST parameters, the DFNS proposed a z-transformation of data, based on the healthy control data (Rolke et al. 2006a; Rolke et al. 2006b). However, so far reference data have only been obtained for three body regions, which may not necessarily correlate with the patients' maximal pain area (Blumenstiel et al. 2011; Maier et al. 2010). Hence calculating z-scores based on data not obtained in the same body region, as has been documented by some (Blumenstiel et al. 2011; Maier et al. 2010), may potentially bias the results.

QST has proven to be a valuable assessment to characterise painful syndromes and to help interpret the pain mechanisms underlying clinical pain presentations (Aasvang

et al. 2008; Chien et al. 2008; Gottrup et al. 2000; Jääskeläinen et al. 2005; Taylor et al. 2010; Werner and Kehlet 2010). Studies on patients with nerve-related spinal neck-arm pain comparable to the cohorts assessed in this dissertation are however scarce. Only one study has documented sensory alterations in patients with cervical radiculopathy (Chien et al. 2008) and one study in patients with dermatomal neck-arm pain without any clinical signs of nerve root damage (Voerman et al. 2000), however the latter study did not report the presence of heightened nerve mechanosensitivity. In both these studies, sensory deficits were documented in the patients' dermatomal area, suggestive of nerve damage, but not necessarily indicative of the presence of NeP. Similarly, vibration hypoaesthesia was reported in peripheral nerve innervation territories in patients with non-specific arm pain due to office work-related upper limb pain (Greening and Lynn 1998; Greening et al. 2003; Tucker et al. 2007). However, none of these QST studies in patients with neck-arm pain, performed QST in the area of maximal pain, as is required for the assessment of NeP (Haanpää et al. 2011). Chien et al (Chien et al. 2008) examined sensory alterations in the area of the cervical spine which may have been the maximal pain area for some patients, although this was not specified. Likewise, while studies in patients with lumbar radiculopathy reported QST measures in affected dermatomal distributions, QST was not reported for the patients' maximal pain area (Freynhagen et al. 2008; Nygaard et al. 2000; Nygaard and Mellgren 1998; Quraishi et al. 2004; Samuelsson and Lundin 2002; Zwart and Sand 2002; Zwart et al. 1998). Furthermore, the studies on patients with neck-arm pain (Greening and Lynn 1998; Greening et al. 2003; Tucker et al. 2007; Voerman et al. 2000) and cervical radiculopathy (Chien et al. 2009) did not incorporate the assessment of all somatosensory modalities (thermal, pressure, pinprick sensation, light touch and vibration), and therefore a complete sensory phenotype for these patient groups has not been documented.

Widespread hypersensitivity to pressure and cold stimuli has been documented in patients with cervical radiculopathy suggesting augmented central pain processing (Chien et al. 2008). Similarly, widespread pressure sensitivity and the presence of cold hypersensitivity have been demonstrated in patients with FM as well as enhanced temporal summation of pain from mechanical and thermal stimulation (Berglund et al. 2002; Blumenstiel et al. 2011; Hurtig et al. 2001; Klauenberg et al.

2008; Koroschetz et al. 2010; Kosek and Ordeberg 2000; Pfau et al. 2009; Staud et al. 2003; Staud et al. 2001). As no local somatic abnormality has been found that is likely to explain the cause of FM (Goldenberg 2009; Wolfe et al. 2010), aberrations in pain inhibitory and pain facilitatory mechanisms as well as central sensitisation/augmentation of sensory input have been associated with enhanced pain sensitivity in patients with FM (Banic et al. 2004; Desmeules et al. 2003; Julien et al. 2005; Lannersten and Kosek 2010). Although patients with cervical radiculopathy and patients with FM may have some sensory parameters in common, the underlying pain mechanisms likely differ. No study has yet explored commonalities or differences in somatosensory profiles of patients with nerve-related neck-arm pain and patients with FM.

2.10 Somatosensory profiling

The mechanism- or symptom based classification of NeP is based on the hypothesis that different clinical signs and symptoms reflect different underlying pathophysiological mechanism of pain generation (Baron 2006; Jensen and Baron 2003; Woolf et al. 1998). As one specific symptom may be generated by several entirely different underlying mechanisms (Woolf and Salter 2000), a combination of positive and negative sensory phenomena, namely a symptom profile, may better predict underlying pain mechanisms (Baron 2009; Cruccu and Truini 2009). However, this symptom based approach is not to be seen in isolation, but as part of the overall patient examination.

2.10.1 QST as tool for somatosensory profiling

The DFNS QST protocol consists of a battery of tests measuring all relevant submodalities of the somatosensory system (Rolke et al. 2006a; Rolke et al. 2006b) (see Chapter 3, Methods). Using this protocol, complete somatosensory profiles have been established for patients with NeP (Freynhagen et al. 2008; Maier et al. 2010) and non-NeP conditions (Blumenstiel et al. 2011; Klauenberg et al. 2008; Pfau et al. 2009; Westermann et al. 2011). Sub-groups of patients with NeP with distinct somatosensory profiles have been identified in patients with diabetic neuropathy and patients with postherpetic neuralgia (Maier et al. 2010), illustrating the heterogeneity of patients within one aetiology. Such heterogeneity has not yet been shown in

patients with nerve-related neck-arm pain, but if it exists, it may be part of the explanation for the variability in responsiveness to pharmaceutical intervention in patients with cervical radiculopathy (Saldaña et al. 2010a). Other factors such as genetic disposition may also contribute to the variance in treatment response. However, although attempts have been made to correlate specific individual sensory profiles with the likely underlying mechanisms (Baron 2006; Baron et al. 2010a), a firm link between the two has not yet been established, and it is still unknown whether patients with different somatosensory phenotypes respond differentially to treatment (Maier et al. 2010).

2.10.2 painDETECT as tool for somatosensory profiling

Self-reported NeP questionnaires such as the Neuropathic Pain Symptom Inventory (NPSI) (Bouhassira et al. 2004) and the PD-Q (Freynhagen et al. 2006a) can also assist clinicians in characterising patients with NeP. The PD-Q has been used, not as a discriminative tool for NeP, but as a tool to identify somatosensory profiles in patients with painful lumbar radiculopathy/radicular pain (Mahn et al. 2011), in patients with diabetic neuropathy and postherpetic neuralgia (Baron et al. 2009) and in patients with FM (Rehm et al. 2010). Using a cluster analysis, all studies documented the presence of sub-groups of patients with distinct somatosensory profiles, hence aiding in the symptom-based classification of patients with persistent pain. However, whilst the assessment of evoked pain (brushing, cold, pressure) in the NPSI was verified with QST data of mechanical and thermal hyperalgesia, such a verification has not been reported for the PD-Q. Hence, it is unknown if self-reported responses to the PD-Q (light touch, pressure, cold and heat) correspond with sensory profiles as demonstrated by QST. Furthermore, the usefulness of the PD-Q in the characterisation of patients with nerve-related neck-arm pain has never been documented and this was the focus of Study 5 (Chapter 8) in this thesis.

2.11 Treatment of nerve-related neck-arm pain

The heterogeneity of nerve-related neck arm pain disorders and the likely presence of a mix of nociceptive and NeP in patients with cervical radiculopathy and patients with NSNAP highlights the importance of targeted treatments. Various management approaches are available such as pharmacological treatment (Attal et al. 2010; Baron et al. 2010b; Saldaña et al. 2010b), physiotherapy (Salt et al. 2011) including manual

therapy (Allison et al. 2002; Coppieters et al. 2003; Leininger et al. 2011), cognitive and behavioural interventions (Daniel et al. 2008; van de Wetering et al. 2010) as well as surgical intervention in case of cervical radiculopathy (Bono et al. 2011). A detailed review of the treatment options and evidence of their efficacy or lack there of is beyond the scope of this thesis. However, it is worth mentioning that studies of evidence are currently constrained by the difficulty of differentiating sub-groups of patients with nerve-related neck-arm pain and the effect heterogeneous study groups have on the power of clinical trials.

2.12   Summary

Patients with cervical radiculopathy and NSNAP may present with similar pain characteristics and sensory symptoms, but based on current literature, the pathophysiology, the pain types, and the underlying pain mechanisms are likely to differ. Identification of these differences may be important for targeting best-evidence management.

While classification systems for the identification of patients with cervical radiculopathy and NSNAP have been in place for over 14 years, no research has yet documented the reliability of these classification systems. Furthermore, guidelines have been established for the assessment of NeP in patients with persistent pain disorders, including the application of a clinical grading system of the certainty of presence of NeP and the application of NeP screening tools. However, the usefulness of these tools for the identification of NeP and determination of the dominant pain type(s) in patients with nerve-related neck-arm pain has not yet been investigated. QST has been recommended for the assessment of NeP components and for complete somatosensory characterisation of patients with persistent pain. The establishment of somatosensory profiles, using QST or the PD-Q, may assist in the interpretation of the pain mechanisms underlying clinical pain presentations. To date, no study has documented the QST somatosensory profiles of patients with cervical radiculopathy and patient with NSNAP. Additionally, no study has verified if the self-reported sensory phenotypes of patients with cervical radiculopathy obtained through the PD-Q, also correspond with the QST somatosensory profile.

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Chapter 3 - Methodology

In this chapter the methodology employed in the studies 'QST somatosensory profiles in patients with cervical radiculopathy are distinct from those in patients with non-specific neck-arm pain (Study 3, Chapter 6) and 'Neuropathic pain components are common in patients with cervical radiculopathy, but not in patients with non-specific neck-arm pain' (Study 4, Chapter 7) and 'Self-reported somatosensory profiles correspond with quantitative sensory testing phenotypes in patients with cervical radiculopathy, but not in patients with fibromyalgia' (Study 5, Chapter 8) is presented. As there were some similarities between studies, and due to the brevity required for journal articles, a detailed description of the methods is provided here.

The methodologies used in the studies 'Clinical classification and sub-grouping of patients with neck-arm pain' (Study 1) and 'Classification of neuropathic pain in neck/upper limb pain: application of a grading system and screening tools'" (Study 2) are outlined in Chapters 4 and 5 respectively. Approval to conduct these studies was obtained from the Human Research Ethics Committee at each of the participating institutions (Appendix 1). The study protocols and recruitment procedures adhered to the ethical guidelines of the Declaration of Helsinki.

3.1   Study design

A cross sectional study design was used for Studies 3 - 5. The aim of Study 3 was to establish the QST somatosensory profiles of patients with cervical radiculopathy and patients with NSNAP. The profiles of these two patient groups were also compared to healthy control (HC) subjects and a positive control group, patients with FM.

In Study 4 the side-to-side differences in QST parameters and the presence of NeP components were investigated in patients with painful cervical radiculopathy and patients with NSNAP.

Study 5 investigated whether the self-reported somatosensory profile of patients with painful cervical radiculopathy and patients with FM, as characterised by responses to

verbal sensory descriptors from PD-Q corresponded with the sensory phenotype as demonstrated by QST.

3.2 Subjects and recruitment

Four groups of subjects were recruited for Studies 3 to 5:

    i.   Patients with neck-arm pain due to the presence of a C6 or C7 cervical radiculopathy

    ii.   Patients with NSNAP with pain in a C6 or C7 dermatomal distribution

    iii.   Patients with FM and

    iv.   Asymptomatic HC subjects, age matched to the patient groups.

Data from all four subject groups were used for Study 3, whereas Study 4 included only patients with cervical radiculopathy and patients with NSNAP and Study 5 included only patients with cervical radiculopathy and patients with FM. The same patients with cervical radiculopathy were used for Studies 3, 4 and 5 and the same patients with NSNAP were used for Studies 3 and 4.

3.2.1 Recruitment

Patient cohorts were recruited from:

- General private physiotherapy, medical, rheumatology and neurosurgery practices within the Perth metropolitan area and surrounds.

- Physiotherapy and pain management departments at five hospitals (Sir Charles Gairdner Hospital, Royal Perth Hospital, Fremantle Hospital, Rockingham Hospital, Bentley Hospital) (Appendix 2).

- The Neurosurgery Outpatient Department and Neurosurgery Triage Clinic at Sir Charles Gairdner Hospital. As part of obtaining ethical approval to recruit patients from the Neurosurgery Triage Clinic the PhD candidate had offered to clinically assess and triage patients referred to this clinic. All referrals of patients with neck/upper limb symptoms to the Neurosurgery Triage Clinic between September 2007 and November 2010 were reviewed by the candidate. Patients with referrals suggesting a unilateral nerve disorder were selected and clinically examined.

- The local community via radio and newspaper advertising.

- Patients with FM were also recruited from FM support groups.

- Healthy control subjects were recruited from the general population by personal invitation and word of mouth.

For recruitment of patients from a) and b), health professionals were given written information with the specific inclusion criteria for each patient group (see 3.2.2). The initial selection criteria for patients recruited from the local community via radio and newspaper advertising and from the Neurosurgery Triage Clinic were one sided neck-arm pain, symptom duration of 3 to 18 months and an age range from 18 to 65 years of age.

Patients with cervical radiculopathy and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity

Potential subjects underwent an initial phone screening examination to ascertain they satisfied the inclusion and exclusion criteria (see screening tool Appendix 3; selection criteria sections 3.2.2.1 and 3.2.2.2; and flow chart of recruitment Figure 3.1). Telephone screening did not apply to patients attending the Neurosurgery Triage Clinic, as their visit was their formal appointment at the clinic. Prior to inclusion in the study, all patients underwent a comprehensive clinical examination in order to further determine they met the inclusion criteria (see assessment form Appendix 3). The clinical assessment comprised the patient's history, pain drawings including location, description and intensity of pain, documentation of pain behaviours, musculoskeletal and related neural tissues assessments and neurological bedside examination of somatosensory and motor function plus a review of results from any other medical investigations that were available (e.g., imaging, electrophysiology). The assessment of each patient required on average one hour.

As there is no universally accepted gold standard for the diagnosis of painful cervical radiculopathy and NSNAP, expert opinions were used to verify the pain conditions, as consistent with previous studies (Bennett 2001; Freynhagen et al. 2006; Freynhagen et al. 2008). The consensus of a Fellowship-trained neurosurgeon and a Fellowship-qualified Specialist in Musculoskeletal Physiotherapy (Fellow of the Australian College of Physiotherapists) were used as the gold standard for the diagnosis of cervical radiculopathy. The expert opinion of the Specialist Musculoskeletal Physiotherapist was used as the reference standard for the

classification of patients with NSNAP. The neurosurgeon was not asked to classify patients with NSNAP as the assessment of heightened nerve mechanosensitivity in the upper limb is not common practice for neurosurgeons. The patient's records, including the findings of the clinical examination and the available investigations, were reviewed by both experts using a blinded design. Where there was not consensus between the experts and clinical examiner, subjects were excluded from the data analyses.

In total 886 patients were recruited, 464 patients were clinically examined and 41 fulfilled the inclusion criteria (Figure 3.1). All recruitment, screening procedures and the clinical examination of potential subjects in this study, implementation of testing protocols and data analyses presented in this thesis were performed by the PhD candidate Brigitte Tampin (BT), unless otherwise indicated.
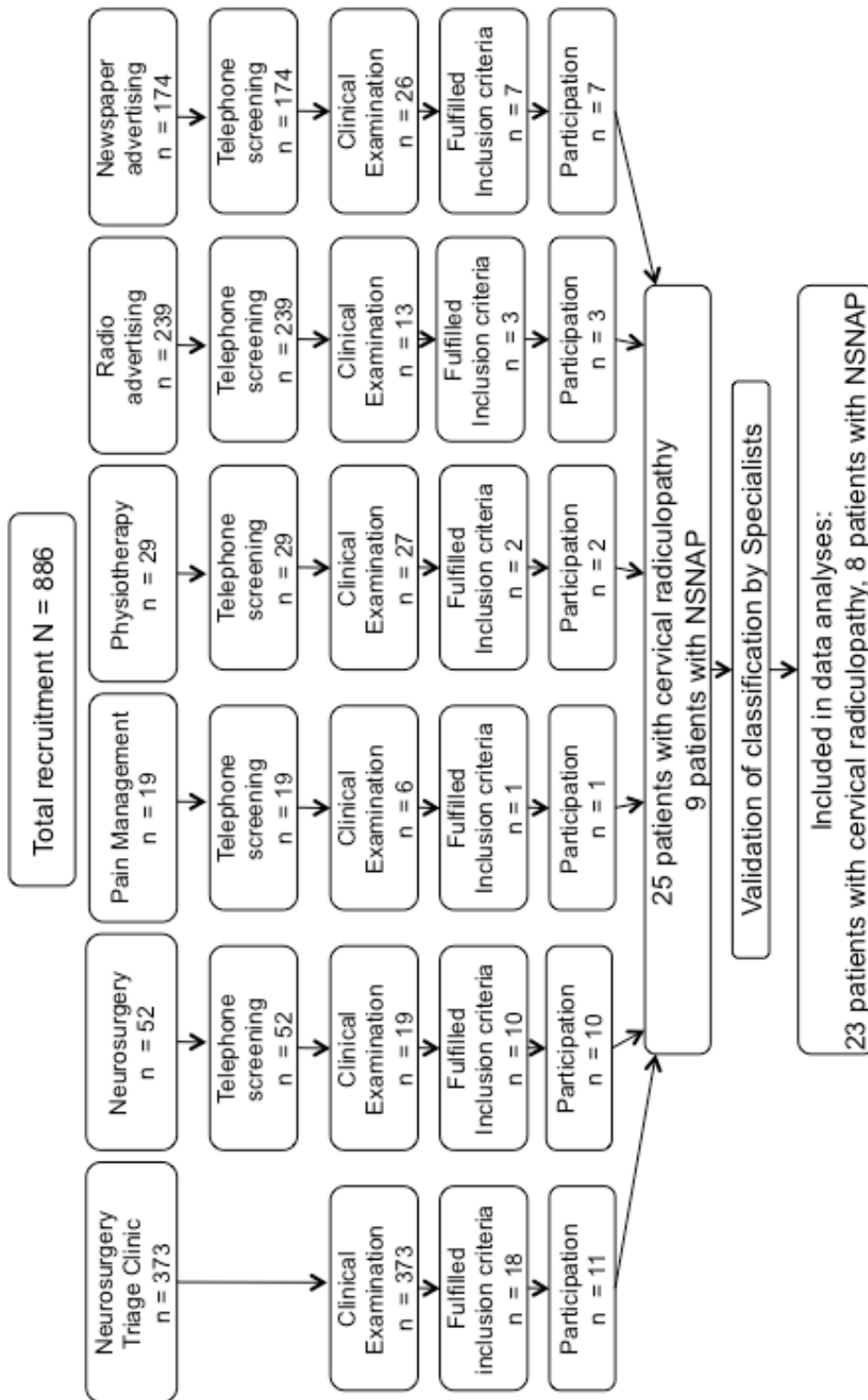
Figure 3.1 A flowchart demonstrating the recruitment of patients with painful cervical radiculopathy and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) for the QST Studies 3-5 for the period January 2007 to December 2010 inclusive.

Patients with fibromyalgia

All patients had to fulfil the diagnostic criteria for FM according to the 1990 American College of Rheumatology (ACR) (Wolfe et al. 1990) which include widespread pain of at least 3 months duration in combination with tenderness at 11 or more of 18 specific anatomical sites. These diagnostic criteria were current at the time of recruitment. All patients underwent an initial phone screening examination to ascertain they satisfied the inclusion and exclusion criteria (see screening tool Appendix 3 and selection criteria section 3.2.2.3). Prior to participation, the diagnosis of FM was confirmed by assessing nine paired points as defined by the ACR Criteria (Wolfe et al. 1990) and two control points (at the center of the right forearm and the right thumb nail) using a pressure algometer (Somedic AB, Farsta, Sweden). The algometer was placed on the examination site, and pressure was gradually increased by 1 kg/s with an application rate of 50 kPa. The patients were asked to press a button when the sensation at the examination site changed from one of pressure to one of pain. Pressure testing was stopped at that moment and the result was recorded as positive if the maximal pressure was ≤ 4kg. If no pain was elicited at ≤ 4kg, the test results were recorded as negative. The patient's clinical history was taken, including the pain locations using a body chart and identification of the maximal pain area as this was the site to be tested by QST (see Appendix 3 assessment form).

3.2.2 Subjects

3.2.2.1 *Patients with cervical radiculopathy*

Inclusion criteria

- Unilateral dermatomal pain distribution consistent with specific radicular distributions (C6/C7)
- Age 18 to 65 years
- Symptom duration of 3 to 18 months (This symptom duration was chosen to represent the clinical profile of patients with chronic pain. A symptom duration below 3 months is considered a sub-acute stage. The influence of psychological factors on pain perception with increasing symptom duration has been well established in the literature. In order to ensure some

homogeneity of the patient cohort, a cut-off of 18 months symptom duration was chosen.)

- Pain intensity ≥ 2 on a visual analogue scale (VAS)
- Signs of C6 or C7 nerve root dysfunction such as sensory impairment and motor impairment (either myotomal weakness and/or absent or diminished reflexes)
- Demonstrable clinically relevant abnormality on imaging studies (Bono et al. 2011; Treede et al. 2008) indicating compromise of the exiting nerve root at the relevant spinal level.

Exclusion criteria

- Pain in contralateral side mirroring the maximal pain area
- Pain in contralateral upper limb
- A history of lumbar surgery and/or sciatica or other musculoskeletal disorders that potentially might affect the sensation in the foot to be tested
- Pain and/or nerve lesion in ipsilateral lower limb/foot of the symptomatic side
- Other neurological or psychiatric disease
- Evidence of medical or metabolic disease
- A history of cardiovascular disease
- The subject is unable to achieve an equal amount of glenohumeral abduction in the asymptomatic limb that is available in the symptomatic limb
- Insufficient level of English (subjects had to be able to understand and fill out the self report questionnaires. They had to be able to understand the instructions and requirements for the QST procedures and be able to give a reliable response that did not depend on translation.)

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

Inclusion criteria

- Unilateral neck/upper limb pain and/or paraesthesia or dysaesthesia
- Age 18 to 65 years
- A symptom duration of 3 to 18 months
- Pain intensity ≥ 2 on a VAS
- An absence of neurological deficits (i.e. absence of signs of radiculopathy)
- Evidence of increased upper quarter nerve sensitivity to movement (Elvey 1997) with adverse responses to the NPT_{MEDIAN}
- Clinical signs of a musculoskeletal dysfunction at the relevant cervical spinal level C5/6 or C6/7 (Elvey 1997)

Exclusion criteria

- The same criteria were used as for patients with cervical radiculopathy

3.2.2.3 Patients with fibromyalgia

Inclusion criteria

- Age 18 to 65 years
- Symptoms duration ≥ 3 months (No limit was set with regard to symptom duration as patients typically present with symptoms for many years and are often not diagnosed with the condition for the first few years of onset of symptoms (Häuser et al. 2011). Therefore limiting the symptom duration to 18 months would not only have restricted the recruitment of patients, but the chosen symptom duration would not have reflected the typical symptom duration seen in this patent cohort.)
- Pain intensity ≥ 2 on a VAS
- Widespread pain
- 11 out of 18 tender points

Exclusion criteria

- A history of lumbar surgery and/or sciatica or other musculoskeletal disorders that potentially might affect the sensation in the foot to be tested
- Pain and/or nerve lesion in ipsilateral lower limb/foot of side to be tested by QST
- Other neurological or psychiatric disease
- Evidence of medical or metabolic disease
- History of cardiovascular disease
- Insufficient level of English as described above (see *3.2.2.1)*

3.2.2.4 Healthy control subjects

Inclusion criteria

- Age 18 – 65 years

Exclusion criteria

- A history of current or chronic upper quarter musculoskeletal pain condition and/or paraesthesia and/or nerve lesion
- A history of current or chronic pain and/or paraesthesia and/or nerve lesion in the lower limbs
- A history of lumbar surgery and/or sciatica or other musculoskeletal disorders that potentially might affect the sensation in the foot to be tested
- Other neurological or psychiatric disease
- Evidence of medical or metabolic disease
- A history of cardiovascular disease
- Intake of medication influencing pain perception
- Insufficient level of English as described above (see *3.2.2.1)*

3.3 Sample sizes

A sample size of 25 in each patient group was estimated to be sufficient to detect a clinically significant difference in pressure pain thresholds of 36% between groups and between the symptomatic and asymptomatic arm (Rolke et al. 2006a) with a power of 80% and 5% level of significance. The sample size calculation was based on QST data from a sample of healthy control subjects with a mean (SD) PPT of 512

(191.6) kPa. A difference of 36% in mean PPTs between sides has been reported to be clinically significant (Rolke et al. 2006a).

3.4   Ethics and Consent

All study protocol and recruitment procedures were approved by the Human Research Ethics Committee of Curtin University and Sir Charles Gairdner Hospital, Royal Perth Hospital and the South Metropolitan Area Health Service which incorporates Fremantle Hospital, Rockingham Hospital and Bentley Hospital (Appendix 1). All studies adhered to the ethical guidelines of the Declaration of Helsinki. All subjects received a study information sheet and gave written informed consent prior to inclusion into each study (Appendix 2). All subjects received a $20 (AUS) voucher to reimburse their travel expenses and they received free parking.

3.5   Measures

A   Patient groups

3.5.1   Pain intensity

Average pain intensity over the week preceding the testing session was determined using a 10 cm VAS with the end points 0 cm (no pain) and 10 cm (maximum tolerable pain) (Appendix 4). High reliability (Crossley et al. 2004; Gallagher et al. 2002; Zusman 1986), validity (Crossley et al. 2004; Gallagher et al. 2002; Jensen et al. 1989; Ohnaus and Adler 1975), and responsiveness (Crossley et al. 2004; Gallagher et al. 2002) for this pain rating scale have previously been demonstrated. The strongest and average pain intensity over the four weeks preceding the testing session and pain intensity at the time of completing the questionnaires were documented on a numeric rating scale (NRS) as part of the PD-Q (0 = no pain, 10 = maximum pain).

3.5.2   Self-reported pain and disability

The Neck Disability Index (NDI) is a ten-item questionnaire used to assess disability in patients with neck pain (Vernon and Mior 1991). Four of the items relate to symptomatology (pain intensity, headache, concentration, sleeping) whilst the remaining six items relate to activities of daily living (personal care, lifting, reading, work, driving and recreation). There are six potential responses to each item ranging

from no disability (0) to total disability (5). Thus the sum of all scores ranges from 0 (no disability) to 50 (maximum disability). A score of < 4 indicates no disability, a score of 5 – 14 mild disability, a score of 15 – 25 moderate disability, 25 – 34 severe disability and scores ≥ 35 complete disability (Vernon and Mior 1991). Good reliability and validity of the NDI have been demonstrated (Chan Ci En et al. 2009; McCarthy et al. 2007). The NDI is the most widely used and most strongly validated instrument for assessing self-rated disability in patients with neck pain (Pietrobon et al. 2002; Vernon 2008). A copy of the NDI is provided in Appendix 4.

3.5.3   Kinesiophobia

Fear avoidance behaviour was quantified using the Tampa Scale of Kinesiophobia (TSK) (Vlaeyen et al. 1995) (Appendix 4). The questionnaire consists of 17 items that relate to fear of movement and fear of (re) injury. Questions are answered on a 4-point Likert style scale, ranging from 'strongly disagree' to 'strongly agree'. A total score is calculated after inversion of the individual scores of questions 4, 8, 12 and 16. Scores range from 17, indicating no kinesiophobia, to 68 (Lundberg et al. 2004). A score ≥ 40 is considered to indicate significant kinesiophobia (Crombez et al. 1999). The reliability of the TSK is considered moderate-to-good (Swinkels-Meerwisse et al. 2003; Vlaeyen et al. 1995) and good validity has been demonstrated (Roelofs et al. 2004).

3.5.4   Neuropathic pain components

Two NeP screening tools were used in this thesis to identify the likely presence of NeP components; the LANSS (Bennett 2001) and the PD-Q (Freynhagen et al. 2006) (Appendix 4). The LANSS is applied in an interview format and contains five sensory descriptor items and two clinical examination items (testing for allodynia with cotton wool and altered pinprick threshold tested in the main pain area with a 23 gauge needle). The scoring of the items ranges from 0 to 5, with the items of the presence of 'tingling', signs of autonomic dysfunction (skin color change) and the presence of allodynia scoring highest (score of 5). A score of ≥ 12 suggests that the responder's pain is of predominantly neuropathic origin and a score of < 12 indicates that neuropathic mechanisms are unlikely to contribute to the responder's pain.

The PD-Q (Freynhagen et al. 2006) consists of one descriptor relating to temporal and one to spatial pain characteristics and of seven weighted sensory descriptors. The lowest weight for each descriptor is 0, indicating that the person does not experience the relevant sensation, and the highest weight is 5, indicating that the person feels the sensation very strongly. PD-Q classifies patients into three groups. A score of 0 – 12 indicates a negative result and a NeP component is unlikely. A score of 13 – 18 is an unclear or ambiguous result that does not preclude a NeP component. A score of $\geq$ 19 indicates a positive result and NeP is likely (Freynhagen et al. 2006).

B   All subjects

3.5.5   Sleep quality

Sleep quality over the week prior to data collection was rated by all subjects on a 10-cm VAS with the end points 0 cm (good sleep) and 10 cm (bad sleep) (Hurtig et al. 2001). Sleep disturbance was assessed by asking the subject if he/she awakened tired or non-refreshed; fatigue was assessed by asking: "Are you fatigued?"(Wolfe et al. 1990). Both questions allowed for answers: "never", "seldom", "often or usually", "always" and were collapsed to a dichotomous scale. "Often or usually" or "always" was scored as positive, and other replies as negative (Appendix 4).

3.5.6   Health related quality of life

The short form-36 health questionnaire (SF-36v2®) (Ware 2000) was used to assess health related quality of life. The questionnaire contains 36 items measuring health on eight dimensions: physical functioning, role physical, bodily pain, role emotion and mental health plus one time that measures health transition (Appendix 4). Two composite scores can be calculated: a physical composite summary score and a mental composite summary score. A higher score indicates better health status. The SF-36 has sufficient reliability and validity to be used for measuring health related quality of life of patients with peripheral NeP conditions (Meyer-Rosberg et al. 2001). A licence was purchased for use of this questionnaire.

3.5.7 Psychological factors

The Hospital Anxiety and Depression Scale (HADS) was used to screen for the presence of depression and anxiety (Zigmond and Snaith 1983) (Appendix 4). Seven items relate to anxiety and seven to depression. Each item has four potential responses, which are scored from 0 to 3. The responder is blinded to these scores. Individual scores for anxiety and depression are generated with a maximum score of 21 for each subscale. Scores of ≤ 10 for each are considered within normal range. The HADS has been demonstrated to be a valid screening tool in patients with musculoskeletal disorders (Härter et al. 2001).

All questionnaires were administered before the QST testing was performed. The sensory testing component of the LANSS questionnaire was performed at the area of maximal pain just prior to administration of the QST testing protocol.

3.6 Quantitative Sensory Testing

3.6.1 Testing protocol

Standardised QST measures were recorded according to the QST protocol of the DFNS (Rolke et al. 2006a; Rolke et al. 2006b), using the same equipment and standardised instructions (Appendix 5). This protocol comprises a battery of standardised tests in the following standardised order:

- Thermal detection and pain thresholds
- Mechanical detection threshold
- Mechanical pain threshold
- Stimulus-response functions: mechanical pain sensitivity and dynamic mechanical allodynia
- Wind-up ratio – the perceptual correlate of temporal pain summation for repetitive pinprick stimuli
- Vibration detection threshold
- Pressure detection and pain thresholds

These tests are used to detect loss or gain of sensitivity of small and large afferent sensory fibres. The QST protocol of DFNS was chosen for this study, as it comprises

all somatosensory submodalities mediated by different primary afferents (C-, Aδ-, Aβ-) and therefore can be used to characterise the somatosensory phenotype of chronic pain patients. The test/retest and inter-observer-reliability of this protocol for measurements within two days was good except for measurements of wind-up ratio and the number of paradoxical heat sensations (Geber et al. 2011). Video clips of the individual testing procedures are available as supplementary material under Rolke et al (Rolke et al. 2006a).

Thermal detection and pain thresholds and paradoxical heat sensation

Thermal detection thresholds for the perception of cold (CDT) and warm (WDT) and cold and heat pain thresholds (CPT, HPT) were measured using the MSA Thermotest system (Somedic AB, Farsta, Sweden). The method of limits was used (Chong and Cros 2004). All thresholds were obtained with ramped stimuli (1° C/s) which were terminated when the subject pressed a button. The subject was asked to press the stop-button as soon as the slightest change of temperature (for detection threshold) or the first painful sensation (for pain threshold) was felt (Appendix 5). The baseline temperature was set at 32˚C; cut-off temperatures were 5˚C and 50˚C. The contact area of the thermode was 2.5 x 5cm. Cold and warm detection thresholds were measured first. The number of paradoxical heat sensations was determined during the thermal sensory limen procedure (the difference limen for alternating cold and warm stimuli), followed by cold pain and heat pain thresholds, The mean threshold temperature of three consecutive measurements was calculated.

Mechanical detection threshold

The mechanical detection threshold (MDT) was determined with a standardised set of modified von Frey hairs (Optihari2-Set, Marstock Nervtest, Germany) that exert forces upon bending between 0.25 and 512mN. Subjects were asked to indicate when they felt the slightest light touch of the filament (Appendix 5). A force of 16mN was used as the starting force. The filament was gently applied perpendicular to the skin and then slightly bent. If the touch was felt, filaments with lower force were then applied in a descending manner until the subject felt no sensation. Subsequently the order of application was reversed until the subject felt a sensation. This procedure

was repeated five times. The final threshold was the geometric mean of five series of ascending and descending stimulus intensities (Rolke et al. 2006b).

Mechanical pain threshold

Mechanical pain threshold (MPT) was measured using a set of seven custom-made weighted pinprick stimulators (flat contact area of 0.2 mm diameter) with fixed stimulus intensities (8 16, 32, 64, 128, 256, and 512 mN) (MRC Systems GmbH, Germany). A needle with 8 mN was used as the starting force. The tip of the needle was gently placed perpendicular to the skin surface, then the weight was applied. The subject was asked to indicate if the sensation was felt as being 'sharp' or 'blunt' (Appendix 5). If the sensation was felt as 'blunt', the next higher needle was applied in sequence until the subject felt a sharp sensation. Then the order of application was reversed until the subject felt a blunt sensation. The final threshold was the geometric mean of five series of ascending and descending stimulus intensities.

Stimulus-response functions: mechanical pain sensitivity for pinprick stimuli and dynamic mechanical allodynia for stroking light touch

Mechanical pain sensitivity (MPS) was assessed using the same weighted pinprick stimuli as for MPT. These seven pinprick stimuli were applied in a balanced order, each one was applied five times. Subjects were asked to give a pain rating for each stimulus on a NRS (0 = no pain, 100 = most intense pain imaginable) (Appendix 5). Pain in response to light touch (dynamic mechanical allodynia; DMA) was assessed using a cotton wisp (3mN), a cotton wool tip fixed to an elastic strip (100mN) and a brush exerting a force of 200-400mN. Each was applied five times with a single stroke of approximately 1-2cm in length over the skin. They were intermingled with the pinprick stimuli in balanced and standardised order and subjects were asked to give a rating on the same scale as for pinprick stimuli (Appendix 5). MPS was calculated as the geometric mean of all numerical ratings for pinprick stimuli and DMA as the geometric mean of all numerical ratings across all three different types of light touch stimulators.

Wind-up ratio – the perceptual correlate of temporal pain summation for repetitive pinprick stimuli

The perceived magnitude of a single pinprick stimulus (256 mN) was compared with that of a series of 10 pinprick stimuli of the same force repeated at a 1/s rate. The time interval of 1 second was standardised using a metronome (Korg MA-30, Japan). The repeated stimuli were given within a small area of 1cm^2. First a single stimulus was applied and the subject was asked to give a pain rating for this stimulus. Then the repeated stimuli were applied and the subject was instructed to give a pain rating representing the pain over that whole series of 10 pinpricks using a 0 – 100 NRS (Appendix 5). Single pinprick stimuli were alternated with the series of 10 stimuli until both were performed five times at five different skin sites within the same body region. The mean pain rating of trains divided by the mean pain rating to single stimuli was calculated as wind-up ratio.

Vibration detection threshold

A Rydel-Seiffer tuning fork (64Hz, 8/8 scale) (Martin, Tuttlingen, Germany (Figure 3.2) was used for the measurement of vibration detection threshold (VDT) (Figure 3.2). Both arms of the fork bear calibrated weights at their ends. A nine-point arbitrary scale from 0 to 8 and the shape of an elongated triangle beside the scale are imprinted on each weight. Once the tuning fork starts to vibrate, the triangle on each arm appears as two virtual, intersecting triangles. With decreasing vibration of the arms, the intersection moves exponentially up the scale. The subjects were asked to say "now" as soon as the vibration was no longer felt (Appendix 5). The nearest value (to the closest half-point) to the point of intersection of triangles was then recorded as the vibration threshold. The thresholds were determined as a disappearance threshold with three stimulus repetitions (Rolke et al. 2006b). The tuning fork was placed over a bony prominence in the body area to be tested. If no bony prominence existed in this test site, VDT was measured over adjacent soft tissues.

Figure 3.2 Tuning fork

Pressure pain threshold

Pressure pain threshold (PPT) was measured using a pressure algometer with a probe size of 1cm and an application rate of 50 kPa/s (Somedic AB, Farsta, Sweden). The subjects were asked to push a button when the sensation changed from one of pressure alone to one of pressure and pain. Triplicate recordings were taken and the mean value of these was used for analysis.

3.6.2   Measurement sites

QST testing was performed for all patients in their maximal pain area (as determined by the patient) and also in the corresponding area of the contralateral asymptomatic (control) side. For patients with FM, given the presence of bilateral pain, the most painful side was chosen as the symptomatic side, and the less painful side as the control side. If patients could not determine a most painful side, control and symptomatic side were determined randomly by the rolling of a die. The test sites in HC subjects were matched to the maximal pain areas in the patients with neck/arm pain and FM. It was anticipated that patients would indicate the area of upper trapezius muscle as their main pain area, therefore bilateral reference data were obtained in 26 HC for this site. However, during the course of patient recruitment it became apparent, that many patients experienced their main pain in other body regions. Therefore unilateral measurements for all other pain areas were obtained in 8 HC, including 3 from the trapezius group. Consequently data were available from at least eight healthy control subjects to standardise the patient data in accordance with established methodology (Blankenburg et al. 2010). In HC subjects, the 'symptomatic' side was determined randomly by rolling a die.

Additionally, patients with cervical radiculopathy were tested precisely in the distal area of their dermatomal sensory deficit (C6 or C7, as determined by bedside examination) and the corresponding contralateral control site. Patients with NSNAP were tested in their distal area of pain/paraesthesia and the corresponding contralateral control site. For practical reasons, it was not possible to match each site of distal sensory deficit or pain or paraesthesia exactly with a HC and FM test site. Therefore, the thenar eminence was determined to be representative of the C6 dermatome and the dorsum of the hand representative of the C7 dermatome. The PPT for dermatome C7 was assessed over the palmar interossei muscles between 2nd and 3rd metacarpal as test sites overlying muscles rather than over tissues with a low compliance (bone) are recommended (Rolke et al. 2005). VDT was measured over the 3rd metacarpophalangeal joint for C7 dermatome and over the radial styloid process for the C6 dermatome. C6 and C7 dermatomes were assessed bilaterally in patients with FM and in 26 HC subjects. Fifty percent of HC subjects and 45% of patients with FM were tested in the C6, and the remaining were tested in the C7 dermatome. The dorsum of the foot ipsilateral to the painful side served as intra-individual control site for each subject. VDT of the foot was recorded over the medial malleolus (Rolke et al. 2006a; Rolke et al. 2006b).

All measurements were conducted on each subject by the same investigator (BT) in a laboratory with a constant room temperature. The investigator was blind to the results of all questionnaires. BT had previously visited the teaching centre of DFNS for familiarization with the testing procedures and protocol. Testing was conducted in a standardised order (control side tested prior to symtomatic side) (Rolke et al. 2006b) but testing of the different body regions was performed in a random order (determined by rolling a die). In order to familiarise subjects, all tests were first conducted over a demonstration area that was not later tested during the QST session. Standardised verbal instructions (Rolke et al. 2006a) were given to all subjects (Appendix 5). Subjects were asked to close their eyes during testing. For each body region to be tested, the subject's positioning remained unchanged, however the positioning did vary between individuals, depending on which position was most comfortable. Utmost attention was made to ensure that the body region to be tested was positioned in such a way that the stimuli for measuring MDT, MPT and MPS could be applied perpendicular to the skin surface. Testing of the full

protocol took approximately 30 minutes per test area (5 areas), with the total examination time taking 2.5 hours. The subjects were requested to refrain from using non–steroidal antiinflammatory drugs and analgesics on the day of examination. All measurements were recorded on a specific data collection sheet (see Appendix 6).

3.7   Nerve Provocation Test (NPT$_{MEDIAN}$)

After completion of the QST protocol, peripheral nerve mechanosensitivity was assessed with the NPT$_{MEDIAN}$ in patients with cervical radiculopathy and patients with NSNAP. The NPT$_{MEDIAN}$ is comprised of a number of components including shoulder girdle fixation, glenohumeral abduction to 90˚, external rotation, forearm supination, elbow extension, and wrist and finger extension (Butler 1991; Elvey and Hall 1997; Quintner 1989). Sensory and pain responses to the testing manoeuvre have been documented in more than 390 healthy control subjects (Bell 1987; Kenneally et al. 1988; Lohkamp and Small 2011; Rubenach 1985). The reliability of this test has been established in the normal and patient population in laboratory settings as well as in clinical settings (Coppieters et al. 2002; Lohkamp and Small 2011; Schmid et al. 2009). In this thesis glenohumeral abduction, shoulder girdle fixation, forearm supination and wrist and finger extension were prepositioned so that only elbow extension had to be performed as the primary movement of the test (see 3.7.1.2, Figure 3.3). Shoulder external rotation was not incorporated in this method, as the role of this position in loading of neural structures is unclear (Ginn 1988; Kleinrensink et al. 1995). The chosen testing procedure has previously been applied in healthy subjects and patients with cervicobrachial pain and demonstrated excellent reliability (Intraclass-Correlation Coefficient (ICC) (0.925) (van der Heide et al. 2001; van der Heide et al. 2006).
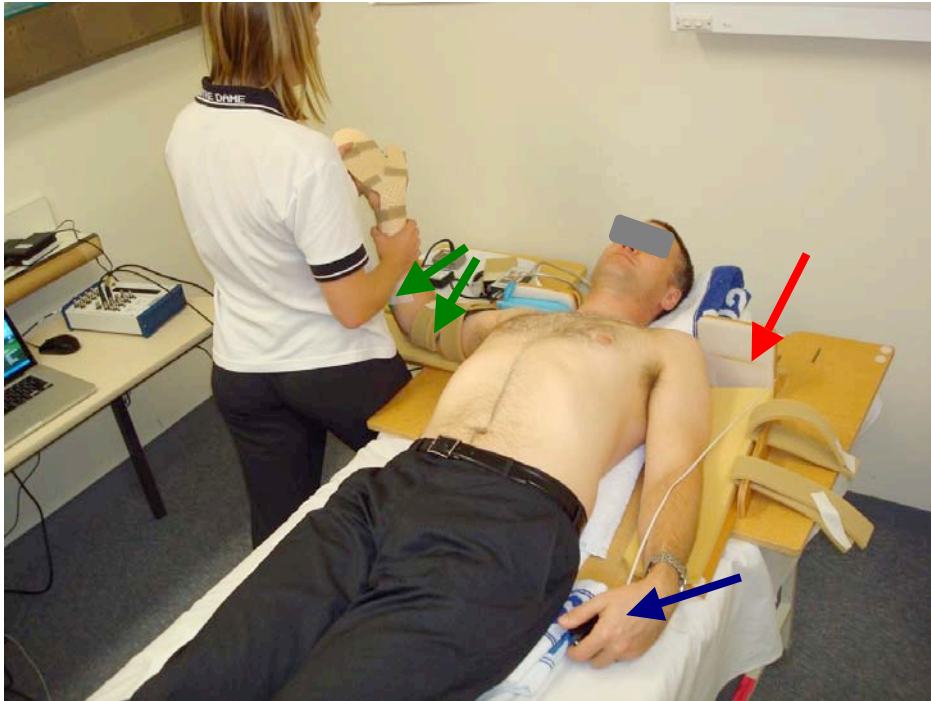
Figure 3.3 Set up of testing procedure of NPT$_{\text{MEDIAN}}$. The two green arrows indicate the location of the goniometer. The red arrow indicates the abduction frame. The blue arrow points to the stop button.

Test position

The subject was positioned supine on a plinth with the arm not being tested resting at the side of the body and the hand placed on the abdomen to operate an external trigger (Figure 3.3). The subject's upper body was positioned on a wooden board with protractor markings on each side that were indicating angles of shoulder abduction in 5^0 intervals. These markings were used to measure and to standardise the available range of shoulder abduction. The arm being tested was positioned in an abduction brace at the available abduction angle. The head was placed in a neutral or non-pain provocative position and rested comfortably on folded towels. Shoulder girdle depression was standardised using an air-filled pressure sensor (Stabilizer, Chattanooga, Australia) folded in three and placed between the apparatus and the subject's shoulder. The reliability of this device has been established in an earlier study (Edgar et al. 1994). Wrist and finger extension were standardised using a rigid (Thermoplastic®) splint strapped onto the forearm and hand. The angle of elbow extension was measured by a computer-linked electro-goniometer (SG110 Biometrics Ltd, United Kingdom) attached to the subject's forearm and upper arm. The electro-goniometer had been calibrated against known angles prior to testing.

Procedure

In some patients, pain limited the degree of shoulder abduction on the symptomatic side. Therefore, it was necessary to test the symptomatic arm first so that testing of the asymptomatic arm could be performed at the same abduction angle. As many patients presented with a high irritability of their pain condition, it was decided that the starting position should not be a provocative pain position. In the case of a patient with constant pain, BT moved the symptomatic arm into shoulder abduction to the range just before the increase of pain. The arm was then fixed with Velcro straps into the abduction brace.

The starting position for testing was shoulder girdle fixation (inflation of the pressure sensor to 40mm/Hg), tolerable shoulder abduction, elbow flexion (90^0), wrist and finger extension (the latter fixed by a Thermoplastic splint). In order to familiarize the subject with the procedure, the NPT_{MEDIAN} was performed once prior to the actual test. The NPT_{MEDIAN} was performed on the subject three times with a between-trial interval of 10 seconds. BT extended the elbow over a standard time frame of 10 seconds within each trial. The subject was asked to press an external trigger at the first onset of pain or increase of their resting pain (P1) and at a second time point when he/she reached their pain tolerance (P2). Elbow extension was performed to the end of range or to P2. At the completion of this test, the subjects were asked to indicate where the pain was felt during the elbow movement and whether the pain provoked by the testing manoeuvre was similar to their usual neck/arm pain. This information was recorded on a body chart (Appendix 6). Subjects were also asked to rate any pain intensity on a VAS before and after the NPT_{MEDIAN}. The testing procedure was performed each time by the same examiner and the arm remained at the same shoulder abduction angle in the abduction frame throughout all four trials. The NPT_{MEDIAN} was then performed in exactly the same way on the asymptomatic side. The angle of elbow extension at the onset of pain (P1) and at pain tolerance (P2) was recorded on the assessment sheet (Appendix 6). If the patient did not experience an onset of pain or pain did not limit the movement, a value of '0' was recorded for P1 or P2.

3.8 Reliability of QST protocol and responses to the NPT$_{MEDIAN}$

For all testing protocols, a series of reliability studies were conducted. Measurements were taken as outlined above in 21 healthy subjects. Not every person was tested for all QST parameters, however all parameters were tested across the cohort of 21 subjects. Three repeated measures on the same day were taken for CDT, WDT, CPT, HPT, VDT, PPT, P1 and P2 and duplicate measurements on different days (interval varying between 1 to 13 days) for MDT, MPT, MPS and WUR. The thenar eminence was chosen as testing site for thermal thresholds, MDT, MPT, MPS and WUR. VDT was measured over the radial styloid process and over the 3rd metacarpophalangeal joint. PPT was measured over the thenar eminence and the dermatome C7 (palmar interossei muscles between 2nd and 3rd metacarpal). The Intraclass Correlation Coefficient (ICC$_{3,1}$) was calculated for each parameter. Reliability coefficients were interpreted according to the following guidelines (Portney and Watkins 2009):

Poor = ICC < 50
Moderate = 0.50 < ICC < 0.75
Good = ICC > 0.75

The results indicate good reliability for 3 repeated measures on the same day for CPT, HPT, VDT, PPT, P1 and P2 and moderate reliability for CDT and WDT (Table 3.1). Reliability of duplicate measurements for MPT and MPS was good (Table 3.1). and reliability for MDT and WUR was moderate. None of the subjects experienced allodynia or any paradoxical heat sensation.

Table 3.1

Intraclass Correlation Coefficients (ICC $_{(3.1)}$) of three repeated measures for cold detection threshold (CDT), warm detection threshold (WDT), cold pain threshold (CPT), heat pain threshold (HPT), vibration detection threshold (VDT), pressure pain threshold (PPT), elbow extension at onset of pain (P1) and at the limitation of movement due to pain (P2), and of two repeated measures for mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS) and wind-up ratio (WUR).

Variable	Measurement site	ICC	Lower limit	Upper limit
CDT	thenar eminence	.509	.156	.802
WDT	thenar eminence	.554	.207	.825
CPT	thenar eminence	.938	.846	.980
HPT	thenar eminence	.938	.846	.980
VDT	radial styloid process	.934	.837	.979
VDT	3rd metacarpophalangeal joint	.947	.867	.983
PPT	thenar eminence left	.918	.801	.973
PPT	thenar eminence right	.920	.805	.974
PPT	C7 dermatome left	.939	.848	.980
PPT	C7 dermatome right	.879	.717	.960
MDT	thenar eminence	.693[a]	.228[a]	.901[a]
MPT	thenar eminence	.946[a]	.811[a]	.984[a]
MPS	thenar eminence	.844[a]	.456[a]	.955[a]
WUR	thenar eminence	.728[a]	.055[a]	.922[a]
P1 Left arm		.980	.949	.994
P2 Left arm		.994	.984	.998
P1 Right arm		.982	.953	.994
P2 Right arm		.993	.981	.998

[a]ICC based on mean ratings.

3.9   Statistical Analysis

Data were analysed with the Statistical Package for Social Sciences (SPSS Version 17.0) for MacOS X 10.5.8. QST data were first entered into an excel-spreadsheet provided by DFNS which automatically generated thresholds and average ratings, and numbers of observed paradoxical heat sensations. The obtained data were

entered into an SPSS data file, together with the raw data of the responses to the NPT$_{MEDIAN}$.

QST data were log-transformed (log10 units) prior to statistical analysis except HPT and VDT which were normally distributed as raw data (Rolke et al. 2006a; Rolke et al. 2006b). To compare a patient's QST data profile with control data independent of the different units of measurement across QST parameters, the patients' data were z-transformed for each single parameter using the following expression:

Z-score = (X $_{single\ proband}$ − Mean $_{health\ controls}$)/SD $_{healthy\ controls}$ (Rolke et al. 2006b). Z-values were calculated based on the included healthy control group data. This approach allowed site specific normalisation of QST data, where each individual parameter was related to its region and age specific reference range and was displayed as the number of standard deviations above or below the healthy control mean. Z-values above '0' indicate a gain in function i.e. the patient is more sensitive to the tested stimulus compared with HC (hyperalgesia, allodynia, hyperpathia), whilst z-scores below '0' indicate a loss of function, referring to a lower sensitivity (hypoaesthesia, hypoalgesia) of the patient. The exact statistical analyses used for the studies in Chapter 6 to 8 are outlined in the respective chapters. Significance was accepted at $p < 0.05$ for all analyses.

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Chapter 4

Clinical classification and sub-grouping of patients with neck-arm pain

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4.1 Abstract

Study Design. A cohort study of patients with neck-arm pain sub-grouped into two different neck-arm pain presentations based on the application of specific classification systems.

Objective. To assess the inter-examiner agreement in classifying patients using specific classification systems; to assess the agreement between two clinical examiners and two clinical experts and to assess the diagnostic accuracy of the two clinical examiners.

Summary of Background Data. Whilst patients with neck-arm pain may demonstrate similar clinical characteristics, their clinical presentation and underlying pain mechanisms can differ. Identification of these differences may assist the classification of patients which is important for provision of targeted best evidence based management.

Methods. Forty patients with unilateral neck-arm pain were examined by two clinicians and, using specific classification systems, classified into (i) cervical radiculopathy, (ii) non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP), (iii) other. The classifications were compared to those made independently by two experts, based on a review of patients' clinical assessment notes and the experts' clinical opinion. The experts' opinion was used as the reference criterion to assess the diagnostic accuracy of the clinical examiners in classifying each patient group.

Results. There was an 80% agreement between clinical examiners, 80% between experts and 70% - 80% between clinical examiners and experts in classifying patients with cervical radiculopathy (kappa between 0.41 and 0.61). Agreement was 72.5% – 80% in classifying patients with heightened nerve mechanosensitivity (kappa between 0.43 and 0.52). Clinical examiners' diagnostic accuracy was high (radiculopathy: sensitivity 79% – 84%; specificity 76% - 81%; NSNAP: sensitivity 78% – 100%; specificity 71% - 81%).

Conclusions. Compared to expert opinion, clinicians were able to identify patients with cervical radiculopathy and patients with NSNAP in 80% of cases, our data supporting the reliability of these classification systems.

4.2 Introduction

The diversity of nerve-related disorders in patients with neck-arm pain is reflected in the variety of terminologies used, such as cervicobrachial pain (Salt et al. 2011), radicular pain (Bogduk 2009; Merskey and Bogduk 1994), radiculopathy (Bogduk 2009; Merskey and Bogduk 1994), neuralgia, brachialgia, neuropathy, neurogenic pain (Merskey and Bogduk 1994), neuropathic pain (Jensen et al. 2011; Treede et al. 2008), and nerve trunk pain (Asbury and Fields 1984; Bennett 2006; Marchettini et al. 2006). Nerve trunk pain is regarded as nociceptive (Marchettini et al. 2006) or inflammatory pain (Bennett 2006) and is characterised by signs of heightened nerve mechanosensitivity such as local tenderness on palpation over accessible nerve trunks (Bennett 2006; Elvey 1997; Quintner and Bove 2001) and pain in response to limb movements that cause nerve provocation (Elvey 1997; Quintner and Bove 2001). Nerve trunk pain can be present in the absence of nerve damage (Bennett 2006; Bove et al. 2003; Dilley et al. 2005; Eliav et al. 2001; Marchettini et al. 2006), but can also occur in combination with neuropathic pain (Bennett 2006; Marchettini et al. 2006).

In this study two groups of patients were investigated: (i) patients with painful cervical radiculopathy and (ii) patients with neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP). Whilst these patients may demonstrate similar clinical characteristics such as pain with or without negative and/or positive sensory signs, their clinical presentation and underlying pain mechanisms may differ. Identification of such differences and the appropriate classification of patients with these neck-arm pain conditions is important for the provision of appropriate best evidence management.

Due to a lack of diagnostic gold standards the classification of these patient groups is largely based on the findings of a comprehensive clinical examination (Butler 2000; Coppieters and Butler 2001; Elvey 1997; Kuijper et al. 2009; Wainner and Gill 2000) incorporating the medical history, an assessment of both musculoskeletal and related neural tissues, a neurological bedside examination of somatosensory and motor function (Cruccu et al. 2010; Hansson 2002; Jepsen et al. 2006; Wainner et al. 2003)

and clinical nerve provocation tests (NPT) in the upper limb (Butler 2000; Elvey 1997; Rubinstein et al. 2007). Upper limb NPTs are analogous to the straight leg raise test which is used for the assessment of nerve mechanosensitivity in the lower limb (Devillé et al. 2000; Freynhagen et al. 2008). Results of medical investigations (e.g. imaging, electrodiagnostic tests) can also aid in the diagnostic work-up of neck-arm pain (Kuijper et al. 2009; Treede et al. 2008). Whilst moderate to substantial inter-examiner reliability (Landis and Koch 1977) has been documented for clinical tests of nerve function (sensory testing, reflexes and manual muscle testing) (Jepsen et al. 2006; Jepsen et al. 2004; Schmid et al. 2009) and for NPTs in the upper limb (Jepsen et al. 2006; Schmid et al. 2009; Vanti et al. 2010; Wainner et al. 2003), no study has investigated the reliability of the overall decision as to whether the primary clinical presentation is a cervical radiculopathy or demonstrates characteristics of heightened nerve mechanosensitivity. For the diagnosis of painful radiculopathy, the opinion and consensus of experienced clinicians/experts has been used for validation of patient classifications (Freynhagen et al. 2008), and this approach will be applied in the current study.

Radhakrishnan et al (1994) proposed certain sets of diagnostic criteria for the presence of definite radiculopathy (Table 4.1). Although this classification system is 16 years old, it is still recommended (Rubinstein et al. 2007), however the reliability has never been assessed. For the clinical presentation of heightened nerve mechanosensitivity, a set of classification criteria has also been established (Elvey 1997) (Table 4.2), but the reliability of these criteria has not yet been evaluated in patients with neck-arm pain. The purpose of this study was threefold: to determine the inter-examiner agreement in classifying patients using these specific classification systems; secondly to assess the agreement in patient classification between two clinical examiners using the specific classification systems and two independent experts; and thirdly to determine the diagnostic accuracy of the clinical examiners using the opinion and consensus of the experts as a reference criterion.

Table 4.1

The classification criteria used in this study to detect definite painful cervical radiculopathy (Radhakrishnan et al. 1994) in patients with neck-arm pain are outlined below. Category I, or II or III had to be met for the classification of definite painful cervical radiculopathy.

Category	Criteria
I	a) Electromyographic evidence of acute denervation in cervical paraspinal muscles and/or in a myotome **or** b) Identification of an affected cervical root at surgery
II	a) Sensory changes in a dermatomal distribution **and** b) Weakness, atrophy or fasciculation in a myotomal distribution **and** c) Unilateral diminished deep tendon reflexes
III	a) Demonstrable abnormality on myelography, computer-assisted myelography, or magnetic resonance imaging correlating with cervical radiculopathy **or** b) Demonstrable abnormality on computed tomography scan at the clinically relevant level correlating with cervical radiculopathy[a] **with** c) Neck pain, arm pain or combined neck and arm pain **and** d) Paraesthesia, hyperaesthesia, or dysaesthesia in a nerve root distribution **or** e) Muscle weakness **and** f) Any of category II[a]

[a]Criterion added to existing criteria. Computed tomography scans are deemed as valid confirmatory tests for nerve root compression (Bono et al. 2011; Treede et al. 2008), therefore Criterion IIIb was added. Signs of nerve root compression on imaging plus the presence of neck-arm pain with paraesthesia or muscle weakness do not necessarily implicate the presence of a cervical radiculopathy. Therefore Criterion IIIf was added.

Table 4.2

The classification criteria used in this study to detect the clinical presentation of heightened nerve mechanosensitivity. The presence of Criteria I and II are essential for the classification of heightened nerve mechanosensitivity, Criterion III may or may not be present (+/-).

Criteria	
I	Abnormal response to a nerve provocation test (reproduction of pain in the area of the patient's symptoms, plus reduced range of motion compared to the asymptomatic side, plus symptom response altered with addition of movements designed to elongate and add mechanical load on the peripheral nerves to be assessed (Elvey 1997)
II	A correlating active movement dysfunction (e.g. limitation of range of motion of shoulder abduction and/or pain on shoulder abduction, which increased with addition of cervical contralateral flexion and/or with wrist extension as loading manoeuvres) (Elvey 1997)
III	An abnormal response on clinically relevant upper limb nerve trunk palpation (hypersensitivity compared to the asymptomatic side) (Elvey 1997)

4.3   Materials and Methods

4.3.1   Study population

The study was conducted between February 2008 and May 2009. The patients with neck-arm pain were recruited from private physiotherapy, medical, and neurosurgery practices; physiotherapy, pain management, neurosurgery outpatient and triage clinics at five metropolitan hospitals; and via radio and newspaper advertising. The study protocols and the recruitment procedures were approved by the Ethics Committees of all participating institutions (Appendix 1). The inclusion criterion was unilateral neck pain with upper limb pain and/or paraesthesia. Exclusion criteria were the presence of a central nervous system disease (except cervical spinal cord compromise) and an insufficient level of English. Patients were screened by phone or in the clinic to establish they satisfied these criteria. Forty patients participated (21 males; 19 female; mean ± SD age 47 ± 10.6 years; duration of symptoms 16.2 ± 27.4

months). The protocol was explained to all patients and all patients consented in writing prior to entering the study.

4.3.2 Clinical examination and classification

The two clinical examiners were experienced clinically active physiotherapists with a minimum of a postgraduate Masters qualification in musculoskeletal physiotherapy. One examiner was a Specialist in Musculoskeletal Physiotherapy (Fellow of Australian College of Physiotherapists) with 28 years experience, the other had 17 years of experience as a Musculoskeletal Therapist. The independent expert clinicians who were consulted to provide the reference standard for diagnostic accuracy were a Neurosurgeon (Fellowship-trained spinal Neurosurgeon) and a Specialist in Musculoskeletal Physiotherapy. The Expert Specialist Physiotherapist did not exceed the qualifications of the Specialist Physiotherapist.

The diagnostic criteria used to detect the presence of a painful cervical radiculopathy were based on the publication by Radhakrishnan et al (1994) and are listed in Table 4.1. If the patients met any one of the three categories for the classification of radiculopathy, they were assigned to this group. If patients fulfilled any of these three categories *and* they demonstrated clinical signs of heightened nerve mechanosensitivity, they were still classified as radiculopathy.

The presence of heightened nerve mechanosensitivity was defined as evidence of increased peripheral nerve sensitivity to mechanical stimuli including NPTs and nerve palpation (Elvey 1997). The underlying concept for these NPTs is that sensitised nerve tissue may become non compliant to limb movements that cause nerve elongation (Elvey 1997) and that pain responses are provoked in response to these limb movements, resulting in movement restriction. In addition, mechanical pressure over sensitised nerve tissue such as in palpation over nerve trunks may provoke a hyperalgesic response (Elvey 1997; Hall and Quintner 1996; Quintner and Bove 2001). The criteria for this classification are demonstrated in Table 4.2. The classification of NSNAP could relate to spinally mediated nerve sensitivity, as well as to clinically diagnosed distal/peripheral neuropathies (eg. carpal tunnel syndrome, ulnar nerve neuropathy). In patients where co-morbid condition(s) existed (e.g.

frozen shoulder plus ulnar nerve neuropathy), patients were still classified as presenting with NSNAP, as long as the relevant classification criteria were met.

Patients were allocated to one of the two examiners. The order of testing by the two examiners varied, but for practical reasons, could not be randomised. A comprehensive clinical examination, as outlined in the introduction, was performed by the first examiner and results of any medical investigations such as imaging and electrodiagnostic studies were reviewed. Ten patients had not any imaging of the cervical spine performed. Nine patients had imaging performed, but no relevant abnormality was reported. Within an interval of 26 days, the second examiner performed a similar full clinical examination and nominated a classification. A hierarchical approach was used to classify patients into either: radiculopathy, or NSNAP or other. Both examiners were blind to the other's classification and examined the patients entirely independently. Patients were asked not to provide the second examiner with any information that was given to the patient during the first examination. The assessment sheets together with the determined classification were placed in a sealed envelope and handed to an independent blinded person for data entry and analysis.

The two experts independently received a copy of each examiner's patient notes plus the results of any medical investigations, without any information on the classification criteria. The Neurosurgeon classified patients into either: radiculopathy or other. The Specialist Musculoskeletal Physiotherapist classified patients into radiculopathy, NSNAP or other. In addition, both experts were given a choice to use a fourth classification of 'undecided', if they were unable to make a classification based on the information provided to them. The experts' classifications were based on their clinical opinion. A clinical examination by the independent experts was not possible for logistic and ethical reasons. Assessment by four practitioners would have imposed a considerable burden on the patients. Moreover, repeated assessment could potentially cause a flare-up of the patient's pain condition raising ethical concerns.

4.3.3   Statistical analysis

A total sample size of 40 subjects (including patient groups) was needed to detect an 80% agreement between two raters, if the null kappa was 0.6 and the true kappa was 0.9 (Flack et al. 1988). A Kappa between 0.40 and 0.60 indicates moderate agreement, a Kappa between 0.61 and 0.80 indicates a substantial strength of agreement and a Kappa of 0.81 to 1.00 an almost perfect strength of agreement (Landis and Koch 1977). Statistical analyses were carried out with SPSS, Version 15.0. The Kappa coefficient, with prevalence and bias index, and the percentage agreement were calculated to determine the proportion of agreement between:

1. The two examiners in classifying
   a) patients across all categories ('radiculopathy, NSNAP, other)
   b) patients with radiculopathy
   c) patients with NSNAP
2. The two experts in classifying patients with radiculopathy
3. The two examiners and the two experts in classifying patients with radiculopathy
4. The two examiners and one expert in classifying patients with NSNAP

Due to differing numbers of classifications between raters (1 - 4), classifications had to be pooled to allow a pairwise comparison (Figure 4.1).

The consensus of experts in classifying patients with radiculopathy was used as the gold standard to determine the diagnostic accuracy (sensitivity, specificity) of both examiners. The opinion of one expert was used as reference criterion to determine the diagnostic accuracy in classifying patients with heightened nerve mechanosensitivity. The receiver operating characteristic (ROC) curves were graphed and the areas under the curve (AUC) plus their 95% confidence intervals were measured. This value of AUC equals the probability of correctly classifying patients with and without the specific pain condition.
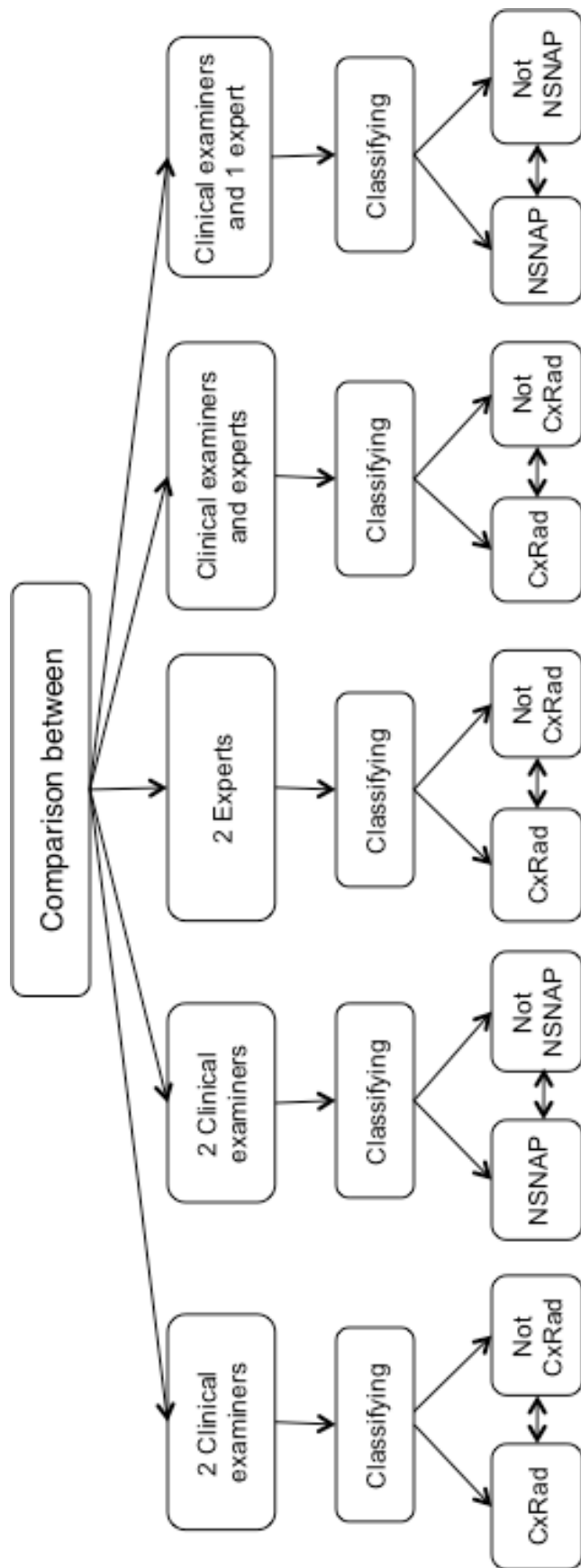
Figure 4.1 Pooling of classifications for pairwise comparison of classifications between clinical examiners and experts. CxRAD = Cervical radiculopathy, NSNAP = Non-specific neck-arm pain associated with heightened nerve mechanosensitivity.

4.4   Results

4.4.1   Agreement between examiners

Examiners agreed in classifying 27 out of 40 patients (Kappa 0.46, 95% CI 0.24 to 0.68) (Table 4.3), yielding a 67.5% agreement. For the classification of patients with radiculopathy, the percentage agreement was 80% and the Kappa coefficient was 0.60 (95% CI 0.35 to 0.85) (Table 4.4). For the classification of patients with NSNAP, percentage agreement was 72.5% and the Kappa coefficient was 0.43 (95% CI 0.16 to 0.70).

Table 4.3
The frequencies of patients (N = 40) classified by two Musculoskeletal Physiotherapists as having cervical radiculopathy, non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) or another pain condition, are shown below.

| | | **Examiner 2[b]** | | | |
		Radiculopathy	NSNAP	Other	Total
Examiner 1[a]	Radiculopathy	**16**	3	0	19
	NSNAP	3	**10**	0	13
	Other	2	5	**1**	8
	Total	21	18	1	40

[a]Musculoskeletal Physiotherapist.
[b]Specialist Musculoskeletal Physiotherapist.

For the 13 patients classified differently by the clinical examiners, there were different findings recorded in the examiners' patient notes in 12 cases: three related to reflex testing, three to strength testing, four to neural tissue testing, and two to inconsistent patient responses. In five of these cases the two experts agreed, in two cases the Specialist Musculoskeletal Physiotherapist classified the patient as NSNAP and the Neurosurgeon as other (i.e. they agreed the patient did not have a radiculopathy) and in the remaining five cases one expert chose the undecided option.

Table 4.4

The kappa coefficient, 95% Confidence Interval (CI) and % agreement, prevalence and bias index in classification of patients with cervical radiculopathy and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) are shown for two examiners.

	Kappa	CI	% agreement	Prevalence Index	Bias Index
Cervical radiculopathy					
Examiner 1 - Examiner 2[#]	0.60	0.35 - 0.85	80	0.00	0.05
Expert 1 - Expert 2*	0.61	0.39 - 0.83	80	0.15	0.20
Examiner 1 - Expert 1	0.41	0.16 - 0.66	70	0.15	0.20
Examiner 1 - Expert 2	0.60	0.35 - 0.85	80	0.05	0.00
Examiner 2 - Expert 1	0.59	0.36 - 0.82	80	0.20	0.15
Examiner 2 - Expert 2	0.60	0.35 - 0.85	80	0.00	0.05
NSNAP					
Examiner 1 - Examiner 2	0.43	0.16 - 0.70	72.5	0.22	0.12
Examiner 1 - Expert 2	0.50	0.21 - 0.79	77.5	0.45	0.10
Examiner 2 - Expert 2	0.52	0.29 - 0.75	80	0.32	0.22

[#]Examiner 1 = Musculoskeletal Physiotherapist, Examiner 2 = Specialist Musculoskeletal Physiotherapist.
*Expert 1 = Neurosurgeon, Expert 2 = Specialist Musculoskeletal Physiotherapist.

4.4.2 Agreement between experts

The frequencies of patients classified by the two experts as having cervical radiculopathy, NSNAP, or another pain condition or where no decision could be made is demonstrated in Table 4.5. For the classification of patients with radiculopathy, the agreement was substantial at 80% with a Kappa of 0.61 (95% CI 0.39 to 0.83) (Table 4.4).

Table 4.5
The frequencies of patients (N = 40) classified by two experts as having cervical radiculopathy, non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP), or another pain condition, or where no decision could be made, are shown.

		Expert 1[a]			
		Radiculopathy	Other	No decision	Total
Expert 2[b]	Radiculopathy	**19**	0	0	19
	NSNAP	1	**8**	0	9
	Other	2	**3**	0	5
	No decision	5	1	**1**	7
	Total	27	12	1	40

[a]Neurosurgeon.
[b]Specialist Musculoskeletal Physiotherapist.

4.4.3   Agreement between examiners and experts

There was 70% to 80% agreement between examiners and experts in classifying patients with cervical radiculopathy and patients with NSNAP. Kappa coefficients indicated moderate agreement (Table 4.4).

4.4.4   Diagnostic accuracy of both examiners

Using the consensus of the two experts as the gold standard, Examiners 1 and 2 demonstrated a sensitivity of 79% and 84% and a specificity of 81% and 76% respectively in classifying patients with cervical radiculopathy. For Examiner 1, the AUC was 0.80 (95% CI .65 to .94) and for Examiner 2, the AUC was 0.80 (95% CI 0.66 to 0.95), indicating that both examiners chose the correct diagnosis 80% of the time. Using the opinion of Expert 2 as the reference criterion for the presentation of NSNAP, Examiner 1 demonstrated a sensitivity of 78% and specificity of 81% (AUC: .79; 95% CI 0.61 to 0.97), Examiner 2 a sensitivity of 100% and specificity of 71% (AUC: 0.85; 95% CI 0.74 to 0.97).

4.5   Discussion

To our knowledge, this is the first study to investigate the use of classification systems to assess the inter-examiner agreement in classifying patients with painful cervical radiculopathy and patients with NSNAP. There was high percentage

agreement with moderate Kappa coefficients between raters in classifying both patient groups, supporting the reliability of the classification systems used. It can be argued that for this study kappa statistics might not be as meaningful as the percentage agreement. Kappa takes into account the agreement occurring by chance. This chance adjustment supposes that, when not completely certain, raters simply guess. Considering that all raters in this study based their classification on a thorough and methodical diagnostic work up, this is a highly unrealistic scenario.

Both examiners demonstrated high sensitivity in classifying patients with cervical radiculopathy. Considering physiotherapists' expanding role in extended scope of practice (Kersten et al. 2007) such as triaging patients in emergency departments (Anaf and Sheppard 2007; Lau et al. 2008) or neurosurgery clinics, high diagnostic accuracy and the risk-benefit implications of making wrong decisions are important. This is of particular significance for patients where alternative medical management is vital to managing their condition effectively, such as in patients with significant nerve root compromise or with dominantly neuropathic pain features. Both examiners were highly skilled and experienced. It is unclear if less experienced physiotherapists would have achieved similar outcomes.

There are limitations with strictly applying classification systems without incorporating a component of clinical judgement. For example, a patient presented with C6 radicular pain and sensory dermatomal deficit, no motor impairment, heightened nerve mechanosensitivity and no clinically relevant abnormality on cervical imaging. The classification based on the clinical opinion of both experts was that of a (sensory) radiculopathy. However, based on the applied classification system, this was not defined as radiculopathy as not all criteria of Category II were met. Therefore both examiners classified this patient as presenting with NSNAP. Furthermore, the criteria of Category II do not allow a differentiation between sensory and motor radiculopathy. Such differentiation is clinically important as each condition is indicative of a nerve root lesion and may need specific intervention.

The percentage agreement in classifying patients with NSNAP was between 70% and 80%, consistent with findings in patients with low back related leg pain (Schäfer et al. 2009). Sensitivity and specificity values for this classification were high in our

study, however results have to be considered in light of the small number of patients classified by the expert (n = 9). The classification system for NSNAP was clinically feasible. Future studies with a larger sample size are recommended to attest further to the reliability.

The main limitation of this study relates to the fact that the experts did not clinically assess the patients. However while the study design could be strengthened by the experts examining the patient, this would also add considerable responder burden for the patients. The clinical examiners differed in their recording of clinical examination findings and consequently in their classification of 12 patients which appears to have impeded the experts' decision making in five cases where one expert chose not to make a diagnosis. Nevertheless, despite this discordance the experts demonstrated agreement in classifying seven out of these 12 patients. Considering the dynamic nature of a pain experience and possible changes in patient's signs on the day of examination, a 100% agreement would be unlikely. Furthermore, heightened nerve mechanosensitivity is not a disease process comparable to axonal damage seen in patients with radiculopathy. It is rather a clinical presentation, which can be transient and can fluctuate.

It can be argued that the time interval between patient examinations may create potential for disagreement between the examiners. Eight patients were not assessed on the same day, however the examiners' classification differed in only one of these patients. Further, the importance of the clinical examination assisting in differential diagnosis becomes apparent, as one expert was not able to classify seven patients of our cohort. For purely logistic reasons, the experts were not able to clinically assess the patients.

One further limitation to the study lies in the hierarchical order of applying the classification systems. This approach treats the clinical pain presentations as being mutually exclusive, and this does not reflect the clinical presentation of our cohort of patients with neck-arm pain. For example, 7 out of 15 patients classified by all 4 raters with cervical radiculopathy also demonstrated clinical signs of heightened nerve mechanosensitivity. A further 5 patients out of these 15, demonstrated some

signs of heightened nerve mechanosensitivity, but did not meet all criteria used for this specific classification.

Methodological considerations

Whilst the straight leg raise test is widely used in medicine to identify heightened nerve mechanosensitivity in lumbar/lower limb pain (Devillé et al. 2000; Freynhagen et al. 2008), this is not the case for the upper limb equivalent NPTs. These upper limb equivalents seem to be used predominantly by physiotherapists (Allison et al. 2002; Coppieters et al. 2006; Coppieters et al. 2003; Elvey 1997; Sterling et al. 2002; van der Heide et al. 2006; Wainner et al. 2003) and their diagnostic value remains unclear (Rubinstein et al. 2007). While the NPT with bias to median nerve demonstrated 97% sensitivity in identifying patients with cervical radiculopathy (Wainner et al. 2003), this NPT is not widely used by neurosurgeons. Thus, the Neurosurgeon in the current study was not asked to classify patients with NSNAP.

Two criteria were added to the classification system for radiculopathy that were deemed clinically relevant for the classification of radiculopathy. In addition, the Radhakrishnan et al (Radhakrishnan et al. 1994) classification system did not mention the presence of neck and/or arm pain for criteria I and II and this should be considered if the system is used for the classification of painful radiculopathies. The system was useful for identification of patients with radiculopathy demonstrating good sensitivity and specificity. However, sensitivity and specificity may even yield higher levels, if the criteria of category II of the classification system would allow for a differentiation between the presence of sensory and motor radiculopathy.

In conclusion, this study demonstrated that the two examiners were able to distinguish between presentations of painful cervical radiculopathy and NSNAP in patients with neck-arm pain. Compared to the expert opinion, the examiners were able to identify 80% of cases with these specific clinical neck-arm pain presentations. As patients may demonstrate similar clinical characteristics for both presentations, such as radicular pain and paraesthesia, the identification of differences in clinical presentations is important for targeting best evidence management.

Acknowledgement

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Chapter 5

Classification of neuropathic pain in neck/upper limb pain: application of a grading system and screening tools

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5.1   Abstract

A new diagnostic grading system of certainty for the presence of neuropathic pain (NeP) has been proposed by the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain. We have investigated: (i) the clinical application of this grading system in patients with neck/upper limb pain with a suspected nerve lesion and; (ii) the level of agreement in detecting likely NeP between this model and two NeP questionnaires; the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS) and painDETECT (PD-Q). One hundred and fifty two patients (age 52 ± 12 years; 53% male) completed both questionnaires and underwent a comprehensive clinical examination. Patients were graded using the NeuPSIG system as; no NeP, possible, probable or definite NeP. The system proved feasible for application in this patient cohort, although required considerable time and clinical expertise. Both questionnaires failed to identify a large number of patients with clinically classified definite and probable NeP (LANSS sensitivity 22%, specificity 88%; PD-Q sensitivity 64%, specificity 62%). The lowered sensitivity scores in our study contrast with those in the original validation studies of LANSS and PD-Q and may result from differences in the clinical characteristics of the populations studied. Both questionnaires seemed unsuitable for the identification of NeP components in this cohort of patients with neck/upper limb pain of mixed aetiologies. NeP screening tools should not replace clinical judgement.

5.2   Introduction

Classification of neuropathic pain (NeP) can be confusing with the different definitions and classification criteria in use (Bennett et al. 2007; Bennett et al. 2006; Merskey and Bogduk 1994; Rasmussen et al. 2004; Treede et al. 2008). The previous definition of NeP by the International Association for the Study of Pain (IASP): "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (Merskey and Bogduk 1994) has now been replaced by a new definition: "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (Jensen et al. 2011). In addition, as no gold standard exists for the diagnosis of NeP, a grading system with different levels of certainty about the presence of NeP (no, possible, probable, definite) has been developed by the Neuropathic Pain Special Interest Group (NeuPSIG) of the IASP (Treede et al. 2008). This new diagnostic approach is based on a stepwise process that requires a history-derived working hypothesis (based on pain distribution and history suggesting a relevant lesion), and confirmatory evidence from a neurological examination and diagnostic tests (e.g. neuroimaging, neurophysiological methods). The application of this grading system has been demonstrated in some case studies (Geber et al. 2009; Haanpää et al. 2009), and more recently in a prospective study following thoracotomy (Guastella et al. 2011), but not in patients with neck/upper limb pain.

Questionnaires are used as screening tools to aid identification of suspected NeP (Bennett et al. 2007; Cruccu et al. 2010). The Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS) (Bennett 2001) classifies patients into two groups, patients with or without pain of predominantly neuropathic origin, and is applied in an interview format. The LANSS contains five sensory descriptor items and two clinical examination items. LANSS was developed utilising 60 patients with distinct clinical diagnostic categories of NeP and non-NeP, and demonstrated a sensitivity of 83% and specificity of 87%, and was further validated in 40 patients (sensitivity 85%, specificity of 80%) (Bennett 2001).

The painDETECT questionnaire (PD-Q) (Freynhagen et al. 2006) is another NeP screening tool, with the additional concept of grading for the certainty of the

presence of NeP. PD-Q classifies patients into three groups: a NeP component is unlikely, results are ambiguous, or a NeP component is likely. The questionnaire is a self–reported tool consisting of seven weighted sensory descriptor items, plus one item relating to spatial pain characteristics and one item relating to temporal characteristics. PD-Q was developed and validated in 392 German patients with clinically diagnosed pain of predominantly either nociceptive or neuropathic origin and demonstrated a sensitivity of 85% and specificity of 80%.

LANSS and PD-Q appear to demonstrate the same level of diagnostic accuracy in identifying NeP. However, it is unclear if they have similar performances when applied to a single patient cohort presenting with mixed musculoskeletal and peripheral NeP conditions. If this were the case, the use of PD-Q would be preferable in primary care, as it would save valuable practitioner time.

The aims of this study were to investigate:

(i) the clinical application of the grading system of the NeuPSIG classification model in patients with neck/upper limb pain and;

(ii) the level of agreement in detecting likely NeP in patients with neck/upper limb pain between the NeuPSIG classification model and the LANSS and PD-Q.

5.3 Materials and methods

5.3.1 Study population

The study (prospective) was conducted between June 2008 and December 2009 inclusive. One hundred and sixty six patients with neck/upper limb pain and suspected nerve lesion had been referred to an outpatient neurosurgery triage clinic in a large metropolitan hospital by their general practitioner or from other departments within the hospital. The patients were selected from the neurosurgery triage waiting list for another concurrent study by the authors. The current study was part of a quality assurance activity and was registered with the Quality Improvement Unit of the hospital and endorsed by the local Ethics Committee.

5.3.2 Clinical examination

All patients were examined by a highly qualified clinician with a postgraduate Masters qualification in musculoskeletal physiotherapy and with extensive clinical experience in triaging musculoskeletal and neuropathic pain disorders in a tertiary neurosurgical setting. The clinical assessment comprised of taking the patient's history, pain drawings including location, description and intensity of pain, documentation of pain behaviours, musculoskeletal assessments and neurological examination. Sensory testing of light touch and pinprick sensation was performed in the most painful area (Jensen and Baron 2003), consistent with previously documented methodology (Bennett 2001; Bouhassira et al. 2005; Weingarten et al. 2007) and compared with findings in the contralateral corresponding control site. In patients with bilateral pain, proximal or distal pain-free sites were used for control testing (Haanpää et al. 2011; Haanpää et al. 2009). Patients were asked to report the stimulus intensity (normal, less = hypoaesthesia; more = hyperaesthesia) and quality (normal or other: paraesthesia, dysaesthesia, allodynia) compared to the control site. Sensory testing was also performed in both upper limbs for determination of dermatomal sensory deficits and in both lower limbs, if spinal cord compromise was suspected. Finally, available results from any other investigations (i.e. imaging, nerve conduction studies (NCS)) were reviewed to identify any evidence of a lesion/disease of the somatosensory system. Based on all the above findings patients' pain conditions were categorised according to the NeuPSIG classification model (Table 5.1) into either no NeP, possible, probable or definite NeP. As some patients presented with multiple pain areas, the classification for NeP was applied to the patient's maximal pain area. The validation of patient classification on the basis of consensus of two clinicians has been applied in previous studies (Bouhassira et al. 2005; Freynhagen et al. 2006), while others used only a single expert clinical judgement (Bennett 2001; Bennett et al. 2005; Weingarten et al. 2007). Our approach has been adopted by the research community (Bennett et al. 2007; Haanpää et al. 2011) and encountered the problem of limited resources for patient assessment by two examiners.

Table 5.1 Proposed grading system for neuropathic pain (Treede et al. 2008).

1. Pain with a distinct neuroanatomically plausible distribution

2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system

3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test (presence of negative or positive sensory signs concordant with the distribution of pain)[a]

4. Demonstration of the relevant lesion or disease by at least one confirmatory test (e.g. neuroimaging, neurophysiological methods)[b]

Definite neuropathic pain (NeP): all (1-4); probable NeP: 1 and 2, plus either 3 or 4; possible NeP: 1 and 2, without confirmatory evidence from 3 or 4 (Adapted from Treede et al (2008))
[a]In our study only sensory abnormalities in the main pain area were classified as a confirmatory response. If no abnormalities were found in the main pain area, but sensory changes existed in further distal areas (e.g. distal dermatomal sensory changes in patients with cervical radiculopathy), this was classified as not fulfilling Criterion 3.
[b]If imaging results were used for radiological confirmation of nerve compression, only reports indicating significant/severe cervical foraminal stenosis and compromise of the exiting nerve root at the clinically relevant level were deemed as a confirmatory test. If the report stated "mild to moderate foraminal narrowing" with no mention of nerve root compromise, this was classified as a non-confirmatory test.

5.3.3   Questionnaires

The LANSS was chosen for this project as it has been documented in several studies to be a reliable and valid tool for the identification of NeP (Bennett 2001; Pérez et al. 2006; Unal-Cevik et al. 2010; Yucel et al. 2004). The PD-Q is a much more recent tool, is easy to implement in clinical practice, is available in English and has been applied in English speaking populations (Gwilym et al. 2009). In contrast to all other NeP screening tools (Bennett et al. 2007), PD-Q was designed for identifying NeP components specifically in low back pain patients with and without referred pain. The PD-Q might be transferable to neck pain conditions and therefore seemed appropriate to be used for our patient cohort.

All participants completed the PD-Q prior to clinical examination whilst they were in the waiting room. No specific instructions were given to patients on how to complete the questionnaire, consistent with the PD-Q format. The PD-Q asks patients to mark their main pain area on a body chart. The weighted sensory item descriptors relate to this marked main pain area. A PD-Q score of ≤ 12 indicates that a NeP component is

unlikely, and a score of ≥ 19 indicates a likely presence of a NeP component (Freynhagen et al. 2006). Scores between 13 and 18 reflect an ambiguous result. The LANSS was administered in an interview format at the end of the clinical examination. The required testing for the LANSS (testing for allodynia with cotton wool, altered pinprick threshold with 23 gauge needle) was performed during the overall neurological bedside examination. A score of < 12 indicates that neuropathic mechanisms are unlikely to contribute to the patient's pain and a score of ≥ 12 suggests that NeP mechanisms are likely to be contributing to the pain presentation.

In addition, sleep quality over the last week was rated by patients on a 10-cm visual analogue scale (VAS) with the endpoints defined as 0 cm (good sleep) and 10 cm (bad sleep) (Hurtig et al. 2001). The strongest and average pain intensity over the last four weeks and pain intensity at the time of the assessment were documented on a numeric rating scale (NRS) as part of the PD-Q (0 = no pain, 10 = maximum pain).

5.3.4 Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS Version 17.0). One-way ANOVA was used to compare patient characteristics between pain classification groups (no, possible, probable, and definite NeP) that were normally distributed. The Kruskal-Wallis test was used to compare symptom duration between pain classification groups, as this variable was not normally distributed. Frequencies of pain descriptors were calculated. A pairwise comparison was performed between:
- clinical classification and LANSS;
- clinical classification and PD-Q;
- LANSS and PD-Q.

The Kappa coefficient and 95% confidence intervals were calculated for all comparisons as well as the percentage of agreement. As the LANSS uses a dichotomous scale, PD-Q and the clinical classification score were transformed into dichotomous variables: PD-Q scores < 19 were defined as no NeP and ≥ 19 as NeP. For the clinical classification, no, possible and probable NeP were all grouped as no NeP. Sensitivity and specificity were calculated for the LANSS and PD-Q, using the clinical classification as the "gold standard". Sensitivity was calculated by dividing the number of patients identified by the questionnaires as having NeP by the total number of patients clinically classified with definite NP and multiplied by 100.

Specificity was calculated by dividing the number of patients identified by the questionnaires as having no NeP by the total number of patients clinically classified as having no NeP and multiplied by 100.

Furthermore, given the concept of grading the certainty of the presence of NeP in both the clinical classification model and PD-Q, an analysis was performed to compare the agreement in classifying patients as having NeP, no NeP and unclear/ambiguous classification. It was felt important to also investigate if the questionnaires were able to identify patients who were clinically classified as having probable NeP, consistent with other studies (Guastella et al. 2011; Unal-Cevik et al. 2010). To enable these comparisons, three categories per classification were defined as follows: LANSS (scores 0 – 8 = no NeP (Bennett et al. 2006), 9 – 11 unclear, 12 – 24 NeP), PD-Q (scores 0 – 12 = no NeP, 13 – 18 = unclear, 19 - 38 = NeP) and clinical classification (no NeP, possible as unclear cases, and probable and definite combined as NeP). The Kappa coefficient and 95% confidence intervals were calculated for all comparisons, as well as the percentage of agreement. Significance was accepted at $p < 0.05$ for all analyses.

5.4   Results

Of the 166 patients with neck/upper limb pain who attended the neurosurgery triage clinic, 13 did not experience any pain or only paraesthesia at the time of assessment. One patient was excluded from data analysis due to errors in completing the PD-Q, so analyses were performed on 152 patients.

5.4.1   Patient characteristics

The patients' characteristics are shown in Table 5.2. No listed characteristic was significantly different between the pain classification groups. Patients more likely to have NeP demonstrated a tendency to higher maximal pain scores during the preceding 4 weeks. A wide spectrum of pain diagnoses/pain presentations was represented (Table 5.3). Ninety-five patients (62.5%) presented with conditions likely to include NeP (radiculopathy, radicular pain, cervical myelopathy and carpal tunnel syndrome) and 57 patients (37.5%) with predominantly musculoskeletal/nociceptive conditions.

Table 5.2 Characteristics of patients (N = 152) with neck/upper limb pain classified according to the NeuPSIG grading system as having no, possible, probable or definite neuropathic pain.

	No NeP	Possible NeP	Probable NeP	Definite NeP	*p*
N	15	27	65	45	
Age (years)[a]	58.0 (14.4)	51.2 (10.0)	51.1 (12.0)	52.6 (11.0)	0.211*
Gender (women/men)	5/10	14/13	33/32	20/25	0.609*
Symptoms duration (months)[b]	18.0	9.0	17.0	10.0	0.098**
	(3.0 – 240.0)	(2.0 – 126.0)	(1.5 – 228.0)	(1.0 – 204.0)	
Pain now (NRS 0 – 10)[a]	3.6 (2.4)	4.5 (2.3)	4.8 (2.3)	4.7 (2.2)	0.337*
			(n = 64)		
Maximal pain intensity during last 4 weeks (NRS 0 – 10)[a]	6.7 (2.6)	7.1 (2.5)	7.5 (2.3) (n = 63)	7.8 (1.9)	0.271*
Average pain intensity during last 4 weeks (NRS 0 - 10)[a]	5.1 (2.8)	6.0 (2.4)	5.9 (2.0) (n = 63)	6.0 (1.9)	0.644*
Sleep quality during last week (VAS 0 – 10 cm)[a]	4.9 (2.2) (n = 13)	5.6 (2.6) (n = 19)	5.4 (2.8) (n = 60)	5.3 (2.2) (n = 38)	0.396*
N on antidepressants, anticonvulsants or opioids	2 (13.3 %)	6[c] (22.2 %)	21[d] (32.3 %)	16[e] (35.5 %)	
N on analgesics (paracetamol, NSAIDS)	2 (13.3 %)	8 (29.6 %)	15 (23.1 %)	17 (37.8%)	

[a] Mean ± SD; [b] Median and range; [c] n = 1 also on analgesic, [d] n = 10 also on analgesic, [e] n = 7 also on analgesic; * ANOVA.
** Kruskal - Wallis Test; NeP: neuropathic pain.

Table 5.3 Pain diagnoses/pain presentations[a] and neuropathic pain classifications in patients (N = 152) with neck/upper limb pain.

Pain diagnoses/presentations	N	Clinical classification				LANSS		painDETECT		
		No NeP	Possible NeP	Probable NeP	Definite NeP	No NeP	Yes NeP	No NeP	Unclear NeP	Yes NeP
N	152	15	27	65	45	129	23	46	36	70
Radiculopathy										
Cervical radiculopathy[b]	33			9	24	24	9	7	7	19
Sensory cervical radiculopathy[c]	11		1	4	6	9	2	3	3	5
Sensory cervical radiculopathy with carpal tunnel syndrome	1				1	1			1	
Motor radiculopathy[d]	3			2	1	3		1	2	
Motor radiculopathy with signs of unilateral carpal tunnel syndrome	1			1		1		1		
Motor radiculopathy with signs of bilateral carpal tunnel syndrome	1			1		1			1	
Radicular pain										
Radicular neck/arm pain with distal paraesthesia in dermatomal distribution	19		4	11	4	16	3	2	5	12
Radicular neck/arm pain	11		1	7	3	10	1	3	4	4
Radicular neck/arm pain with non dermatomal distal paraesthesia	8		2	5	1	6	2	1	2	5
Radicular pain with bilateral hand paraesthesia (signs of carpal tunnel syndrome)	3			2	1	3			1	2
Neck pain	13	5	4	3	1	13		7	3	3
Neck pain with unilateral pain areas/paraesthesia										
Neck/arm pain	5		2	3		4	1		2	3
Neck pain with distal dermatomal paraesthesia	3	1	1	1		3		2		1

Table 5.3 continued

Pain diagnoses/presentations	N	Clinical classification				LANSS		painDETECT		
		No NeP	Possible NeP	Probable NeP	Definite NeP	No NeP	Yes NeP	No NeP	Unclear NeP	Yes NeP
Neck/shoulder pain with paraesthesia hand	2		2			2		1		1
Neck pain with paraesthesia hand	1			1		1		1		
Neck pain with signs of carpal tunnel syndrome	1	1				1				1
Neck/shoulder pain	1		1			1		1		
Neck/arm/thumb pain	1	1				1		1		
Post cervical surgery neck/arm pain	1			1		1				1
Neck/thoracic/arm pain	1			1		1		1		
Neck/thoracic pain	1	1				1		1		
Neck/face pain	1	1				1		1		
Neck pain with bilateral pain areas/paraesthesia										
Neck pain/headache	5	2		3		5		4		1
Neck pain with bilateral arm paraesthesia	2	1		1		2		1		1
Neck pain with bilateral paraesthesia hands	2	1	1			2		2		
Neck pain with bilateral arm pain and paraesthesia	1			1			1			1
Neck pain with bilateral arm and hand paraesthesia	1		1			1				1
Neck pain with bilateral arm pain and hand paraesthesia	1		1			1				1
Neck pain with bilateral arm pain/paraesthesia and hand paraesthesia	1			1		1				1
Neck pain with bilateral signs of carpal tunnel syndrome	1			1		1			1	

Table 5.3 continued

	N	Clinical classification				LANSS		painDETECT		
		No NeP	Possible NeP	Probable NeP	Definite NeP	No NeP	Yes NeP	No NeP	Unclear NeP	Yes NeP
Whiplash injury related pain	6		4	2		4	2	1	2	3
Cervical myelopathy	2				2	2		1		1
Carpal tunnel syndrome	2			2		2		1		1
Other										
Post surgical face and arm pain (removal of brain tumor)	1				1		1			1
Arm pain with bilateral hand paraesthesia	1		1				1	1		
Bilateral forearm pain with signs of carpal tunnel syndrome	1		1				1		1	
Shoulder pain with paraesthesia arm	1	1					1	1		
Hand pain	1			1			1		1	
Complex regional pain syndrome type 1	1			1			1			1

[a]As determined by clinician based on history, examination results (neurological and musculoskeletal status) and results of investigations.

[b]Dermatomal pain/symptom distribution plus sensory dermatomal deficit plus myotomal deficit (either reflex absent/diminished or myotomal weakness).

[c]Dermatomal pain/symptom distribution plus sensory dermatomal deficit, no myotomal deficit.

[d]Dermatomal pain/symptom distribution plus myotomal deficit, no sensory dermatomal deficit.

Neuropathic pain (NeP).

Clinical presentations ranged from the presence of a single pain area to multiple causally related pain areas (e.g. neck pain with referred or projected arm pain and paraesthesia) or multiple independent areas (e.g. neck/arm pain with signs of carpal tunnel syndrome). Some patients experienced bilateral symptoms (n = 24). Apart from the pain presentations shown in Table 3, 24 patients presented with additional pain areas, which were independent of their main pain area/main complaint (low back pain (LBP) n = 11, LBP with leg pain n = 4, leg pain n = 3, shoulder pain n = 5, wrist pain n = 1). Seventy patients had various co-morbidities such as diabetes, thyroid dysfunction, hepatitis B and C, heart and lung disease, migraine, irritable bowel syndrome, cancer, polymyalgia rheumatica, Parkinson's disease, transient ischemic attack, gout, fibromyalgia, epilepsy, brain aneurysm and depression and anxiety disorders.

5.4.2   Clinical classification of neuropathic pain

The assessment of each patient required on average a 45 minutes consultation. The NeuPSIG grading system was applied for each patient using a hierarchical order (Table 5.1). If criteria 1 and 2 were satisfied, the level of evidence for criteria 3 and 4 was evaluated and a classification of probable or definite NeP was made. Fifteen patients were classified as no NeP, 27 as possible NeP, 65 as probable NeP and 45 as definite NeP (Table 5.3).

Criterion 1

Fifteen patients were classified as having no NeP as their pain distribution was not in a distinct neuroanatomically plausible distribution.

Criterion 2

Seventy patients with spinal pain could not recall a specific onset of their pain, therefore it was not possible to establish an exact temporal link between history and pain distribution. An insidious onset is common for the development of pain associated with spinal degenerative changes (Roth et al. 2009) and it was determined that these cases therefore satisfied Criterion 2.

Criterion 3

Sensory abnormalities in the main area of pain were demonstrated in 41 out of the 65 patients classified as having probable NeP and in all patients with definite NeP. Fifty-two patients presented with more than one sensory abnormality (no NeP, n = 1; possible NeP, n = 0; probable NeP, n = 24; definite NeP, n = 27). Five patients demonstrated allodynia. The presence of hyposensitivity to one or several modalities (light touch, pinprick) (n = 44) was more common than hyperaesthesia (n = 31). Ten patients presented with mixed hypo- and hypersensitivities.

Seven patients classified as having probable NeP and three patients with possible NeP, did not have any sensory abnormalities in their main pain area. However, all these patients demonstrated sensory deficits in a distal dermatomal distribution, and this combined with the clinical history supported the likely presence of a nerve lesion. According to our interpretation these cases did not satisfy Criterion 3. In three patients with probable NeP, no sensory abnormalities were found in the main area of pain, but sensory abnormalities were present in a distal, non-dermatomal distribution, and were not causally related to the main area of pain. These cases were also interpreted as not fulfilling Criterion 3. For two patients, sensory abnormalities were not recorded in the area of maximal pain (neck pain), but in a projected pain area (arm), and this was interpreted as a confirmatory test for Criterion 3. In 14 patients classified as probable NeP, no sensory abnormalities were found in the main pain area or in distal dermatomal areas, but confirmatory tests of nerve compression were available to determine the classification of probable NeP (NCS: n = 1; surgery: n = 1; Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI): n = 12). CT scans and MRI are deemed to be valid confirmatory tests for nerve root compression (Bono et al. 2011; Treede et al. 2008).

Criterion 4

Imaging results of the cervical spine to allow possible radiological confirmation of nerve compression were available for 140 patients (plain radiography n = 7; CT n = 108; MRI n = 25). Considering the possibility of false positive findings on imaging (Lehto et al. 1994; Matsumoto et al. 1998), we adapted a very conservative approach and defined only reports indicating significant/severe cervical foraminal stenosis and compromise of the exiting nerve root at the clinically relevant level as a confirmatory

test. Plain radiography was not considered as a confirmatory test. Results of nerve conduction studies were available for six patients. Of nine patients without any diagnostic tests, three were classified with probable NeP, three with possible and three with no NeP.

5.4.3 Pain descriptors

The frequency of reported pain descriptors from patients classified as having no NeP, possible, probable or definite NeP are shown in Figure 5.1. The description of electric shock type pain occurred only in the probable and definite NeP groups. Tingling sensations and the presence of sharp pain was most frequently reported in the probable and definite NeP groups (20% - 28.9%) and not at all in the no NeP group. Other pain descriptors associated with NeP (e.g. numb, hot, shooting) were also not used in the no NeP category and occurred infrequently in the probable and definite group (4.4% - 12.3%). Burning sensation and the descriptor ache were reported in all groups in the following proportions: burning pain 26.7% in no NeP, 22.2% in possible NeP, 32.3% - 35.6% in probable and definite NeP respectively; ache 33.3% in no NeP, 11.1% in possible NeP, 24.6% in probable and 26.7% in definite NeP. Spontaneous pain was reported in 62 patients during the clinical examination and on the LANSS with increased frequency and increased likelihood of NeP (no NeP, n = 1; possible NeP, n = 10; probable NeP, n = 26; definite NeP, n = 25).
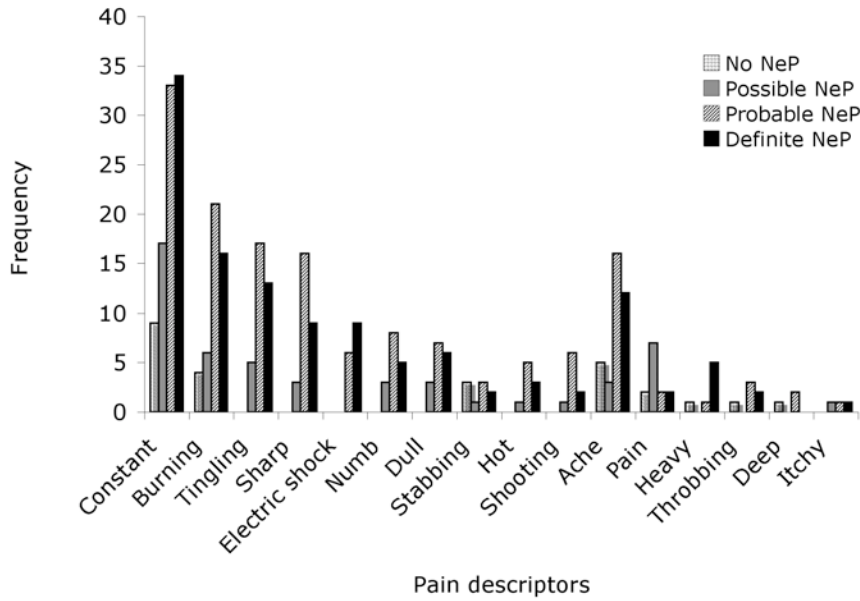
Figure 5.1 Histogram of the frequency of pain descriptors volunteered by 152 patients with neck/upper limb pain, classified as no neuropathic pain (NeP), possible NeP, probable NeP and definite NeP.

5.4.4 Agreement between clinical classification and questionnaires where patients were classified as having NeP or no NeP

5.4.4.1 *LANSS and clinical classification of NeP*

The LANSS classified 23 patients with predominantly NeP (median score 14.0, interquartile range (IQR) 4.0; mean score 14.3, standard deviation (SD) ± 2.0) and 129 patients without predominantly NeP (median score 7.0, IQR 6.0; mean score 6.0, SD ± 3.8) (Table 5.3). There was agreement between the LANSS and the clinical classification in 104 of the 152 cases (no NeP: n = 94, NeP: n = 10; Kappa 0.12, 95% CI -0.04 to 0.28) (Table 5.4), which yielded a 68.4% agreement.

Using the clinical classification as the gold standard, LANSS demonstrated a sensitivity of 22% and specificity of 88%. Out of 48 discordant cases between LANSS and clinical classification, 16 patients (33%) scored very close to the cut off score (11 patients scored 11; 5 patients scored 10).

Table 5.4
Frequencies of neuropathic pain (NeP) in patients (N = 152) with neck/upper limb pain, using two classification categories: no NeP – NeP.

		Clinical classification		
		No NeP	**NeP**	**Total**
LANSS[a]	No NeP	94	35	129
	NeP	13	10	23
	Total	107	45	152
		Clinical classification		
		No NeP	NeP	Total
painDETECT[b]	No NeP	66	16	82
	NeP	41	29	70
	Total	107	45	152
		painDETECT		
		No NeP	NeP	Total
LANSS[c]	No NeP	77	52	129
	NeP	5	18	23
	Total	82	70	152

[a]68.4% of agreement between clinical classification and LANSS.
[b]62.5% of agreement between clinical classification and painDETECT.
[c]62.5% of agreement between LANSS and painDETECT.

Twelve patients who were classified as having NeP according to the NeuPSIG model, demonstrated hypoaesthesia to light touch (stroking with cotton wool) in their area of maximal pain. However in the LANSS, only allodynia is scored as a relevant sensory abnormality in response to light touch. If hypoaesthesia was scored as a relevant sensory abnormality for NeP, all these patients would have been classified as having NeP. In this case, the percentage of agreement would increase to 76.3% and LANSS sensitivity would increase to 48% and specificity would reduce to 77%. One question in the LANSS addresses symptoms of possible autonomic nervous system dysfunction (Question 2: "Does your pain make the skin in the painful area look different from normal?"). This question, like the verbal descriptor of tingling sensation and testing of allodynia, yields the highest score (score = 5) that is obtainable for a single question in LANSS. Thirteen patients out of 152 (no NeP n = 7, NeP n = 6) reported symptoms of possible autonomic nervous system dysfunction.

5.4.4.2 *PD-Q and clinical classification of NeP*

The PD-Q classified 70 patients with a likely NeP component (median score 22.0, IQR 6.0; mean score 23.2, SD ± 3.7) and 46 cases with an unlikely NeP component (median score 9.5, IQR 5.25; mean score 8.7, SD ± 3.4) (Table 5.3). In 23.9% of cases (36/152), results were unclear (median score 15.5, IQR 3.0; mean score 15.5, SD ± 1.6). There was agreement between the PD-Q and the clinical classification in 95 cases (no NeP: n = 66, NeP: n = 29; Kappa 0.23, 95% CI 0.07 to 0.37) (Table 5.4), yielding 62.5% agreement with a sensitivity of 64% and a specificity of 62%. Out of the remaining 57 cases, a larger number of patients (n = 41) were classified as having NeP with PD-Q compared to the clinical classification, which indicated no NeP. Most of these patients scored highly (≥ 4) on the verbal descriptors for the presence of burning pain, tingling sensation, numbness and sudden pain.

5.4.4.3 *Agreement between questionnaires*

There was agreement between LANSS and PD-Q in classifying NeP in 95 of the 152 cases (no NeP: n = 77, NeP: n = 18; Kappa 0.21, 95% CI 0.09 to 0.33) (Table 5.4), yielding a 62.5% agreement between questionnaire outcomes. For the discordant 57 cases, a NeP component was demonstrated in only five patients for LANSS, but in 52 patients for PD-Q. Questions in the LANSS refer to how the patient's pain felt over the last week. Seven patients did not experience much pain in the week prior to the assessment, but answered the PD-Q questions in relation to how their pain had felt in the past 4 weeks. This resulted in the PD-Q score indicating NeP.

The PD-Q and LANSS have a number of questions in common. These include the presence of a tingling/prickling sensation and burning sensation, if light touch is painful in the area of pain and if pain can come on suddenly. However, when comparing responses to the common questions from the two survey tools, 20 patients answered the questions affirmatively in the PD-Q, resulting in the classification of NeP, but responded in the negative in the LANSS. The main discrepancies related to the presence/absence of burning pain (n = 13), sensitivity to light touch (n = 12) and sudden pain (n = 9). In the remaining 25 discordant cases and in five cases scoring positive on the LANSS but negative on PD-Q, discrepancies were found in responses to the above named descriptors in 15 patients. However, had patients answered these questions in PD-Q as answered in LANSS, the final score of PD-Q (NeP or no NeP)

would not have changed. In 15 patients all questions were answered equally in both questionnaires, but due to scoring differences the overall outcome differed.

5.4.5 Agreement between clinical classification and questionnaires where patients were classified as having NeP, no NeP or where the classification is unclear

5.4.5.1 *LANSS and clinical classification of NeP*

There was agreement between the LANSS and the clinical classification in 38 cases (no NeP: n = 14, unclear: n = 1, NeP: n = 23; Kappa 0.04, 95% CI -0.01 to 0.09) (Table 5.5), which yielded a 25.0 % agreement.

5.4.5.2 *PD-Q and clinical classification of NeP*

There was agreement between the PD-Q and the clinical classification in 77 cases (no NeP: n = 11, unclear: n = 8, NeP: n = 58; Kappa 0.17, 95% CI 0.06 to 0.28) (Table 5.5), which yielded a 50.7 % agreement.

5.4.5.3 *Agreement between questionnaires*

There was agreement between LANSS and painDETECT in classifying NeP in 67 cases (no NeP: n = 40, unclear: n = 9, NeP: n = 18; Kappa 0.19, 95% CI 0.09 to 0.29) (Table 5.5), resulting in 44.1 % agreement between questionnaire outcomes.

Table 5.5
Frequencies of neuropathic pain (NeP) in patients (N = 152) with neck/upper limb pain, using three classification categories: no NeP – unclear – NeP.

		Clinical classification			
		No NeP	Unclear	NeP	Total
LANSS[a]	No NeP	14	26	47	87
	Unclear	1	1	40	42
	NeP	0	0	23	23
	Total	15	27	110	152
		Clinical classification			
		No NeP	Unclear	NeP	Total
painDETECT[b]	No NeP	11	10	25	46
	Unclear	1	8	27	36
	NeP	3	9	58	70
	Total	15	27	110	152
		painDETECT			
		No NeP	Unclear	NeP	Total
LANSS[c]	No NeP	40	25	22	87
	Unclear	3	9	30	42
	NeP	3	2	18	23
	Total	46	36	70	152

[a]25% of agreement between clinical classification and LANSS.
[b]50.7% of agreement between clinical classification and painDETECT.
[c]44.1% of agreement between LANSS and painDETECT.

5.5 Discussion

The NeuPSIG's proposed diagnostic grading system (Treede et al. 2008) was feasible for application in this cohort of neck/arm pain patients with a suspected nerve lesion. LANSS (Bennett 2001) and PD-Q (Freynhagen et al. 2006) failed to identify a large number of patients with clinically classified definite and probable NeP. The PD-Q demonstrated a higher sensitivity, but a lower specificity than LANSS.

Clinical examination and classification

The NeuPSIG classification model has been recommended for use in primary care and by non-specialists (Haanpää et al. 2009). In the current study, the majority of patients were referred by their general practitioner and were therefore representative of patients seen in primary care. The clinical assessment and classification of our

cohort necessitated considerable time and specific clinical expertise. Considering an average general practice consultation time of 15 minutes (Bindman et al. 2007; Campbell 2007), health professionals working in primary care may not have time for an appropriate in-depth clinical assessment or have the requisite knowledge and skills to apply this grading system.

In our study, 82 patients (54%) indicated the neck/trapezius/scapula/shoulder area as their main area of pain which correlates with specific cervical nerve root pain distributions (Tanaka et al. 2006), but is also a common area for musculoskeletal pain and referred somatic pain (Dalton and Jull 1989). Mixed nociceptive and NeP pain mechanisms, which were likely to co-exist in our patient sample, have been acknowledged by numerous authors (Backonja 2003; Baron and Binder 2004; Freynhagen et al. 2006; Marchettini et al. 2006; Treede et al. 2008). Furthermore, musculoskeletal disorders can also present with sensory abnormalities (Geber et al. 2008; Leffler et al. 2003; Westermann et al. 2011) and are common in suspected cervical radiculopathy (Cannon et al. 2007), thus can mimic nerve lesions (Lauder 2002). In the context of predominant pain mechanism, the value of sensory pain descriptors has been raised (Baron et al. 2010; Bouhassira and Attal 2011). The combination of some items can discriminate between non-NeP and NeP groups (Bennett 2001; Bennett et al. 2005; Bouhassira et al. 2005; Dworkin et al. 2007; Krause and Backonja 2003), however their relevance and incorporation into the NeuPSIG grading system is under debate (Behrman et al. 2007; Hansson and Haanpää 2007; Marchettini 2005; Treede et al. 2008). In our study, the most dominant discriminators between the no NeP group and all others were the sensory descriptors electric shock, followed by tingling, sharp and spontaneous pain, numbness, hot and shooting. Unlike other studies (Bennett 2001; Bennett et al. 2005; Bouhassira et al. 2005; Dworkin et al. 2007; Krause and Backonja 2003), pain descriptors were volunteered, not chosen from a nominated descriptors list, thus lending credence to their existence. Our data suggest that the assessment of pain descriptors might be a valuable adjunct to determine the predominant pain type. The descriptor ache, commonly associated with nociceptive pain (Bennett 2006; Dworkin et al. 2009; Marchettini et al. 2006; Merskey and Bogduk 1994; Scholz et al. 2009),

was reported in our patients with NeP components, consistent with other studies (Dudgeon et al. 2005; Scholz et al. 2009; Wilkie et al. 2010) and with mixed pain presentations.

For the diagnosis of NeP, sensory abnormalities have to be present within the neuroanatomically correlated pain area (Baron and Tölle 2008; Haanpää et al. 2011; Haanpää et al. 2009; Jensen and Baron 2003). The wording of this definition (Criterion 3) by Treede et al (Treede et al. 2008) as: "the presence of negative or positive sensory signs concordant with the distribution of pain" may however be open to different interpretations and could influence patient classification. 'Concordant' can be defined as: "being in agreement with" (Collins 1991), allowing for interpretations including "sensory abnormalities have to spatially overlap the area of pain" or "sensory abnormalities are associated with the pain distribution and innervation territory of the affected nervous structure, but they do not necessarily overlap the pain area". For example, hypoaesthesia in a dermatomal distribution, (as seen in radiculopathy), could indicate a lesion of the somatosensory system, but its presence does not necessarily indicate the presence of NeP in an associated proximal main pain area. This interpretation is consistent with the proposition that radiculopathies involve a mixed type pain (Baron and Binder 2004; Gálvez et al. 2007; Marchettini et al. 2006) and that nerve lesions can be pain free (Landerholm et al. 2010; Taylor et al. 2010).

Pain questionnaire classification of NeP
The sensitivity of LANSS and PD-Q was much lower compared to previously reported studies (Bennett 2001; Freynhagen et al. 2006), and may partly be explained by the differences in clinical characteristics of respective study cohorts. Both questionnaires were validated in specific pain clinic populations with and without NeP, and patients with mixed pain were excluded (Bennett 2001; Freynhagen et al. 2006). In contrast, our cohort consisted of mixed pain aetiologies (e.g. spinal degenerative conditions, radiculopathy, musculoskeletal) suggesting the possibility of a substantial proportion of mixed pain presentations. The diagnostic accuracy of both questionnaires diminished further with the classification of patients with NeP (probable and definite NeP combined), non-NeP and unclear cases.

The presence of mixed pain presentations seems to influence the discriminative ability of LANSS. Whilst LANSS demonstrated high sensitivity (70% - 89%) and specificity (94.2% - 96.6%) in patient groups resembling the cohorts in the validation study (Unal-Cevik et al. 2010; Yucel et al. 2004), sensitivity reduced slightly from 85.9% to 81.8% with the inclusion of mixed pain presentations in a cohort of 156 patients (42.9% NeP, 14% mixed pain) (Rejas et al. 2006). In a large sample of patients with cancer, which was labelled as having a mixed pain mechanism (Baron and Tölle 2008; Mercadante et al. 2009), sensitivity was 29.5% (Mercadante et al. 2009), similar to our data.

The LANSS may be most sensitive in patient cohorts who demonstrate mainly positive sensory gains (paraesthesia, hyperaesthesia, allodynia) rather than negative sensory signs. Specifically, only 3.3% of our patients demonstrated allodynia, and a positive response to the question of autonomic dysfunction was found in only 8.5% of patients compared to 90% and 55% respectively in the LANSS validation study (Bennett 2001). Similar observations to ours have been reported in patients with low back-related leg pain (Scholz et al. 2009). In the original LANSS studies (Bennett 2001) a significant association between allodynia and hyperalgesia was found, however in our cohort, hyposensitivity seemed to be more frequent than hypersensitivity, consistent with findings from previous studies (Rasmussen et al. 2004; Scholz et al. 2009). In addition, the pain descriptor tingling, which is scored very highly in the LANSS, was only reported by 27% of patients with probable and definite NeP and burning sensation by only 34% of patients. The specificity of LANSS was comparable to previous studies (Bennett 2001; Mercadante et al. 2009; Rejas et al. 2006; Unal-Cevik et al. 2010; Yucel et al. 2004), indicating its usefulness in ruling out NeP components in patients with chronic musculoskeletal pain.

The PD-Q demonstrated a sensitivity of 64% which is similar to the sensitivity (68%) reported in spinal cord injury patients with central NeP (Hallström and Norrbrink 2011), however our calculated sensitivity might not truly reflect the identification of NeP components. As a self-reported tool, the PD-Q is open to individual interpretation. Eight of our patients failed to identify their main area of pain on the PD-Q body chart and 45 patients indicated additional, multiple pain areas (78% related to LBP and leg pain). Thus, it is possible that in 35% of our patient

cohort the responses given in PD-Q might not have been related just to the main area of pain. Out of these 53 patients, 36 were clinically classified as definite and probable NeP patients and PD-Q identified 24 of these patients. Our findings support the statement that the discriminative ability of NeP screening tools is only reliable when applied to one specific painful area (Bouhassira and Attal 2011). Hence, in a recent study using a computer version of the PD-Q (Junker et al. 2008) for sensory profiling of patients with lumbar radiculopathy/radicular pain, patients were asked to mark their main pain area on predefined body regions (Mahn et al. 2011). Out of our 29 patients classified by PD-Q and the clinical assessment as having NeP, there were inconsistent responses to the common questions between LANSS and PD-Q in 25% of cases. If responses to these questions had been similar in the PD-Q as in LANSS, the sensitivity of PD-Q would have reduced to 48.9%. It would seem important to give patients specific instructions on how to complete the PD-Q.

With a lack of published studies documenting clinical diagnostic accuracy and reliability of PD-Q in patients with peripheral NeP and lack of evidence of clinical validation of the English version of the questionnaire (Attal 2010; Bouhassira and Attal 2011), the validity for use of PD-Q in patients with neck/arm pain may be questionable. It is unclear if the lowered sensitivity of PD-Q in our study might be related to variations in patient cohorts, as specific patient characteristics were not reported in the original validation study (Freynhagen et al. 2006).

Fundamental differences also exist between LANSS and PD-Q design, i.e. the timeframe of the presenting pain, the number and type of items included, the phrasing of the questions and the scoring method. Whilst LANSS uses fixed scores for each question, sensory descriptor items are weighted in PD-Q, thus responses could be vulnerable to psychological factors such as catastrophizing and hypervigilance, and potentially contribute to an overall higher score. These differences in questionnaire design, together with the low level of agreement between instruments, would not support the interchangeable use of LANSS and PD-Q. Furthermore, the discriminative ability of these tools in identifying NeP components in patients with neck/upper limb pain of mixed aetiology is questionable. Our findings strongly support the notion that the results of NeP screening tools should always be used in conjunction with comprehensive clinical

assessment of the patient and should not replace clinical judgement (Cruccu et al. 2010; Haanpää et al. 2011; Hansson and Haanpää 2007).

Limitations of study

The publication regarding the grading of NeP by the NeuPSIG (Treede et al. 2008) does not specify the type of sensory testing required for the assessment of NeP. Sensory testing of thermal sensibility was not performed in this study, our approach being consistent with previous methodology (Weingarten et al. 2007), but it is possible that this might have increased the number of patients demonstrating sensory alterations. The clinical classification of patients in this study was performed by one clinician. An assessment by a second clinician would have enhanced the validity of the findings.

Conclusions

The NeuPSIG's proposed diagnostic grading system could readily be applied to a cohort of patients with neck/upper limb pain. This diagnostic approach might not be feasible in primary care settings for patients with complex pain presentations due to the time and specific expertise required for classification. The diagnostic accuracy of LANSS and PD-Q for the identification of NeP in patients with neck/upper limb pain appears limited.

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Chapter 6

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

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6.1 Abstract

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

6.2 Introduction

This study focused on two nerve-related spinal neck-arm pain presentations: painful cervical radiculopathy and non-specific (i.e. no clinical signs of the presence of a radiculopathy) neck-arm pain associated with heightened nerve mechanosensitivity (hereafter NSNAP). The latter is characterised in experimental studies (Dilley et al. 2005; Eliav et al. 2001) by peripheral nerve sensitivity to mechanical stimuli and clinically by pain in response to limb movements that cause nerve elongation (Allison et al. 2002; Chien et al. 2008; Elvey 1997; van der Heide et al. 2006) and local tenderness on nerve trunk palpation. Heightened nerve mechanosensitivity, a feature of nerve trunk pain, is regarded as a nociceptive (Marchettini et al. 2006) or inflammatory pain (Bennett 2006). It can coexist with painful cervical radiculopathy (Chien et al. 2008), but can also occur independently in patients with neck-arm pain (Elvey 1997; van der Heide et al. 2006). The latter applied to our chosen cohort.

While patients with the two above named neck-arm pain conditions can present with similar pain characteristics and sensory symptoms, the pathophysiology, the pain type (nociceptive/neuropathic) and the underlying pain mechanisms do likely differ. Identification of differences between these pain conditions is important for the provision of appropriate best-evidence management. Moreover, the possible dominance of one pain type is of therapeutic relevance (Baron et al. 2010a; Harden and Cohen 2003), and may account for individual differences in responsiveness to anti-neuropathic agents, such as pregabalin, as documented in recent clinical trials of patients with lumbar and cervical radiculopathies (Baron et al. 2010b; Saldaña et al. 2010).

One approach to assist in the interpretation of pain mechanisms underlying clinical pain presentations is the use of quantitative sensory testing (QST) (Chien et al. 2008; Jääskeläinen et al. 2005; Landerholm et al. 2010; Maier et al. 2010; Taylor et al. 2010). To our knowledge, no study has profiled patients with unilateral NSNAP comparable to our cohort, and only one study documented sensory abnormalities in patients with cervical radiculopathy (Chien et al. 2008). However, in the latter,

recordings were not taken from the patients' maximal pain area, as is required for the assessment of NeP components (Haanpää et al. 2011; Treede et al. 2008).

The purpose of this study was to establish the somatosensory profiles of patients with painful cervical radiculopathy and patients with NSNAP in order to explore differences or commonalities in sensory parameters. For each group, sensory profiles were documented in the area of maximal pain, in the respective dermatome and in the foot as a remote control site and were compared to healthy control (HC) data. In order to better characterise the neck-arm pain presentations, a group of patients with fibromyalgia (FM) was included as a positive control group to allow comparison to a group with widespread pain. We chose the presentation of FM as this pain disorder is characterised by enhanced sensitivity to a wide array of somatosensory stimuli and features of central pain processing mechanism in the absence of demonstrable local somatic abnormality (Goldenberg 2009; Wolfe et al. 2010). The significance of the study was the potential for better understanding of pain characteristics and sensory signs in different patient groups to assist clinicians in targeting management of these patient sub-groups. We hypothesised that: (1) the sensory phenotypes between the two neck-arm pain groups would be different; (2) in patients with cervical radiculopathy localised sensory abnormalities would be restricted to the maximal pain area and to the area of dermatomal sensory loss; (3) in patients with NSNAP sensory abnormalities would be found only in the maximal pain area; and 4) sensory profiles of the neck-arm pain groups would differ from that of patients with FM.

6.3   Materials and methods

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

6.3.1   Study population

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

Patients with painful C6 or C7 cervical radiculopathy (n = 23; 8 female; mean age 46.3 ± 9.6 years) had to fulfil the following inclusion criteria: unilateral neck pain and arm pain/paraesthesia distribution consistent with radicular distributions; symptom duration of 3 to 18 months; pain intensity ≥ 2 on a visual analogue scale (VAS); signs of C6 or C7 nerve root dysfunction such as motor impairment (either absent or diminished reflex and/or myotomal weakness) and sensory impairment; and a demonstrable clinically relevant abnormality on imaging studies (Bono et al. 2011; Treede et al. 2008) indicating compromise of the exiting nerve root at the relevant spinal level. The inclusion criteria for patients with NSNAP (n = 8; 7 female; mean age 45.1 ± 14.9 years) were: unilateral neck pain and arm pain/paraesthesia distribution consistent with C6/C7 distribution; absence of any signs of nerve root dysfunction i.e. absence of radiculopathy, symptom duration of 3 to 18 months; pain intensity ≥ 2 on a VAS; and evidence of increased peripheral nerve sensitivity to mechanical stimuli (Elvey 1997). The latter included pain in response to a nerve provocation test in the upper limb (Elvey 1997; Sterling et al. 2002; Wainner et al. 2003), a test analogous to the straight leg raise test in the lower limb (Devillé et al. 2000; Freynhagen et al. 2008). Exclusion criteria for both patient groups consisted of evidence of metabolic or medical disease; other neurological or psychiatric disease; a history of lumbar surgery and/or sciatica or other musculoskeletal disorders that potentially might affect the sensation in the foot to be tested; a history of cardiovascular disease; and an insufficient level of English. A comprehensive clinical examination was conducted by one clinician (author BT) on all potential participants in order to confirm that patients satisfied the requirements for inclusion into the study.

The consensus of two clinical experts, a Fellowship-trained spinal neurosurgeon and a Specialist Musculoskeletal Physiotherapist (Fellow of the Australian College of Physiotherapists), was used to verify the diagnosis of cervical radiculopathy, as consistent with a previous study (Freynhagen et al. 2008). The classification of NSNAP was verified by the Specialist Musculoskeletal Physiotherapist. Whilst the straight leg raise test is widely used to assess heightened nerve mechanosensitivity in the lower limb (Devillé et al. 2000; Freynhagen et al. 2008), the upper limb analogue (Elvey 1997) is less widely used in medicine although it has been extensively

investigated in musculoskeletal physiotherapy (Coppieters et al. 2006; Sterling et al. 2002; van der Heide et al. 2006; Wainner et al. 2003). Therefore the neurosurgeon in the current study was asked to determine if patients with NSNAP did have a radiculopathy or not. Both experts were blinded to the clinician's patient classification, and independently reviewed the patient notes including the findings of the clinical examination plus the results of any medical investigations. Three patients were excluded from data analysis as the experts did not make the same diagnosis as the clinical examiner.

Patients with FM (n = 22; 20 female; mean age 46.1 ± 11.5 years) underwent an initial telephone screening examination to verify they met the inclusion and exclusion criteria. Inclusion criteria were the diagnostic guidelines for FM presented by the American College of Rheumatology (ACR) (Wolfe et al. 1990) which include widespread pain of at least 3 months duration in combination with tenderness at 11 or more of 18 specific anatomical sites. These guidelines were current at the time of recruitment, however the clinical profile of our FM group appears to also correspond with the new diagnostic criteria (Wolfe et al. 2010) (Table 6.1). Nine patients had been diagnosed with FM by a rheumatologist, 8 patients by their general practitioner by exclusion (negative blood tests) and positive tender point count, 4 patients by a medical specialist (specific specialty unknown to the patient), and in one patient the origin of the diagnosis was not recorded. Prior to participation, tender point count was confirmed using a pressure algometer (probe size $1cm^2$) (Somedic AB, Farsta, Sweden), and assessing nine paired points as defined by the ACR Criteria (Wolfe et al. 1990) and two control points (at the centre of the right forearm and the right thumb nail). The exclusion criteria for patients with FM were the same as for the neck-arm pain groups. All patients were requested to refrain from taking non–steroidal anti-inflammatory medications and analgesics on the day of examination.

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

Table 6.1
Demographics and profiles of healthy control (HC) subjects, patients with cervical radiculopathy (CxRAD), patients with neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) and patients with fibromyalgia (FM).

	HC (n = 31)	CxRAD (n = 23)	NSNAP (n = 8)	FM (n = 22)	p-value ANOVA
Age (years), (SD)	45.6 (12.5)	46.3 (9.6)	45.1 (14.9)	46.1 (11.5)	0.992
Gender (female, n)	15	8	7	20	
Symptom duration (months)*		7.6 (4.1)	8.1 (3.0)	124.9 (83.1)[c, e]	<0.001
Average pain intensity during last week (VAS)*		5.2 (2.0)	6.0 (1.5)	7.3 (1.2)[c]	<0.001
Maximal pain intensity during last 4 weeks (NRS 0-10)*		7.2 (2.2)	7.6 (0.6)	8.3 (1.2)	0.116
Average pain intensity during last 4 weeks (NRS 0-10)*		5.0 (2.1)	5.1 (0.6)	6.2 (1.3)[d]	0.043
Sleep quality during last week (VAS)*	2.9 (2.6)	5.3 (2.7)[b]	5.9 (2.2)[b]	6.8 (2.3)[a]	<0.001
Sleep disturbance (n)					<0.001[###]
Negative	26	11	1	1	
Positive	5 (16%)	12 (52%)	7 (87%)	21 (95%)	
Fatigue (n)					<0.001[###]
Negative	25	9	4	2	
Positive	6 (19%)	14 (61%)	4 (50%)	20 (91%)	
Hospital Anxiety and Depression Scale					
Anxiety score (HADS)[#]	3.0 (5.0)	6.0 (5.0)[b]	8.0 (4.2)[b]	12.0 (6.2)[a, c, f]	<0.001[##]
Within normal range (≤ 10), n	29 (93%)	21(91%)	6 (75%)	7 (32%)	
Depression score (HADS)[#]	1.0 (1.0)	3.0 (4.0)[a]	3.5 (5.5)[b]	6.0 (4.2)[a, d]	<0.001[##]
Within normal range (≤ 10), n	31 (100%)	21 (91%)	8 (100%)	19 (86%)	

Table 6.1 continued

	HC (n = 31)	CxRAD (n = 23)	NSNAP (n = 8)	FM (n = 22)	*p*-value ANOVA
SF-36					
Physical Component[#]	57.7 (3.7)	40.6 (12.6)[a]	46.4 (12.0)[b]	36.4 (11.9)[a, f]	<0.001[##]
Mental Component[#]	56.0 (7.6)	52.3 (17.4)[b]	48.4 (20.5)[b]	30.8 (21.5)[a, d, f]	<0.001[##]
Neck Disability Index		16.2 (7.7)	13.4 (5.9)	19.7 (4.0)[f]	0.032
Tampa Scale of Kinesiophobia		40.9 (8.1)	36.7 (7.5)	38.4 (5.4)	0.281
Patients with medication, n		15 (65.2%)	3 (37.5%)	12 (54.5%)	
Current medication[◊]					
Selective serotonin reuptake inhibitor, n		1 (4.3%)	1 (12.5%)	7 (31.8%)	
Serotonin-norepinephrine reuptake inhibitor, n		2 (8.7%)		2 (9.1%)	
Tricyclic antidepressant, n		1 (4.3%)		3 (13.(%)	
Tetracyclic antidepressant, n				1 (4.5%)	
Antiepileptics, n		2 (8.7%)			
Opioids, n		4 (17.4%)		1 (4.5%)	
Benzodiazepine, n		2 (8.7%)			
Analgesics, n		7 (30.4%)	1 (12.5%)	3 (13.(%)	
Non-steroidal anti-inflammatories, n		7 (30.4%)	2 (25%)		

*Data are mean (SD); [#]Data are median (IQR); [##]Kruskal–Wallis Test; [###]Fisher's Exact Test.
[a]Significantly different to HC (p < 0.001); [b]Significantly different to HC (p < 0.05); [c]Significantly different to CxRAD (p < 0.001);
[d]Significantly different to CxRAD (p < 0.05); [e]Significantly different to NSNAP (p < 0.001); [f]Significantly different to NSNAP (p < 0.05).
[◊]Multiple answers possible.

6.3.2 Questionnaires

The following questionnaires were used to characterise the patient groups. They were administered before the QST testing was performed.

- Disability was assessed using the Neck Disability Index (NDI) (Vernon and Mior 1991), a well validated ten-item questionnaire (Vernon 2008). Scores of < 4 indicate no disability, $5 - 14$ mild disability, $15 - 25$ moderate disability, $25 - 34$ severe disability, and > 35 complete disability (Vernon and Mior 1991).

- Fear avoidance behaviour was quantified using the Tampa Scale of Kinesiophobia (TSK) (Vlaeyen et al. 1995). This questionnaire consists of 17 items that relate to fear of movement and fear of (re) injury. A score ≥ 40 is considered to indicate significant kinesiophobia (Crombez et al. 1999).

- Average pain intensity over the last week was determined with a VAS with the end points 0 cm (no pain) and 10 cm (maximum tolerable pain) (Jensen et al. 1989). The strongest and average pain intensity over the last four weeks was recorded on a numeric rating scale (NRS) (0 = no pain, 10 = maximum pain).

- Symptom duration was recorded via face to face interview.

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

- The short form-36 health questionnaire (SF-36v2®) (Ware 2000) was used to assess health-related quality of life.

- The Hospital Anxiety and Depression Scale (HADS) is a self-administered questionnaire to screen for the presence of psychological factors (Zigmond and Snaith 1983). Two independent scores for anxiety and depression are generated with a maximum score of 21 for each parameter. Scores of ≤ 10 for each are considered within normal range.

- Sleep disturbance was determined by asking: "Do you awake tired or non-refreshed?" Fatigue was assessed by asking: "Do you feel fatigued?" (Wolfe et al. 1990). Both sleep and fatigue questions allowed for answers: "never", "seldom", "often or usually", "always". "Never" or "seldom" was scored as negative, and other replies as positive. In addition, all subjects had to rate

their sleep quality over the last week on a 100-cm VAS with the end points 0 cm (good sleep) and 10 cm (bad sleep) (Hurtig et al. 2001).

6.3.3   Quantitative sensory testing

Standardised QST was performed according to the QST protocol of the German Research Network on Neuropathic Pain (DFNS) (Rolke et al. 2006a; Rolke et al. 2006b) by one investigator (BT) in a laboratory with a constant room temperature. This protocol comprises all of the somatosensory sub-modalities that are mediated by different primary afferents (C-, Aδ-, Aβ-) as outlined in the following sections. Good test/retest- and inter-observer-reliability of this protocol has been demonstrated for all sub-modalities except wind-up ratio and the number of paradoxical heat sensations (Geber et al. 2011). QST measurements were taken from the main pain area nominated by the patients (upper trapezius muscle n = 24; paravertebral cervical spine n = 4; paravertebral thoracic spine n = 13; above and below spine scapula n = 3; upper arm n = 6; forearm n = 2; just lateral above the elbow n = 1). For patients with FM, the most painful side was assessed. Bilateral measurements in the upper trapezius muscle were obtained in 26 HC and unilateral measurements in all other pain areas in 8 HC, including 3 from the trapezius group, in accordance with established methodology to standardise the data (Blankenburg et al. 2010). For patients with radiculopathy, QST was also performed unilaterally in the dermatomal area of sensory loss (C6 or C7 dermatome) as determined precisely during clinical examination, and for patients with NSNAP in the area of distal paraesthesia or pain (C6 or C7 dermatomal distribution). Patients with FM were randomly assessed in the C6 dermatome (thenar eminence) (n = 10) or C7 dermatome (dorsum hand) (n = 12). HC subjects were tested bilaterally in the C6 (n = 13) and C7 (n = 13) dermatome. All patients and 26 HC subjects underwent QST on the dorsum of the foot ipsilateral to the symptomatic side as a remote control site (Rolke et al. 2006a; Rolke et al. 2006b). In HC subjects, the 'symptomatic' side was determined randomly by rolling a die.

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

Thermal thresholds were measured using the MSA Thermotest system (Somedic AB, Farsta, Sweden) with a 12.5cm^2 probe. The baseline temperature was set at 32˚C;

cut-off temperatures were 5˚C and 50˚C. All thresholds were obtained with ramped stimuli (1° C/s) which were terminated when the subject pressed a button. First, cold and warm detection thresholds (CDT, WDT) were assessed, followed by the determination of the number of paradoxical heat sensations during the thermal sensory limen procedure, and finally the measurement of cold and heat pain thresholds (CPT, HPT). The mean threshold temperature of three consecutive measurements was calculated.

Mechanical detection threshold

The mechanical detection threshold (MDT) was determined using a standardised set of modified von Frey hairs (Optihari2-Set, Marstock Nervtest, Germany) that exert forces upon bending between 0.25 and 512mN. Five ascending and five descending series of stimuli were applied. The final threshold was the geometric mean of these series of ascending and descending stimulus intensities (Rolke et al. 2006a).

Mechanical pain threshold

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

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

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

MPS was calculated as the geometric mean of all numerical ratings for pinprick stimuli and DMA as the geometric mean of all numerical ratings elicited by light touch stimulators.

Wind-up ratio to repetitive pinprick stimuli

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

Vibration detection threshold

The vibration detection threshold (VDT) was measured using a Rydel-Seiffer tuning fork (64Hz, 8/8 scale). The threshold was determined as a disappearance threshold with three stimulus repetitions (Rolke et al. 2006a). Measurements were taken over bony prominences unless the maximal pain area did not exhibit a bony surface (n = 12), in which case, measurements were taken over adjacent soft tissue. Measurements in the dermatomal area of patients with cervical radiculopathy and patients with NSNAP were recorded over bony prominences. For patients with FM and HC subjects, VDT of dermatome C6 was measured over the radial styloid and VDT of dermatome C7 was measured over the third 3rd metacarpophalangeal joint. VDT of the foot was recorded over the medial malleolus (Rolke et al. 2006a; Rolke et al. 2006b) in all patients and HC.

Pressure pain threshold

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

6.3.4 Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS Version 17.0). QST data were log-transformed prior to statistical analysis (Rolke et al. 2006b) except HPT and VDT which were normally distributed as raw data. To compare and illustrate patients' QST data profiles with the group mean of age-matched healthy controls patients' data were z-transformed for each single parameter by using the following expression: Z-score = ($X_{single\ proband}$ – Mean $_{healthy\ controls}$)/SD $_{healthy\ controls}$ (Rolke et al. 2006b). Z-values were calculated based on the included HC group data (data from trapezius muscle and dermatomes from left and right body side pooled). For clarity of data presentation, the algebraic sign of z-score values for each parameter was adjusted so that it reflects the individual patient's sensitivity for each parameter. Z-values above '0' indicate a gain of function, meaning the patient is more sensitive to the tested stimuli compared with HC, a z-value below '0' indicates as loss of function, meaning a reduced sensitivity of the patient.

Differences of z-score QST data between the 3 patient groups and controls and tested body regions were compared using a two-way analysis of covariance (ANCOVA) with tested body areas (maximal pain area, dermatome, foot) as the within-subjects factor. Group (patients/controls) and the potential confounding factor gender were entered as between-subjects factors. Anxiety and depression were entered as covariates to account for potential influence of these factors on pain responses (Rhudy and Meagher 2000). If individual confounding factors did not demonstrate a significant effect, they were removed from the model. The LSD (LSD; least significant difference) post-hoc test was used to identify differences between body regions for variables that showed a statistical significant difference on ANCOVA. A univariate analysis was conducted for each QST parameter with post-hoc analyses (LSD-post hoc tests) to assess specific group differences within one tested body region. Any confounding factor that was found to be significant in the ANCOVA model was included in the univariate analysis. Frequencies of sensory abnormalities lying outside of the 95% confidence interval (i.e. z-score < -1.96 or > 1.96 standard deviation) of our HC were calculated within each group for each test site. Age, symptom duration, pain intensity, sleep quality, scores of the NDI and TSK were compared between groups using a one-way ANOVA. Post hoc comparisons were calculated using LSD-post hoc tests. Differences in frequency of sleep disturbance

were determined by means of the Fisher's exact test. Anxiety and depression scores and the physical and mental component summary scores of the SF-36 were compared between groups using the Kruskal-Wallis Test. If there was a difference between groups, further pairwise analyses were performed using the Mann-Whitney-U Test. Significance was accepted at $p < 0.05$ for all analyses.

6.4   Results

6.4.1   Patient characteristics

A summary of the demographics is presented for each group in Table 6.1. There were no statistically significant differences between the two neck-arm pain groups in any of the measures including pain intensities, symptom duration, sleep quality, fear avoidance behaviour, anxiety and depression scores, physical and mental component summary score of the SF-36 and NDI scores. The NDI indicated moderate disability for patients with cervical radiculopathy and mild disability for patients with NSNAP. Both neck-arm pain groups differed from HC with significantly poorer sleep quality, lower physical and mental component summary scores of the SF-36 and higher anxiety and depression scores, however over 75% of anxiety and 91% of depression scores fell within the normal range. Compared to patients with FM, both neck-arm pain patient groups demonstrated a significantly shorter symptom duration, lower anxiety scores and higher mental component score of the SF-36. Patients with cervical radiculopathy showed lower average pain intensity during the last week and the last 4 weeks prior to testing and a lower depression score compared to patients with FM. Patients with NSNAP demonstrated a significantly higher physical component score of the SF-36 and lower score on the NDI compared to patients with FM.

In the cervical radiculopathy group, 11 patients presented with a C6 radiculopathy and 12 patients with a C7 radiculopathy. The most common pain descriptors used by patients with radiculopathy for their neck pain were constant pain (n = 17), ache (n = 10), dull (n = 7), burning (n = 6) and sharp (n = 6), and for their arm pain constant pain (n = 11), burning (n = 7), ache (n = 6) and shooting (n = 5). Eight patients with cervical radiculopathy indicated their arm pain as the maximal pain area. All patients reported the presence of paraesthesia (pins and needles, tingling or numb sensation)

in their arm. Seventeen patients reported spontaneous pain. In the patient group with NSNAP, 7 patients presented with pain in a C7 dermatomal distribution and one patient with pain in a C6 dermatomal distribution. The most common pain descriptors for the neck pain were constant pain (n = 5), burning (n = 5) and ache (n = 3), and for the arm pain intermittent pain (n = 5), burning, shooting and nerve pain (n = 2). For all patients in this group, the maximal pain area was located in the neck/upper thoracic area. All patients reported the presence of paraesthesia in their arm. Three patients indicated the presence of spontaneous pain. Two patients had undergone medical imaging (computed tomography) of their cervical spine, which demonstrated no compromise of the exiting nerve root at the relevant spinal level. All other patients had no imaging performed.

6.4.2 Sensory profile and number of abnormal findings

The QST sensory profiles for each body region (maximal pain area, dermatome and foot) and by group (cervical radiculopathy, NSNAP and FM) shown as z-scores are illustrated in Figure 6.1A – 6.1C. To allow for easy visual comparison, the z-score sensory profiles are also shown for all pain conditions by each area independently (maximal pain area, dermatome and foot) (Figure 6.2A – 6.2C).
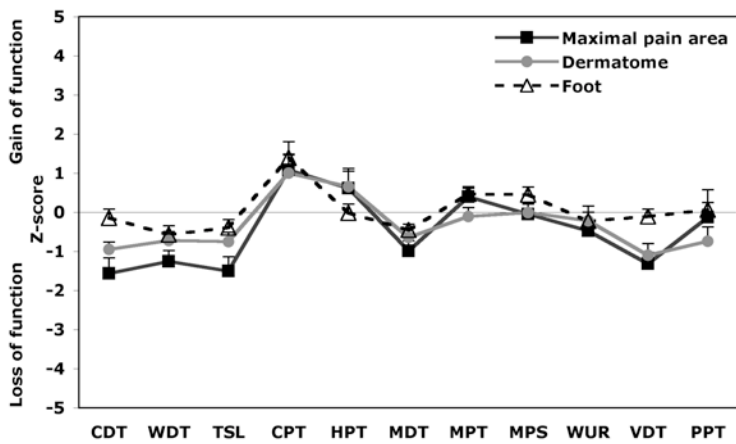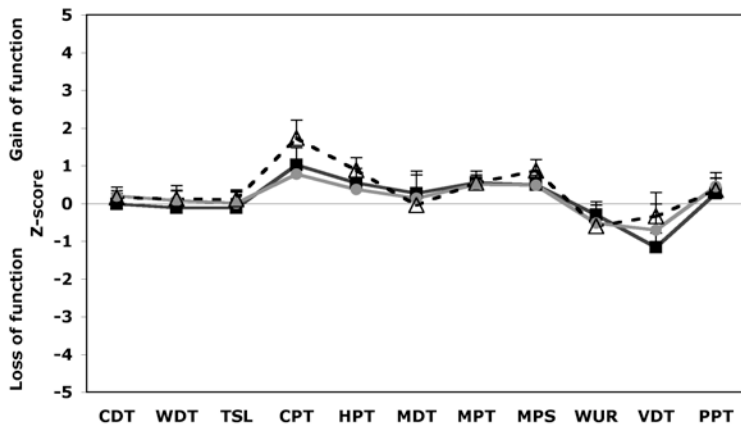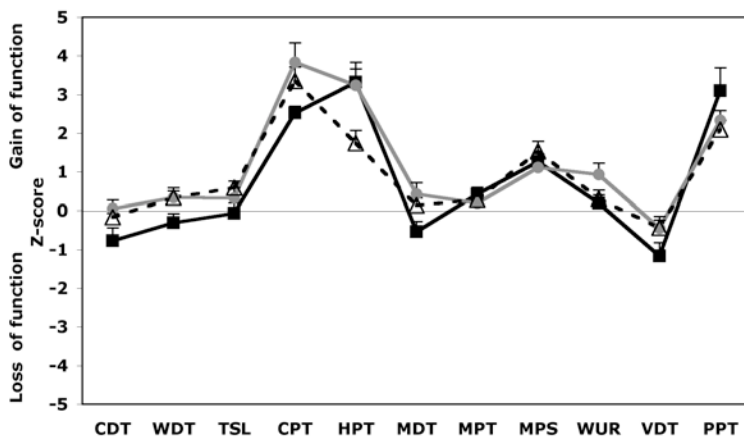
Figure 6.1 Sensory profiling. The z-score sensory profiles are shown of patients with cervical radiculopathy (A), patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) (B) and patients with fibromyalgia (FM) (C) in the maximal pain area (filled square), dermatome (filled circle) and foot (empty triangle). Error bars indicate the standard error of measurement. CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold.
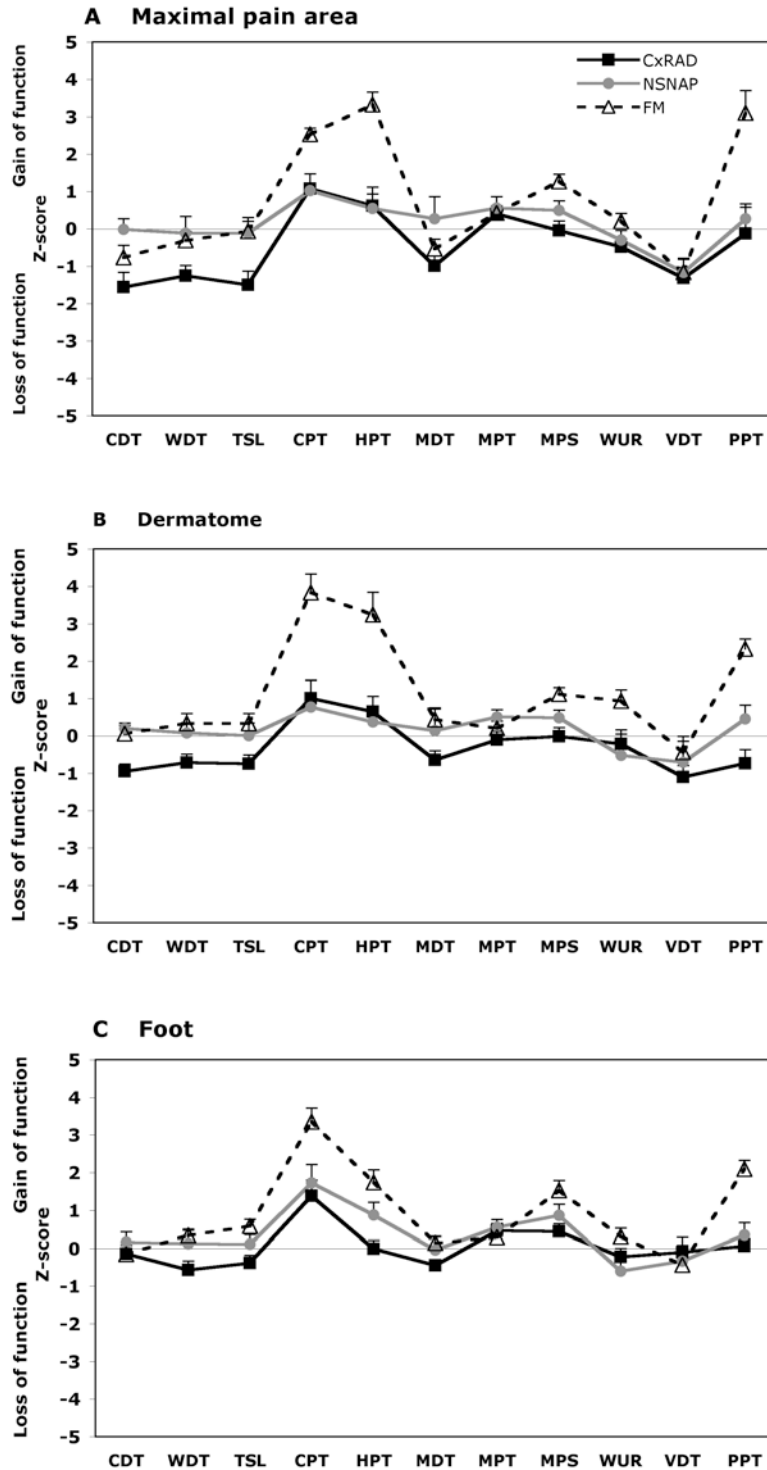
Figure 6.2 Sensory profiling. The z-score sensory profiles are shown of patients with cervical radiculopathy (filled square), patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) (filled circle) and patients with fibromyalgia (FM) (empty triangle) in the maximal pain area (A), dermatome (B) and foot (C). Error bars indicate the standard error of measurement. CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold.

6.4.2.1 *Patients with cervical radiculopathy*

For patients with cervical radiculopathy, the mean values of all QST parameters were within the 95% confidence interval of the reference group (Fig. 6.1A). Patients with cervical radiculopathy demonstrated mixed, bi-directional sensory abnormalities, i.e. signs of a loss of function as well as a gain of function. Compared to HC, a loss of function was demonstrated for the non-nociceptive parameters CDT, WDT, TSL, MDT and VDT in the maximal pain area ($p \leq 0.008$) and CDT, WDT, TSL and VDT in the dermatome ($p < 0.03$) and for the nociceptive parameter PPT in the dermatome ($p = 0.038$) (Table 6.2). Although MDT was elevated in the dermatome (Fig. 6.1A), it did not reach statistical significance compared to HC data (MDT: $p = 0.069$).

The frequencies of z-score values outside the 95% confidence interval of the HC group (Table 6.3) indicating a loss of function (< -1.95) were as follows (in order: maximal pain area; dermatome; foot): CDT (39%; 17%; 4%), WDT (26%; 9%; 4%), TSL (39%; 13%; 4%), MDT (26%; 13%; 0%), VDT (22%; 22%; 4%) and PPT (22%; 17%; 0%). In comparison with HC data, a gain of function was evident for one nociceptive parameter (CPT) (Fig 6.1A), data indicating an increased cold sensitivity primarily in the maximal pain area ($p = 0.001$) and in the foot ($p = 0.003$) (Table 6.2). The frequencies of z-scores > 1.95 indicating a gain of function for CPT were: 39%, 30% and 30% for the maximal pain area, dermatome and foot respectively (Table 6.3). WUR was not consistently present in any of the examined body regions (Table 2). DMA was demonstrated by one patient in both the maximal pain area and in the dermatome. PHS in the maximal pain area was reported once in one patient. PHS in the foot was reported once in three patients and three times in four patients.

Table 6.2
QST parameters are shown of healthy controls (HC), patients with cervical radiculopathy (CxRAD), patients with neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) and patients with fibromyalgia (FM) in the maximal pain area (MPA), dermatome (DERM) and foot (FOOT). QST data are shown as mean for untransformed data (HPT, VDT) and retransformed mean for log-normally distributed data.

QST Parameter	HC n = 31	CxRAD n = 23	NSNAP n = 8	FM n = 22	*p-* Group/ region	*p-* Group	*p-* Body region
CDT (°C)					0.003	0.003	0.003
MPA	1.31	1.89[d, e]	1.16	1.57			
DERM[a]	1.57	2.68[c, e, f]	1.55	1.56			
FOOT[a]	3.42	3.06	3.86	3.02			
WDT (°C)					0.529	<0.001	0.037
MPA	2.65	3.83[d, e, f]	2.64	2.79			
DERM[a]	2.94	4.17[c, f]	3.14	2.56			
FOOT[a]	4.70	6.30[c, f]	4.42	3.95			
TSL (°C)					0.302	<0.001	0.028
MPA	4.26	6.22[d, e, g]	4.17	4.11			
DERM	4.71	6.87[c, f]	5.11	4.03			
FOOT[a]	9.39	11.78[f]	8.84	6.69[c]			
CPT (°C)					0.050	<0.001	0.095
MPA	7.1	11.16[c, g]	12.16[c, f]	24.2[d]			
DERM	6.11	8.08[g]	7.80[g]	18.03[d]			
FOOT	5.76	9.39[c, g]	10.59[c, f]	18.73[d]			
HPT (°C)					0.183[h]	<0.001[h]	0.949[h]
MPA	46.6	45.4[g]	45.1[f]	39.5[d]			
DERM	47.3	46.1[f]	46.4[f]	40.8[c]			
FOOT	46.3	46.4[g]	44.0	41.8[c]			
MDT (mN)					0.193	0.014	0.112
MPA	2.11	3.79[c, e]	1.37	3.08			
DERM	2.24	4.53[f]	2.65	1.50			
FOOT	6.34	10.15	6.67	5.50			
MPT (mN)					0.241[h]	0.512[h]	0.282[h]
MPA	66.24	29.85	28.10	31.60			
DERM	72.81	84.45	34.90	54.68			
FOOT	58.45	34.92	31.72	42.23			

Table 6.2 continued

QST Parameter	HC n = 31	CxRAD n = 23	NSNAP n = 8	FM n = 22	*p-* Group/ region	*p-* Group	*p-* Body region
MPS (rating 0-100)					0.193[i]	0.009[i]	0.034[i]
MPA	0.44	0.45[f]	0.77	1.90[c]			
DERM	0.36	0.34[f]	0.74	1.38			
FOOT[a, b]	0.41	0.66[f]	1.04	2.10[c]			
WUR (ratio)					0.050	0.029	0.236
MPA	3.80	2.81	2.98	4.36			
	(n = 16)	(n = 18)	(n = 8	n = 22)			
DERM	2.77	2.45[f]	2.15[f]	4.34[c]			
	(n = 17)	(n = 15)	(n = 8)	(n = 22)			
FOOT	3.30	2.86	2.24	4.04			
	(n = 21)	(n = 21)	(n = 8)	(n = 22)			
VDT (x/8)					0.133	0.032	0.001
MPA	6.1	5.4[c]	5.2	5.5[c]			
DERM	7.0	6.2[c]	6.6	6.7			
FOOT[a, b]	5.9	5.7	5.5	5.4			
PPT (kPa)					0.194[j]	0.004	0.787[j]
MPA	427	403	390	183			
DERM	471	572[c, e, g]	417[g]	249[d]			
FOOT	584	573[g]	522[g]	299[d]			

CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold. [a]Significantly different to maximal pain area ($p < 0.05$); [b]Significantly different to dermatome ($p < 0.05$); [c]Significantly different to HC ($p < 0.05$); [d]Significantly different to HC ($p < 0.001$); [e]Significantly different to NSNAP ($p < 0.05$); [f]Significantly different to FM ($p < 0.05$); [g]Significantly different to FM ($p < 0.001$); [h]adjusted for anxiety; [i]adjusted for depression, [j]adjusted for gender.

Table 6.3 Number of individuals within each group with z-score values outside the 95% confidence interval of healthy control subjects (+/- 1.96 standard deviation).

QST Parameter	Maximal pain area								Dermatome								Foot							
	HC n = 31		CxRAD n = 23		NSNAP n = 8		FM n = 22		HC n = 26		CxRAD n = 23		NSNAP n = 8		FM n = 22		HC n = 26		CxRAD n = 23		NSNAP n = 8		FM n = 22	
	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
CDT	1	0	1	9	0	0	1	8	0	0	0	4	0	0	0	1	0	2	1	1	0	0	0	0
WDT	1	0	0	6	0	0	1	1	0	3	0	2	0	0	0	2	0	0	0	1	0	0	0	0
TSL	0	0	0	9	0	1	1	1	0	0	0	3	0	0	0	1	0	2	1	1	0	0	1	0
CPT	1	0	9	0	2	0	21	0	0	0	7	0	3	0	18	0	1	0	8	0	3	0	19	0
HPT	2	0	5	0	1	0	19	0	2	0	6	0	0	0	15	0	0	0	1	0	1	0	10	0
MDT	0	0	0	6	1	1	1	3	0	0	0	3	0	2	3	1	1	0	0	0	0	0	0	0
MPT	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MPS	1	0	2	0	0	0	7	0	0	0	2	0	0	0	4	0	1	0	1	0	1	0	8	0
WUR	0	0	0	2	0	0	1	0	0	1	1	2	0	1	3	0	1	0	0	0	0	0	1	0
VDT	0	0	0	5	0	2	0	5	0	1	0	5	0	3	0	2	0	1	0	1	0	2	0	1
PPT	0	1	6	5	1	0	15	1	1	0	2	4	1	0	14	0	1	0	0	0	0	0	13	0
DMA*	0	0	1	0	0	0	3	0	0	0	1	0	0	0	3	0	0	0	0	0	0	0	5	0

HC: healthy control subjects; CxRAD: cervical radiculopathy; NSNAP: non-specific neck-arm pain associated with heightened nerve mechanosensitivity; FM: fibromyalgia;CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold; DMA: dynamic mechanical allodynia.

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

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

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

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

For patients with NSNAP, the mean values of all QST parameters were within the 95% confidence interval of the reference group (Fig. 6.1 B). This group's dominant sensory characteristic was a gain of function for cold pain sensitivity primarily in the maximal pain area ($p = 0.024$) and in the foot ($p = 0.008$) (Fig. 6.1 B, Table 6.2). Two of the 8 patients with NSNAP recorded z-scores for CPT > 1.95 in the maximal pain area indicating a gain of function, and three patients demonstrated this gain in the dermatome and the foot (Table 6.3). There was a tendency for a loss of function in vibration detection in the maximal pain area (Fig. 6.1B), however this observation did not reach statistical significance ($p = 0.064$) (Table 6.2). Two of the 8 patients recorded z-scores of < -1.95 indicating a loss of function for VDT in the maximal pain area (Table 6.3). WUR was present in all examined body regions (Table 6.2). No patients demonstrated DMA in any body region. PHS in the maximal pain area was reported twice by one patient and in the foot on three occasions by another patient.

6.4.2.3 Patients with fibromyalgia

Patients with FM demonstrated z-scores beyond the 95% confidence interval of the HC group for CPT and PPT in all body regions and for HPT in the maximal pain area and dermatome (Fig. 6.1C). Their sensory profiles were characterised predominantly by a gain of function, indicated by increased thermal and pressure sensitivity in all body regions (CPT, HPT, PPT $p \leq 0.005$) and increased MPS in the maximal pain area ($p = 0.026$) and foot ($p < 0.001$) (Table 6.2). The following frequencies of z-scores were > 1.95 indicating a gain of function (order: maximal pain area; dermatome; foot) (Table 6.3): CPT (95%; 82%; 86%), HPT (86%; 68%; 45%), MPS (32%; 18%; 36%), WUR (4%; 14%; 4%) and PPT (68%; 64%; 59%). In addition, patients with FM demonstrated signs of a loss of sensory function with elevated VDT in the maximal pain area ($p = 0.009$). Five patients with FM recorded z-scores < -1.95 for VDT indicating a loss of function. WUR was present in all examined body regions (Table 6.2). Three patients demonstrated DMA in the maximal pain area and dermatome and five patients demonstrated DMA in the foot. PHS was reported by one patient in the foot once.

6.4.3　Comparison of sensory profiles between groups and body regions

Sensory profiles differed between groups and also between body regions. An ANCOVA of all QST data demonstrated group differences for all variables except MPT (Table 6.2). Differences in thermal detection thresholds, MDT and VDT were mainly driven by the loss of function seen in patients with cervical radiculopathy (Fig. 1). Differences in pain thresholds (CPT, HPT, PPT) and mechanical pain sensitivity (MPS) were mainly driven by the increased sensitivity to these stimuli in patients with FM.

There were significant differences between tested body regions (Fig. 6.2, Table 6.2) with greater thermal and vibration sensation loss in the maximal pain area compared to the dermatome (CDT $p = 0.031$; WDT $p = 0.049$; VDT $p < 0.001$) and foot (CDT $p = 0.002$; WDT $p = 0.029$; VDT $p = 0.017$) and greater TSL threshold elevation in the maximal pain area compared to the foot ($p = 0.017$). MPS was less dominant in the maximal pain area ($p = 0.022$) and the dermatome ($p = 0.002$) compared to the foot. A significant group by region interaction was evident for CDT ($P = 0.003$) (Table 6.2; Fig. 6.2). Patients with cervical radiculopathy demonstrated significantly reduced CDT in the maximal pain area and the dermatome (Fig. 6.2A, B) when compared to HC and patients with NSNAP (Table 6.2). There was an association between anxiety and HPT in patients with FM, demonstrating higher anxiety scores and increased heat sensitivity. Higher depression scores in patients with FM were correlated with increased mechanical pain sensitivity. Gender had a significant effect on PPT measurements (group*gender $p = 0.041$). For comparison of PPT in the maximal pain area the inclusion of gender in the univariate analysis decreased the significance between all 4 groups from significant to non-significant. Further pairwise comparison between groups, including gender adjustment, demonstrated lowered PPT in patients with FM compared to HC ($p = < 0.001$) and compared to patients with NSNAP ($p = 0.011$). PPT measurements were significantly lower in female than males for all body regions ($p < 0.001$)

6.5 Discussion

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

Concordant with our hypothesis, patients with cervical radiculopathy were characterised by localised sensory abnormalities in the maximal pain area (reduced thermal, mechanical and vibration detection) and dermatome (reduced thermal and vibration detection and pressure pain sensitivity), indicating a loss of small and large sensory fiber function. The presence of these negative sensory signs is indicative of peripheral neuronal damage and consistent with the presence of NeP components (Hansson 2002; Treede et al. 2008). Loss of function occurred in all primary sensory fibers tested (C, Aδ, Aβ), data consistent with previous findings in patients with peripheral nerve injuries (Kleggetveit and Jørum 2010) and in patients with lumbar radiculopathy (Nygaard and Mellgren 1998), although others studies of patients with lumbar radiculopathy report selective loss of function in Aδ fibers (Mosek et al. 2001) or Aδ and Aβ fibers (Freynhagen et al. 2008). In contrast, Chien et al (Chien et al. 2008) did not find elevated CDT in tested areas representative of C6/7/8 dermatome, but it is unclear if these areas correlated with each individual patient's area of sensory loss.

Patients with cervical radiculopathy demonstrated cold hypersensitivity in the maximal pain area, a common sequel of peripheral nerve injury (de Medinaceli et al. 1997; Kleggetveit and Jørum 2010; Landerholm et al. 2010; Taylor et al. 2010) and has been demonstrated locally at the cervical spine in patients with cervical

radiculopathy (Chien et al. 2008). The clinical significance of our finding is unclear, as the group mean value for CPT fell within the 95% confidence interval of our HC group, fell within the DFNS reference data (Magerl et al. 2010) and was also below the value of defined cold hyperalgesia ($\geq 15°$) (Bennett et al. 2006). Nevertheless, when evaluating individual results 11 patients demonstrated cold hyperalgesia in their maximal pain area. A novel finding was cold hypersensitivity also occurring in the foot. Only two patients documented cold hyperalgesia in all body regions and only 4 patients showed cold hyperalgesia in both maximal pain area and foot. These data suggest a heterogeneity in our patient group i.e. sub-groups may exist within our cohort, consistent with data on patients with NeP (Baron et al. 2009; Maier et al. 2010) and lumbar radiculopathy(Mahn et al. 2011).

Mechanisms underlying cold evoked pain are still not fully understood (Belmonte et al. 2009; Viana 2009) and likely include both peripheral (Serra et al. 2009; Wasner et al. 2004) and central nervous mechanisms (Craig et al. 2000; Jørum et al. 2003; Woolf and Mannion 1999; Yarnitsky and Ochoa 1990). Cold hypersensitivity is not necessarily associated with the presence of pain or with nerve damage as evidenced in patients with painless peripheral nerve injuries (Kleggetveit and Jørum 2010), by patients with FM (Berglund et al. 2002; Blumenstiel et al. 2011; Hurtig et al. 2001; Klauenberg et al. 2008; Pfau et al. 2009) and by patients with depression without pain (Klauenberg et al. 2008). While psychological factors can enhance pain sensitivity (Rhudy and Meagher 2000), our patients with cervical radiculopathy demonstrated scores within the normal range for anxiety and depression and measurements of CPT were not affected by anxiety or depression. Summarized, the significance of the cold hypersensitivity in the foot in our patient cohort remains unclear.

Contrary to Chien et al (Chien et al. 2008) who demonstrated widespread increased pressure sensitivity in patients with cervical radiculopathy, we did not observe mechanical hyperalgesia in our cohort. Apart from differences in body areas assessed, Chien et al's patients demonstrated longer symptom duration (19.7 ± 14.2 months) and higher disability on the NDI compared to our patients. It is possible that the chronicity of symptoms led to altered pain processing in the central nervous system, resulting in this hypersensitivity. In our study, 6 patients recorded z-scores >

1.96 in their pain area, indicating increased pressure pain sensitivity, and 5 patients < -1.96, indicating reduced sensitivity. This dichotomy of pressure pain sensitivity is consistent with likely sub-groups of patients with differing somatosensory profiles within a radiculopathy cohort, as demonstrated recently in patients with lumbar radiculopathy (Mahn et al. 2011). These data highlight the need for individual patient assessment in order to determine sensory phenotypes.

Patients with NSNAP did not differ to HC except for the presence of cold hypersensitivity in their maximal pain area and foot. No comparative data exist for this patient cohort. Three patients with NSNAP used pain descriptors suggestive of NeP (spontaneous pain and burning) (Bennett 2001; Dworkin et al. 2007), and they all demonstrated a loss of function in vibration detection in their maximal pain area compared to HC. Then again, hyposensitivity towards vibration stimuli does not necessarily indicate neuronal damage and has been documented in patients with FM (Koroschetz et al. 2010) and chronic low back pain (Blumenstiel et al. 2011), possibly consistent with neuroplastic changes in the central nervous system. Also these findings are in line with tactile hypoaesthesia documented in non-NeP pain conditions (Geber et al. 2008; Leffler et al. 2000; Magerl and Treede 2004; Westermann et al. 2011). Similar to the radiculopathy group, the group mean for CPTs was within the 95% confidence interval of our HC group and other reference data (Magerl et al. 2010). Cold hypersensitivity was also observed in the foot, but no patient demonstrated cold hypersensitivity in all tested body regions.

Patients with FM were characterised by a widespread gain of function in the majority of nociceptive parameters (thermal and pressure pain) and mechanical pain sensitivity in their maximal pain area and foot. While our finding of generalised increased pressure sensitivity is consistent with previous studies (Blumenstiel et al. 2011; Klauenberg et al. 2008; Koroschetz et al. 2010; Kosek et al. 1996; Pfau et al. 2009) and likewise that of increased cold and heat sensitivity (Berglund et al. 2002; Blumenstiel et al. 2011; Hurtig et al. 2001; Kosek et al. 1996), others did not report increased cold (Klauenberg et al. 2008) or heat sensitivity (Klauenberg et al. 2008; Pfau et al. 2009). Our demonstration of increased MPS in patients with FM corresponds with some (Blumenstiel et al. 2011), but not with others (Klauenberg et al. 2008; Pfau et al. 2009); similarly reduced vibration sense was demonstrated by

some (Koroschetz et al. 2010), but not others (Klauenberg et al. 2008; Pfau et al. 2009). These differing observations are indicative of the heterogeneity of FM and the existence of various sub-groups (Giesecke et al. 2003; Hurtig et al. 2001; Rehm et al. 2010). The demographic characteristics of our patients with FM were consistent with previous data (Gormsen et al. 2010; Wolfe et al. 2010). Our results point to a more generalised sensory discriminative dysfunction in patients with FM compared with our neck-arm pain groups.

Both neck-arm pain groups shared similarities in their demographics and pain characteristics, except a larger proportion of patients with cervical radiculopathy were on medication compared to patients with NSNAP. While a possible influence of medication on pain sensitivity cannot be disregarded, both patient groups were similar in their measurements of cold hypersensitivity. Despite commonalities in clinical profiles of these two neck-arm pain groups a distinct difference in somatosensory profiles was shown. The sensory phenotype of sensory loss in patients with radiculopathy is likely reflective of the underlying pathology. Based on the recently proposed grading system of NeP (Treede et al. 2008), our patients with cervical radiculopathy fulfilled the definition of "definite" NeP. However, this does not exclude coexistent nociceptive pain and the presence of mixed pain (Baron and Binder 2004), considering the variations in profiles observed in our cohort. Patients with NSNAP would be classified as having "possible" or "probable" NeP, depending if cold hypersensitivity was regarded as a relevant sensory abnormality for the presence of NeP.

Both neck-arm pain groups differed in their sensory phenotypes compared to patients with FM, where the somatosensory profile showed mainly increased pain sensitivity across nociceptive submodalities in almost all body regions. Such generalised heightened sensitivity was not present in our neck-arm pain patient groups and may point to differences in the underlying pain mechanisms. In the absence of evidence of tissue damage in FM, aberrations in pain inhibitory (Ingvar 2009; Julien et al. 2005; Lannersten and Kosek 2010) and pain facilitatory mechanisms (Lannersten and Kosek 2010) as well as central sensitisation/augmentation of sensory input (Banic et al. 2004; Desmeules et al. 2003; Staud et al. 2008) have been associated with enhanced pain sensitivity in FM.

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Limitations of the study

The group of patients with NSNAP was comparatively small and a type II error cannot be excluded. However, the recruitment of these patients proved to be extremely difficult. Out of 464 clinically examined patients with neck-arm pain, only 8 fulfilled the inclusion criteria of our study. The prevalence of this pain condition may be overestimated. As QST parameters vary significantly over body areas (Rolke et al. 2006b), comparative HC reference data have to be obtained for all body regions that are examined in patients. Numerous researchers have reported similar difficulties in this matter (Blumenstiel et al. 2011; Landerholm et al. 2010; Maier et al. 2010). Whilst we were able to obtain age matched HC data for all assessed body regions, we were not able to gender match these data. The size of some HC reference groups was small (n = 8), thus these reference data should not be referred to as 'normative' data.

A further limitation of this study relates to the fact that the experts' patient classification was based on reading notes only and not on a clinical assessment of the patient. However while the study design could be strengthened by the experts examining the patient, this was not possible for logistic and ethical reasons. Assessment by three practitioners would have imposed a considerable burden on the patients plus repeated assessment could potentially cause a flare-up of the patient's pain condition raising ethical concerns.

It has been suggested that in patients with unilateral pain, a side-to-side comparison of QST data enhances the sensitivity to detect sensory abnormalities (Rolke et al. 2006a). This was not addressed in the current study, but will be reported in a forthcoming paper.

Conclusion

Despite similarities in pain characteristics and sensory signs between the patients with cervical radiculopathy and NSNAP, distinct somatosensory profiles were demonstrated for each group, possibly reflecting differences in the underlying pathophysiology, pain types and associated pain mechanisms. Our data suggest the possible presence of sub-groups with differing somatosensory profiles within these

two neck-arm pain patient groups. The findings of this study may assist clinicians in targeting management of these patient sub-groups.

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Chapter 7

Neuropathic pain components are common in patients with cervical radiculopathy, but not in patients with non-specific neck-arm pain

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7.1 Abstract

This study investigated in patients with unilateral painful cervical radiculopathy and patients with unilateral non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) side-to-side differences of quantitative sensory testing (QST) parameters and the presence of neuropathic pain (NeP) components, using QST and the painDETECT (PD-Q) NeP screening questionnaire. All patients completed the PD-Q prior to QST. QST was performed in the maximal pain area and the affected dermatome in 23 patients with painful C6 or C7 cervical radiculopathy and 8 patients with NSNAP following a C6/7 dermatomal pain distribution. Patients with cervical radiculopathy demonstrated a significant loss of function in mechanical ($p \leq 0.027$) and vibration sense ($p \leq 0.002$) on the symptomatic side compared to the asymptomatic side in both tested body regions and in cold detection (CDT $p = 0.019$) and pressure pain sensitivity (PPT $p = 0.001$) in the dermatome, findings consistent with nerve root damage. Thermal detection was reduced bilaterally, consistent with a loss of function. These sensory alterations in the maximal pain area/symptomatic side are confirmative for the presence of NeP. In contrast to these QST data, only 30% of patients with cervical radiculopathy demonstrated a NeP component according to the PD-Q score. In patients with NSNAP, a significant side-to-side difference was demonstrated for warm detection threshold in the dermatome. The PD-Q score indicated that NeP components were unlikely in this group. In conclusion, QST data suggest that NeP is common in patients with painful cervical radiculopathy, but not in patients with NSNAP.

7.2   Introduction

Quantitative sensory testing (QST) has been recommended for accurate sensory profiling in the assessment of patients with NeP (Haanpää et al. 2011). Using laboratory QST in patients with painful cervical radiculopathy and comparison to reference data, we recently demonstrated a loss of function to non-nociceptive stimuli (thermal, mechanical, vibration detection) in the maximal pain area and the affected dermatome (thermal detection, vibration detection) and to nociceptive stimuli (pressure pain) in the dermatome, plus a gain of function (cold sensitivity) in the maximal pain area. These findings are indicative of peripheral neuronal damage and the presence of a NeP component (Haanpää et al. 2011; Treede et al. 2008). In contrast, patients with non-specific neck-arm pain (no clinical signs of radiculopathy) associated with heightened nerve mechanosensitivity (NSNAP) were characterised by a gain of function of a single sensory parameter, cold hypersensitivity in their maximal pain area. Heightened nerve mechanosensitivity is defined as pain in response to upper limb movement that causes nerve elongation (Elvey 1997). Our findings suggest that the mix of nociceptive and NeP components varies between these groups. Determination of the "pain mix" is of therapeutic relevance (Baron and Tölle 2008), as NeP in particular requires targeted management.

In order to investigate further the "pain mix" for each patient group, a side-to-side comparison of QST data within each group is recommended (Hansson et al. 2007; Rolke et al. 2006a), as patients may have presented with subtle sensory alterations not identifiable by comparison to our reference data. Such side comparison is in line with standard clinical examination of patients with unilateral pain presentations and is considered crucial to establish clinically-relevant abnormalities (Haanpää et al. 2011).

Further, the use of NeP screening tools for identification of NeP components has been recommended (Haanpää et al. 2011). The painDETECT (PD-Q) (Freynhagen et al. 2006a), a validated self reported NeP screening tool, has increasingly been employed for the identification of NeP in patients with low back and leg pain (Beith

et al. 2011; Freynhagen et al. 2006a; Kaki et al. 2005; Prout et al. 2010), however, its usefulness in the screening of NeP in patients comparable to our cohorts, has not been reported.

Using three assessment tools (previous established QST findings, side-to-side difference and PD-Q) this study aimed to further characterise patients with cervical radiculopathy and patients with NSNAP and to investigate the presence of NeP components in these groups. We hypothesized that:

1. in patients with cervical radiculopathy, there would be a significant side-to-side difference between the symptomatic and asymptomatic side in the previously documented sensory alterations (hypoaesthesia to non-nociceptive stimuli and cold hypersensitivity) in their maximal pain area and the affected dermatome (hypoaesthesia to non-nociceptive stimuli and pressure pain),
2. in patients with NSNAP, there would be a significant side-to-side difference between the symptomatic and asymptomatic side in the previously documented cold hypersensitivity in their maximal pain area, with greater cold hypersensitivity on the symptomatic side,
3. patients with cervical radiculopathy would be more likely to present with NeP components and therefore to score higher on the PD-Q than patients with NSNAP.
4. there would be an association between the clinical parameters of average pain intensity over the last 4 weeks and symptom duration and QST parameters and PD-Q.

7.3   Materials and methods

7.3.1   Participants

Twenty-three patients with painful C6 or C7 cervical radiculopathy (8 female; mean age 46.3 ± 9.6 years) and 8 patients with NSNAP following a C6/C7 dermatomal distribution (7 female; mean age 45.1 ± 14.9 years) participated in the study. Patients were recruited from private clinics and departments of various disciplines (physiotherapy, pain management, neurosurgery) at five local metropolitan hospitals in Perth, Western Australia, and from the local community via radio and newspaper

advertising (see flow chart of recruitment Fig.7.1). All referrals of patients with neck/upper limb symptoms to the neurosurgery triage clinic received between September 2007 and November 2010 were reviewed by the investigator (author BT). Patients in whom the referral indicated the possible presence of a unilateral nerve lesion/disease were selected and were clinically examined. For inclusion into the study, all participating patients were required to fulfill the inclusion criteria of unilateral neck pain and arm pain/paraesthesia in a C6/7 distribution, symptom duration of 3 to 18 months and current pain intensity ≥ 2 on a visual analogue scale (VAS). Patients with cervical radiculopathy were required to demonstrate signs of either C6 or C7 nerve root dysfunction with neurological deficits consistent with the affected nerve root level and with compressive radiculopathy (either absent or diminished reflexes and/or myotomal weakness and dermatomal sensory deficits of light touch and/or vibration sense). Additionally, patients were required to have a demonstrable clinically relevant abnormality on imaging studies (Bono et al. 2011; Treede et al. 2008) that indicated compromise of the exiting nerve root at the relevant spinal level. Inclusion criteria for patients with NSNAP were no clinical signs of radiculopathy and evidence of increased peripheral nerve sensitivity to mechanical stimuli (Elvey 1997), including pain in response to a nerve provocation test in the upper limb (NPT_{MEDIAN}) (Elvey 1997). Exclusion criteria for both groups were: evidence of a metabolic or a medical disease; other neurological or psychiatric disease; a history of cardiovascular disease; and an insufficient level of English.

Prior to participation, all patients were examined by a highly qualified Musculoskeletal Physiotherapist (Master qualification) who had extensive clinical experience in triaging patients with suspected nerve lesions and associated NeP to ascertain they met the inclusion criteria (BT). The assessment included the patient's history, pain drawings, pain description and pain behaviours, musculoskeletal and neurological examination and review of reports of diagnostic tests (imaging, nerve conduction studies). While all patients with cervical radiculopathy had undergone medical imaging (Computed tomography (CT) n = 1, magnetic resonance imaging n = 22), only two patients with NSNAP had a CT performed of the cervical spine. In these two patients, CT did not demonstrate any abnormality indicating compromise of a nerve root at the relevant spinal level. The diagnostic classification of both patient groups was verified by a Fellowship-trained spinal neurosurgeon and a

Fellowship–qualified (Fellow of the Australian College of Physiotherapists) Specialist in Musculoskeletal Physiotherapy, both of whom were blinded to the clinician's patient classification. Each Fellow independently reviewed the patient notes and the results of any medical investigations. Only patients whose clinical presentation was confirmed by all three examiners were included in the data analyses (see Fig. 7.1).

HC data from our previous study was used to transform QST raw scores into z-scores. The HC group, consisting of 31 age-matched subjects (15 female, 45.6 ± 12.5 years), was recruited from the local community. Subjects with a history of current pain or a chronic pain condition, or any of the additional exclusion criteria described for the patient groups, were excluded (including taking medications known to influence pain perception). The study protocol and recruitment procedures were approved by the local Ethics Committees of all participating institutions and adhered to the ethical guidelines of the Declaration of Helsinki.
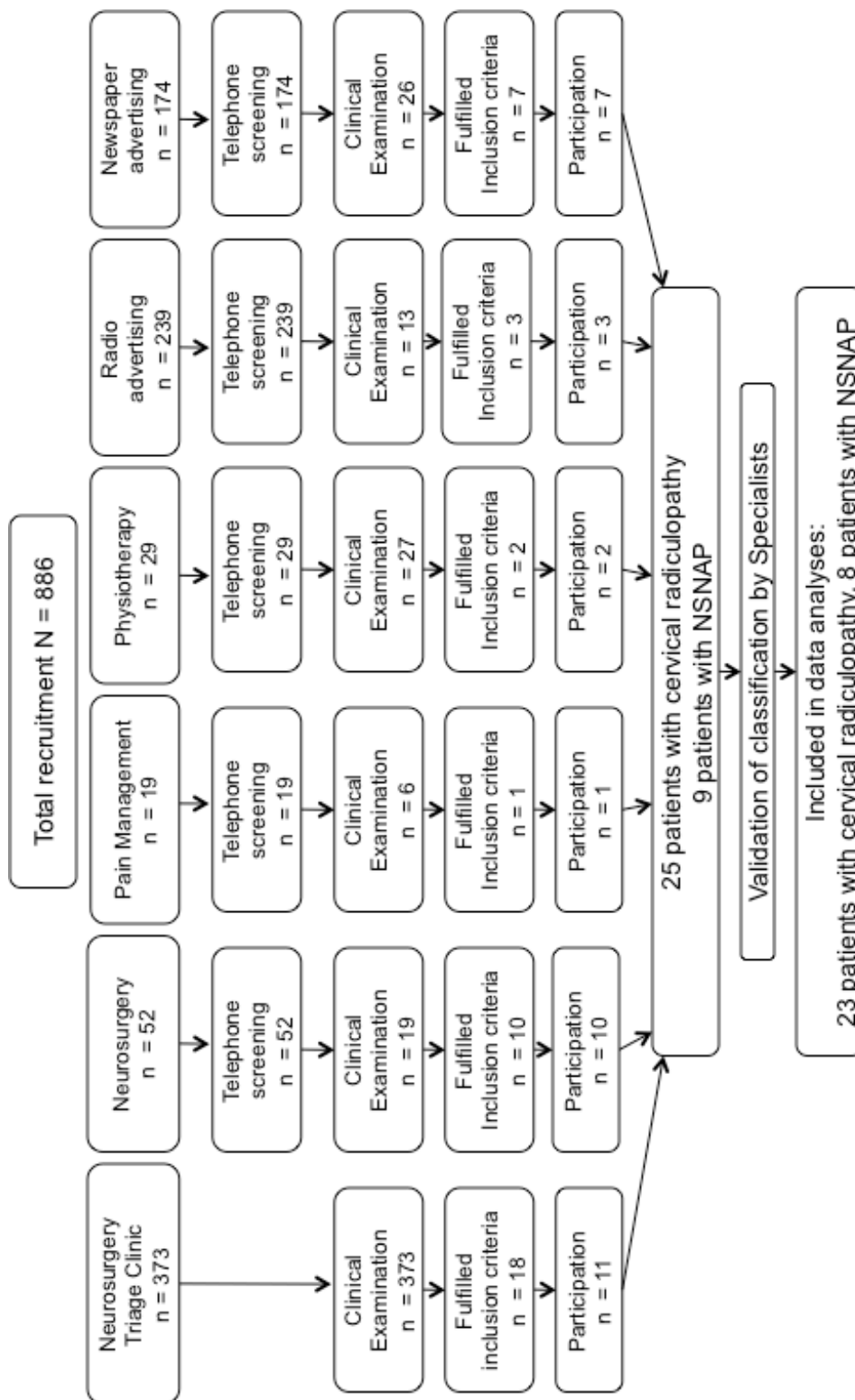
Figure 7.1 Flowchart of recruitment of patients with cervical radiculopathy and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP).

7.3.2 Questionnaires

A battery of questionnaires was used to clinically characterise the patient groups. This battery was administered immediately before the QST. All patients completed the short form-36 health questionnaire (SF-36v2®) (Ware 2000) to assess health-related quality of life. The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) was used to screen for anxiety and depression, with two outcome scores generated, each with a maximum score of 21 for each parameter. Scores of ≤ 10 for each are considered within normal range. Sleep quality over the last week was recorded on a 100-cm VAS with the end points 0 cm (good sleep) and 10 cm (bad sleep) (Hurtig et al. 2001). In addition, to assess fear avoidance behaviours, patients completed the Tampa Scale of Kinesiophobia (TSK) (Vlaeyen et al. 1995). This questionnaire contains 17 items that relate to fear of movement and fear of (re) injury. A score ≥ 40 is considered to indicate significant kinesiophobia (Crombez et al. 1999). The Neck Disability Index (NDI) (Vernon and Mior 1991) was used to assess the level of patient disability. It is a well-validated ten-item questionnaire (Pietrobon et al. 2002; Vernon 2008). Scores of < 4 indicate no disability, 5 – 14 mild disability, 15 – 25 moderate disability, 25 – 34 severe disability, and > 35 complete disability (Vernon and Mior 1991). The average pain intensity over the last week was determined using a VAS with the end points 0 cm (no pain) and 10 cm (maximum tolerable pain) (Jensen et al. 1989). The strongest and average pain intensity over the last four weeks was recorded on a numeric rating scale (NRS) (0 = no pain, 10 = maximum pain) as part of the PD-Q (Freynhagen et al. 2006a). The PD-Q (Freynhagen et al. 2006a) consists of one descriptor relating to temporal and one to spatial pain characteristics and of seven weighted sensory descriptors. The lowest weight for each descriptor is 0, indicating that the person does not experience the relevant sensation, and the highest weight is 5, indicating the sensation is felt very strongly. PD-Q classifies patients into three groups, defined by Freynhagen et al as follows (Freynhagen et al. 2006a): the result is negative = a NeP component is unlikely (score 0 – 12), the result is unclear = the result is ambiguous, however a NeP component can be present (score 13 – 18), or the result is positive = a NeP is likely (score 19 – 38).

7.3.3 Quantitative sensory testing

The standardised QST protocol of the German Research Network on Neuropathic Pain (DFNS) was employed using the same equipment and standardised instructions as outlined by Rolke et al (Rolke et al. 2006a; Rolke et al. 2006b). The test battery comprised the following assessments: cold and warm detection thresholds (CDT, WDT); the number of paradoxical heat sensations (PHS) during the procedure of alternating warm and cold stimuli (thermal sensory limen (TSL)); cold and heat pain thresholds (CPT, HPT); mechanical detection threshold (MDT); mechanical pain threshold (MPT); stimulus-response functions: mechanical pain sensitivity (MPS) and dynamic mechanical allodynia (DMA); wind-up ratio (WUR); vibration detection threshold (VDT) and pressure pain threshold (PPT). For complete description see Rolke et al (Rolke et al. 2006a; Rolke et al. 2006b).

QST was performed over the maximal pain area, as indicated by the patients (radiculopathy group: upper trapezius muscle n = 4; paravertebral cervical spine n = 2; paravertebral thoracic spine n = 7; above and below spine scapula n = 2; upper arm n = 5; forearm n = 2; just above the elbow n = 1; NSNAP group: upper trapezius muscle n = 6; paravertebral thoracic spine n = 2), and the corresponding contralateral mirror side. Twenty-six HC subjects were assessed bilaterally in the upper trapezius muscle. Thirteen of these subjects were assessed bilaterally in the C6 (thenar eminence) and the remaining 13 in the C7 (dorsum hand, n = 13) dermatome. Eight HC, including 3 from the trapezius group, were examined unilaterally in all other pain areas. Consequently data were available from at least eight health control subjects to standardise the patient data in accordance with established methodology to standardise the data (Blankenburg et al. 2010). In patients with cervical radiculopathy, additional testing was conducted in the exact dermatomal area of sensory loss as determined during clinical examination, and for patients with NSNAP in the area of distal paraesthesia or pain, plus in the contralateral side for both groups. While the QST in the dermatome does not give information about the presence of NeP components (Treede et al. 2008), it does assist to further characterise each patient group and to detect possible sensory alterations that may be indicative of a nerve root lesion. Testing was conducted by one investigator (BT) in a laboratory with a constant room temperature. The investigator was blind to the results of the questionnaires. As the clinical examination of patients and QST testing

were not necessarily performed on the same day, the key inclusion criteria for each group (for radiculopathy: signs of nerve root dysfunction, for NSNAP absence of nerve root dysfunction and presence of heightened nerve mechanosensitivity) were reassessed prior to QST. Patients were asked not to take any analgesics on the day of testing.

7.3.4 Nerve provocation test (NPT$_{MEDIAN}$)

The NPT$_{MEDIAN}$ was performed after the QST as described previously (van der Heide et al. 2006). The range of elbow extension was measured with an electro-goniometer (SG110, Biometrics Ltd, United Kingdom). The patient was asked to press an external trigger at the first onset of pain or at the increase of their resting pain (P1) if present, and at a second time point when the patient reached their pain tolerance (P2) for this movement. Elbow extension was performed to the end of joint range or to P2, whichever occurred first. The NPT$_{MEDIAN}$ was performed three times on each side and the mean value of three recordings of P1 and P2 was used for analysis. Patients who did not report consistently an onset of P1 or P2 in all three trials (i.e. they reported an onset in only 1 or 2 trials) were excluded from the analysis (P1 asymptomatic side n = 3). Four patients with cervical radiculopathy could not be tested due to high pain levels and the associated potential for exacerbation of their condition.

7.3.5 Statistical analysis

SPSS version 17.0 was used for all analyses. An independent T-test was used to compare symptom duration, pain intensity, sleep quality, the NDI, TSK and PD-Q scores between patient groups. Anxiety and depression scores and the physical and mental component summary scores of the SF-36 were compared using the Mann-Whitney-U Test.

All QST data except HPT and VDT were normally distributed in log-space and were log-transformed prior to statistical analysis (Rolke et al. 2006b). Each single QST parameter was then z-transformed by using the following expression: Z-score = (X$_{single\ proband}$ – Mean$_{healthy\ controls}$)/SD$_{healthy\ controls}$ (Rolke et al. 2006b). This procedure provides a site-specific normalisation of QST data for each tested symptomatic body region (Rolke et al. 2006b), based on our obtained HC group data (data from the

trapezius muscle and dermatomes with left and right body sides pooled). For clarity of data presentation, the sign of the resulting z-score was adjusted to reflect the individual patient's sensitivity for each parameter. Z-values above '0' indicated a gain of function, meaning the patient was more sensitive to the tested stimulus compared with HC, a z-value below '0' indicated a loss of function, pointing to reduced sensitivity of the patient. Within each group, z-score QST data were compared between sides using a paired T-test, and responses to the NPT_{MEDIAN} using Wilcoxon Signed Ranks Test. To examine associations between QST and clinical parameters Pearson's correlations were performed within each group for each of the QST parameters (measured in maximal pain area, symptomatic side) and clinical parameters (symptom duration, average pain intensity over the last four weeks, PD-Q score). Significance was accepted at $p < 0.05$ for all analyses.

7.4   Results

7.4.1   Patient characteristics

Eleven patients presented with a C6 radiculopathy and 12 patients with a C7 radiculopathy. In the patients with NSNAP, one patient presented with pain in a C6 dermatomal distribution and 7 patients with pain in a C7 dermatomal distribution. The patients' pain descriptors are documented in Table 7.1. Both patient groups demonstrated clinical signs of heightened nerve mechanosensitivity in the symptomatic arm, indicated by a significant side-to-side difference in the range of motion of elbow extension deficit at the onset of P1 ($p < 0.03$) and P2 ($p < 0.013$) between arms (Table 7.2). In both groups, the pain onsets occurred much earlier in range in the symptomatic arm compared to the asymptomatic arm.

Table 7.1
Percentage* of all pain descriptors volunteered by patients with cervical radiculopathy and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) for their neck pain and arm pain.

	Cervical radiculopathy (n = 23)		NSNAP (n = 8)	
	Neck pain	Arm pain	Neck pain	Arm pain
Constant, n	17 (74%)	11 (48%)	5 (62%)	3 (38%)
Intermittent, n	6 (26%)	12 (52%)	3 (38%)	5 (62%)
Spontaneous[#][◊], n	17 (74%)		3 (37%)	
Paraesthesia[#][◊], n	23 (100%)		8 (100%)	
Numbness	12 (52%)		3 (38%)	
Tingling	12 (52%)		3 (38%)	
Pins and needles	11 (48%)		4 (50%)	
Burning[#], n	6 (26%)	7 (30%)	5 (62%)	2 (25%)
Shooting, n		5 (22%)		2 (25%)
Electric shock[#], n	1 (4%)	3 (13%)		
Nerve pain, n				2 (25%)
Dead[#], n		3 (13%)		2 (25%)
Numbish[#], n	1 (4%)		1 (12%)	
Ache, n	10 (43%)	6 (26%)	3 (37%)	1 (12%)
Dull, n	7 (30%)	4 (17%)		
Sharp, n	6 (26%)	3 (13%)	1 (12%)	
Heavy, n		2 (9%)		
Deep, n	2 (9%)	2 (9%)	1 (12%)	2 (25%)
Pain, n	2 (9%)	3 (13%)		
Sore, n	1 (4%)		2 (25%)	
Muscle pain, n	1 (4%)			
Throbbing, n	1 (4%)			

Common descriptors for neuropathic pain are highlighted in grey.
[#]Descriptor consistent with descriptor in painDETECT.
[◊]Descriptor obtained through specific questioning
*The percentages do not add to 100% as some patients used several descriptors to describe their pain.

Table 7.2

Elbow extension ROM deficit at onset of pain (P1) and at the limitation of movement due to pain (P2) in the asymptomatic and symptomatic arm in patients with cervical radiculopathy (CxRAD) and patients with non-specific neck-arm pain with associated heightened nerve mechanosensitivity (NSNAP). Data are presented as medians with interquartile range (IQR).

	CxRAD$^\Diamond$		NSNAP	
	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic
P1 (°)	0.0 (24.7)[a]	23.9 (32.4)* [c]	25.3 (44.2)[b]	40.9 (32.0)*
P2 (°)	0.0 (0.0)[c]	12.3 (33.1)* [c]	0.0 (30.8)	34.7 (32.1)*

$^\Diamond$4 missing cases.
*Significantly different to asymptomatic side (p < 0.05).
[a] n = 17, [b] n = 7; [c] n = 19.

There were no significant differences between patient groups in age, symptom duration, pain intensities, sleep quality, anxiety and depression scores, physical and mental components of the SF-36, fear avoidance behaviour and scores on the NDI (Table 7.3). NDI scores reflected moderate disability for patients with cervical radiculopathy and mild disability for patients with NSNAP. A larger proportion of patients with cervical radiculopathy were on pain medication compared to the group with NSNAP.

Table 7.3

Demographics and profiles of patients with cervical radiculopathy (CxRAD) and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP).

	CxRAD (n = 23)	NSNAP (n = 8)	p
Age (years)*	46.3 (9.6)	45.1 (14.9)	0.833
Gender (female, n)	8	7	
Symptom duration (months)*	7.6 (4.1)	8.1 (3.0)	0.766
Average pain intensity during last week (VAS)*	5.2 (2.0)	6.0 (1.5)	0.277
Maximal pain intensity during last 4 weeks (NRS 0-10)*	7.2 (2.2)	7.6 (0.6)	0.686
Average pain intensity during last 4 weeks (NRS 0-10)*	5.0 (2.1)	5.1 (0.6)	0.914
Sleep quality during last week (VAS)*	5.3 (2.7)	5.9 (2.2)	0.591
Hospital Anxiety and Depression Scale			
Anxiety score (HADS)#	6.0 (5.0)	8.0 (4.2)	0.295
Within normal range (≤ 10), n	21(91%)	6 (75%)	
Depression score (HADS)#	3.0 (4.0)	3.5 (5.5)	0.982
Within normal range (≤ 10), n	21 (91%)	8 (100%)	
SF-36			
Physical Component#	40.6 (12.6)	46.4 (12.0)	0.121
Mental Component#	52.3 (17.4)	48.4 (20.5)	0.187
Neck Disability Index*	16.2 (7.7)	13.4 (5.9)	0.351
Tampa Scale of Kinesiophobia*	40.9 (8.1)	36.7 (7.5)	0.211
painDETECT*	17 (5)	12 (6)	**0.038**
Negative: NeP component unlikely, n	2 (9%)	4 (50%)	
Unclear: result ambigious, n	14 (61%)	3 (37%)	
Positive: NeP component likely, n	7 (30%)	1 (12%)	
Patients with medication, n	15 (65.2%)	3 (37.5%)	
Current medication◊			
Selective serotonin reuptake inhibitor, n	1 (4.3%)	1 (12.5%)	
Serotonin-norepinephrine reuptake inhibitor, n	2 (8.7%)		
Tricyclic antidepressant, n	1 (4.3%)		
Antiepileptics, n	2 (8.7%)		
Opioids, n	4 (17.4%)		
Benzodiazepine, n	2 (8.7%)		
Analgesics, n	7 (30.4%)	1 (12.5%)	
Non-steroidal anti-inflammatories, n	7 (30.4%)	2 (25%)	

*Data are mean (SD); #Data are median (IQR); ◊Multiple answers possible.

7.4.2 Side-to-side comparison of QST sensory profiles

Z-score QST sensory profiles of the symptomatic and asymptomatic arms are illustrated for each group (cervical radiculopathy Fig 7.2, NSNAP Fig 7.3) in the maximal pain area and the dermatome. Healthy controls are represented by a z-score of "zero". In both groups all QST parameters fell within the 95% confidence interval of our HC data (i.e. z-score > -1.96 or < 1.96 standard deviation).

7.4.2.1 Patients with cervical radiculopathy

In patients with cervical radiculopathy, in the maximal pain area vibration and mechanical detection sense were significantly reduced on the symptomatic side compared to the asymptomatic side (VDT: p = 0.002; MDT: p = 0.027) (Table 7.4, Fig 7.2A). Side-to side comparisons of all other QST parameters in the maximal pain area were not significant. In the dermatome, there was a loss of function on the symptomatic side in cold detection (CDT: p = 0.019), mechanical detection (MDT: p = < 0.001), vibration detection (VDT: p = 0.001) and pressure pain sensitivity (PPT: p = 0.011) (Table 7,5, Fig 7.2B). There were no side-to-side differences in any other QST parameters. Reports of DMA and PHS were infrequent. One patient with cervical radiculopathy demonstrated DMA bilaterally in the maximal pain area and on the symptomatic side in the dermatome. PHS was reported by one patient once in the maximal pain area on the symptomatic side, and by a different patient once on the asymptomatic side. Two patients reported PHS once on the asymptomatic side of the dermatome.

7.4.2.2 Patients with NSNAP

In patients with NSNAP, in the dermatome, the side-to-side comparison demonstrated a significant loss of function on the symptomatic side in WDT (p = 0.029) (Table 7.5). No other side-to-side comparisons were statistically different. In the maximal pain area, there was no side-to-side difference in any QST parameter (Table 7.4). No patient with NSNAP demonstrated DMA in any body region. PHS was reported by one patient twice on the symptomatic side in the maximal pain area.

7.4.3 Correlations between QST and clinical parameters

In patients with cervical radiculopathy, MDT and VDT in the maximal pain area correlated significantly with the average pain intensity over the last 4 weeks (MDT: r = 0.418, p = 0.047; VDT: r = -0.491, p = 0.017), indicating the higher the pain intensity, the greater the loss of mechanical and vibration detection. The PD-Q score correlated significantly with the average pain intensity over the last 4 weeks (r = .517, p = 0.011). Symptom duration was not correlated with any measurement. In patients with NSNAP, symptom duration correlated significantly with HPT measured in the maximal pain area (r = -.770, p = 0.025), the longer the symptom duration, the lower the HPT (increased heat sensitivity). Neither average pain intensity over the last 4 weeks nor the PD-Q score were correlated with any QST parameter.

7.4.4 Responses to painDETECT

Patients with cervical radiculopathy had a significantly higher score on the PD-Q compared to patients with NSNAP (Table 7.3). Seven patients (30%) with cervical radiculopathy reported a score of ≥ 19, indicating the 'likely' presence of NeP (Table 7.3) and one patient (12.5%) with NSNAP scored ≥ 19.
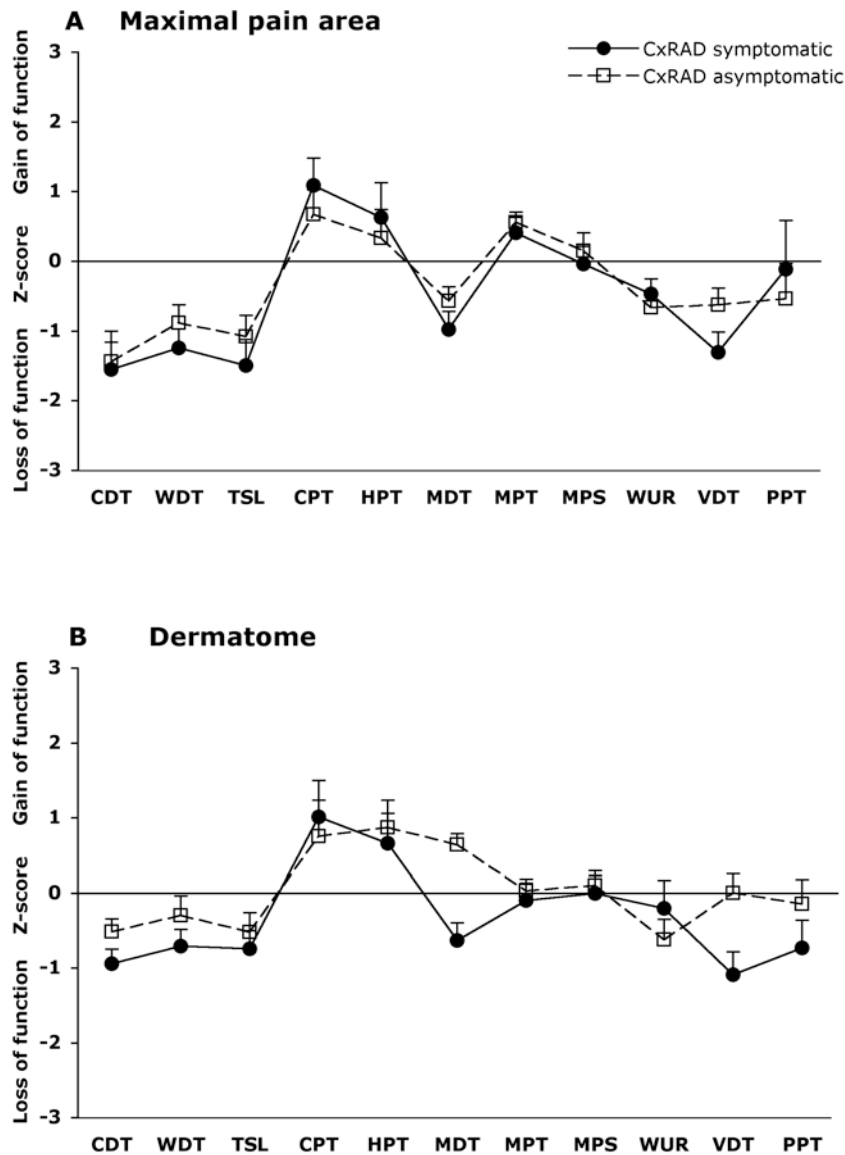
Figure 7.2 Z-score sensory profiles of the symptomatic (filled circle symbol) and asymptomatic (empty square symbol) side in patients with cervical radiculopathy (CxRAD) in the maximal pain area (A) and dermatome (B). Error bars indicate the standard error of measurement. Healthy control subjects are represented by a z-score of "zero". CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold.
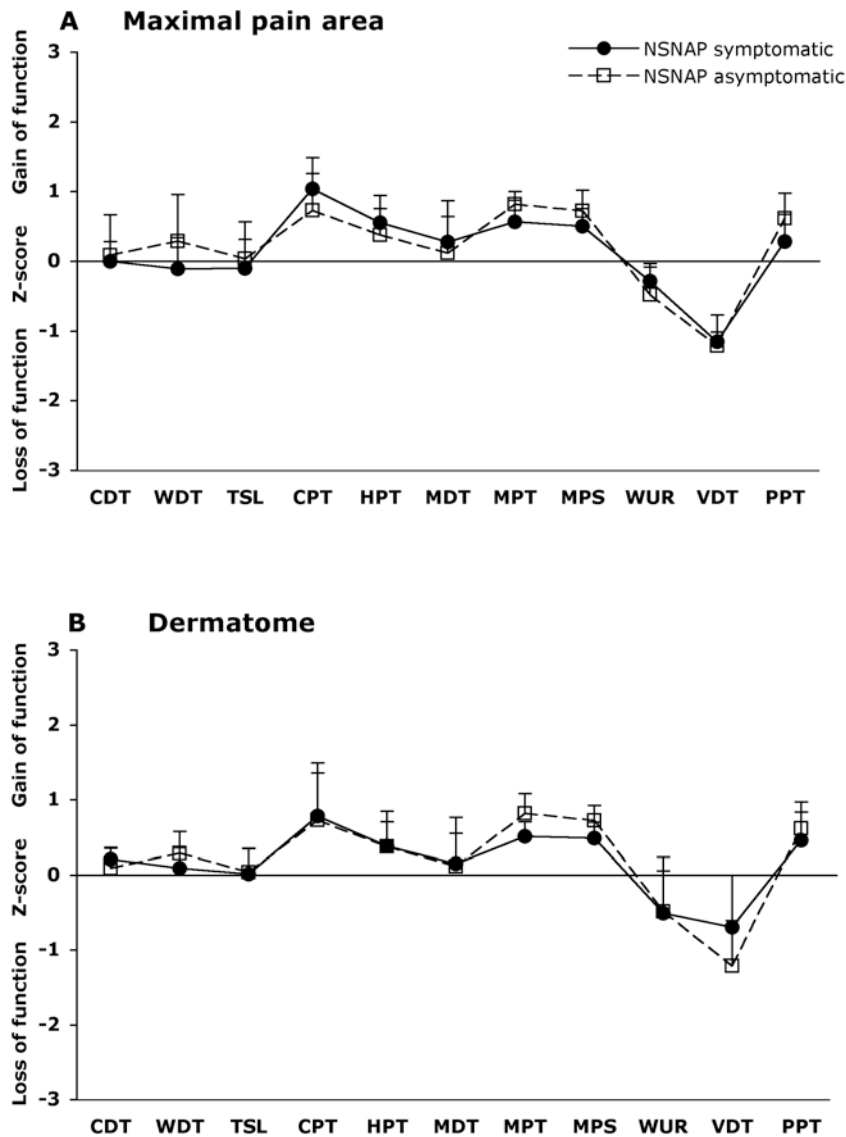
Figure 7.3 Z-score sensory profiles of the symptomatic (filled circle symbol) and asymptomatic (empty square symbol) side in patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP) in the maximal pain area (A) and dermatome (B). Error bars indicate the standard error of measurement. Healthy control subjects are represented by a z-score of "zero". CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; MDT: mechanical detection threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; VDT: vibration detection threshold; PPT: pressure pain threshold.

Table 7.4 QST parameters are shown for the maximal pain area in the symptomatic and asymptomatic sides of patients with cervical radiculopathy (CxRAD) and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP). Data are shown as mean for untransformed data (HPT, VDT) and retransformed mean for log-normally distributed data.

	MAXIMAL PAIN AREA					
	Cervical radiculopathy			NSNAP		
QST Parameters	Asymptomatic side	Symptomatic side	p	Asymptomatic side	Symptomatic side	p
CDT (°C)	1.86	1.89	0.767	1.12	1.16	0.803
WDT (°C)	3.45	3.83	0.209	2.28	2.64	0.536
TSL (°C)	5.51	6.22	0.132	3.94	4.17	0.664
CPT (°C)	9.10	11.16	0.069	10.50	12.16	0.294
HPT (°C)	45.9	45.4	0.386	45.3	45.1	0.736
MDT (mN)	2.10	3.79	**0.027**	1.57	1.37	0.555
MPT (mN)	23.75	29.85	0.376	19.87	28.10	0.352
MPS (NRS$_{100}$)	0.53	0.45	0.328	1.01	0.77	0.166
WUR (ratio)	2.68[a]	2.81[a]	0.579	2.49	2.98	0.548
VDT (x/8)	5.9	5.4	**0.002**	5.2	5.2	0.864
PPT (kPa)	434	403	0.248	366	390	0.290

[a]n = 18

Table 7.5 QST parameters are shown for the dermatome in the symptomatic and asymptomatic sides of patients with cervical radiculopathy (CxRAD) and patients with non-specific neck-arm pain associated with heightened nerve mechanosensitivity (NSNAP). Data are shown as mean for untransformed data (HPT, VDT) and retransformed mean for log-normally distributed data.

| | DERMATOME | | | | | |
| | Cervical radiculopathy | | | NSNAP | | |
QST Parameters	Asymptomatic side	Symptomatic side	p	Asymptomatic side	Symptomatic side	p
CDT (°C)	2.12	2.68	**0.019**	1.43	1.55	0.405
WDT (°C)	3.43	4.17	0.118	2.25	3.14	**0.029**
TSL (°C)	6.15	6.87	0.269	4.2	5.11	0.121
CPT (°C)	7.56	8.08	0.625	8.4	7.80	0.709
HPT (°C)	45.6	46.1	0.586	46.2	46.4	0.720
MDT (mN)	1.18	4.53	**<0.001**	2.26	2.65	0.683
MPT (mN)	70.91	84.45	0.465	36.13	34.90	0.867
MPS (NRS$_{100}$)	0.39	0.34	0.400	0.84	0.74	0.517
WUR(ratio)	2.01[a]	2.45[a]	0.358	2.04	2.15	0.620
VDT(x/8)	7.0	6.2	**0.001**	6.6	6.6	0.926
PPT (kPa)	492	572	**0.011**	405	417	0.211

[a]n = 14

7.5 Discussion

This study investigated differences in QST parameters between symptomatic and asymptomatic sides and the presence of NeP components in patients with cervical radiculopathy and patients with NSNAP, using QST and the PD-Q. In patients with cervical radiculopathy, QST findings demonstrated a significant loss of function mediated by non-nociceptive sensory fibers in the painful innervation territory of the affected nerve root on the symptomatic side compared to the asymptomatic side, findings consistent with the characteristics of NeP (Haanpää et al. 2011). The PD-Q identified 30% of patients with cervical radiculopathy demonstrating the likely presence of NeP. The significant loss in the affected dermatome of cold, mechanical and vibration detection and pressure sensitivity, provide data further supporting the presence of nerve root damage. In patients with NSNAP, the absence of significant side-to-side differences in any QST parameters in the maximal pain area and the results of PD-Q suggest that NeP components were unlikely in this group.

Concordant with our hypothesis, patients with cervical radiculopathy demonstrated significant side-to-side differences in mechanical and vibration detection in their maximal pain area, the symptomatic side being less sensitive to the stimuli than the control side. The hypoaesthesia on the symptomatic side is consistent with a loss of function due to nerve root damage and with the presence of NeP components (Treede et al. 2008). QST data in cervical radiculopathy is scarce, with only one study profiling this patient group (Chien et al. 2008), and findings demonstrated bilateral cold and pressure pain hypersensitivity in the cervical spine area. Comparison of our data to these findings is limited, as the majority of our patients did not have their maximal pain area in the cervical spine, plus the cervical spine area tested in the Chien et al study (Chien et al. 2008) did not necessarily reflect the maximal pain area of these patients. We documented previously that our patients with cervical radiculopathy demonstrated increased cold sensitivity in the maximal pain area compared to HC subjects. In the current study, although we did not detect a significant difference for CPT between sides, the difference approached significance ($p = 0.069$).

We have also previously reported a significant loss of thermal detection sense (CDT, WDT, TSL) in the maximal pain area compared to HC. Our current data indicate thermal hypoaesthesia occurred bilaterally. Contralateral thermal hypoaesthesia has been observed in patients with unilateral traumatic partial nerve injury (Leffler and Hansson 2008) and with unilateral traumatic trigeminal neuropathy (Jääskeläinen et al. 2005). In the latter study, contralateral thermal hypoaesthesia was associated with the presence of ipsilateral NeP. This phenomenon was explained by "means of increased inhibition or disturbed excitatory connections within the central pathways mediating non-noxious thermal information from the contralateral side" (Jääskeläinen et al. 2005), this explanation reportedly being in line with peripheral nerve damage induced central plasticity (Davis et al. 2011).

The side-to-side analysis of QST data in the dermatome of patients with cervical radiculopathy enhanced the sensitivity to detect a loss of Aβ function. MDT in the affected dermatome was not statistically different compared to HC, but was then compared to the asymptomatic arm, a finding that further supports the presence of nerve root damage. Our previously documented loss of thermal detection did not significantly differ in the present study from the asymptomatic side, except for CDT (difference 0.56°). The interpretation of what entails a clinically significant difference for thermal detection thresholds is inconsistent (Landerholm et al. 2010; Leffler and Hansson 2008; Rolke et al. 2006a; Treede and Baron 2008). Based on clinical judgment, some authors consider a side difference of $\geq \pm 1°$ as pathological (Leffler and Hansson 2008), others argue a side difference $\pm 1°$ is within normal range (Rolke et al. 2006a; Treede and Baron 2008). The bilateral loss of thermal detection is consistent with findings in dermatomes of patients with cervical (Chien et al. 2008) and lumbar radiculopathy (Freynhagen et al. 2008; Nygaard and Mellgren 1998), but contrary to findings of others (Samuelsson and Lundin 2002; Zwart and Sand 2002; Zwart et al. 1998). The occurrence of bilateral alterations may limit the utility of side comparison of thermal detection testing as a diagnostic instrument for small nerve fiber function loss.

A diagnostic grading system of certainty for the presence of NeP has recently been proposed, based on pain distribution and a history suggesting a relevant nerve lesion, the presence of sensory alterations in the innervation territory of the affected nerve

structure and confirmative evidence of a nerve lesion/disease from diagnostic tests (Treede et al. 2008). According to this grading system, our patient group with cervical radiculopathy demonstrated definite NeP, however this does not exclude the simultaneous presence of nociceptive pain. Other structures (e.g. joints, discs, muscles) are likely involved in contributing to nociceptive input and potentially impacting the total "pain experience". In our current study, the likely presence of mixed pain (Baron and Binder 2004) as reported for patients with lumbar radiculopathy (Baron and Tölle 2008; Freynhagen et al. 2006b; Pérez et al. 2009), is reflected in the PD-Q scores and the self-volunteered pain descriptors. Patients used pain descriptors commonly identified for NeP (Dworkin et al. 2007), some of these matching the descriptors used in PD-Q, but patients also used descriptors commonly identified for nociceptive pain (Merskey and Bogduk 1994). The fact that 30% of our radiculopathy cohort reported a score of ≥ 19, and 65% reported a score ≥ 16, suggests that on the continuum between "purely nociceptive" and "purely neuropathic" pain (Horowitz 2007), some of these individuals were characterised by NeP components more than nociceptive pain. The PD-Q results match our QST data to some extent. At a group level, while patients with cervical radiculopathy demonstrated sensory changes in the painful innervation territory of the affected nerve root, we documented previously that the magnitude and frequency of these alterations differed between individuals. This variability highlights the importance of individual assessment for the identification of NeP components for patients with mixed pain syndromes and furthermore, that the PD-Q should not be used as a surrogate for clinical examination.

Contrary to our hypothesis for patients with NSNAP, the previously established cold hypersensitivity on the symptomatic side of the maximal pain area was also evident on the asymptomatic side. No comparative data exists for this patient group. Bilateral cold hypersensitivity has been reported in patients with cervical radiculopathy and patients with whiplash associated disorders and has been interpreted to reflect augmented central pain processing mechanisms (Chien et al. 2008). Of interest, the graphed z-score QST profile (Fig. 7.3) gives the impression of a bilateral lowered vibration sense in patients with NSNAP. This was not statistically different between sides, nor was it significantly different compared to HC, thus it is not necessarily indicative of nerve damage. Hypoaesthesia to vibration has been documented in

patients with non-NeP pain (Blumenstiel et al. 2011; Koroschetz et al. 2010), in line with reduced tactile sensation in patients with non-NeP (Geber et al. 2008; Voerman et al. 2000; Westermann et al. 2011). With the exception of reduced warm detection in the symptomatic arm, where the difference between sides was < 1° and of doubtful clinical significance, we did not find any side differences for QST parameters in the dermatome in patients with NSNAP.

The QST findings in our patients with NSNAP in the current study, do not suggest the presence of NeP components and on the whole this is in accordance with the PD-Q score in this group, with the exception of one individual who scored >19. Apart from the descriptor 'paraesthesia' being used by all patients, a minority of patients used pain descriptors common to NeP. According to the grading system of NeP (Treede et al. 2008), and based on the pain distribution and history and the presence of cold hypersensitivity on the symptomatic side this patient group would be classified as having 'probable' NeP. The main characteristic for this group was the side-to-side difference in pain response to the NPT_{MEDIAN}, which indicated a heightened pain response in the symptomatic arm. Our results suggest that the clinical presentation of heightened nerve mechanosensitivity and heightened pain responses to the NPT_{MEDIAN} should not equate with the presence of a NeP component. It is important to emphasize however, that heightened nerve mechanosensitivity can coexist with nerve lesions and NeP, as demonstrated in our patients with cervical radiculopathy and another patient group (Chien et al. 2008).

Our data (of the current and previous study), do suggest that this patient group with NSNAP does not meet the new definition of NeP, i.e. "pain caused by a lesion or disease of the somatosensory nervous system" (Jensen et al. 2011) as the combination of clinical examination findings, QST data and available diagnostic tests did not provide evidence for the presence of a nerve lesion.

The sample size of our patient group with NSNAP was modest and this might limit the power to demonstrate significant side-to-side differences. Our initial sample size calculation, based on QST data by Rolke et al (Rolke et al. 2006a), estimated that a sample of 25 in each patient group was needed to detect clinically significant differences between the symptomatic and asymptomatic arm. Despite extensive

recruitment efforts over the period of three years, we were not able to recruit more patients fulfilling the criteria for NSNAP inclusion. Based on our recruitment strategy, and given the fact that many patients were recruited from a neurosurgery triage clinic, the prevalence of the discrete disorder of NSNAP would appear to be low.

Conclusion

Although patients with cervical radiculopathy and patients with NSNAP have commonalities in their clinical pain pattern, the dominant pain type differs between patient groups, as indicated by the specific QST profiles and associated responses to the PD-Q. NeP components were more common in patients with cervical radiculopathy, whereas patients with NSNAP were characterised by predominantly nociceptive pain components. The side-to-side comparison of QST data enhanced the sensitivity to detect sensory alterations. Our somatosensory profiles for these clinical groups may assist clinicians in targeting more specific management for these patients.

Acknowledgement

7.6   References

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Chapter 8

Self-reported somatosensory profiles correspond with quantitative sensory testing phenotypes in patients with cervical radiculopathy, but not in patients with fibromyalgia

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8.1 Abstract

The painDETECT questionnaire (PD-Q) has been used as a tool to characterise sensory abnormalities in chronic pain patients. This study investigated if the self-reported somatosensory profile of patients with painful cervical radiculopathy and patients with fibromyalgia (FM), as characterised by responses to verbal sensory descriptors from PD-Q (sensitivity to light touch, cold, heat, slight pressure, feeling of numbness in the main area of pain), corresponded with the sensory phenotype as demonstrated by quantitative sensory testing (QST). Forty-five patients (28 females, 46 ± 10 years) completed the PD-Q. Standardised QST of dynamic mechanical allodynia, cold and heat pain thresholds, pressure pain thresholds, mechanical and vibration detection thresholds (VDT) was recorded from the maximal pain area. Comparative QST data from 31 age-matched healthy controls (HC; 15 females) were obtained. Patients with radiculopathy demonstrated a match between their self-reported sensory phenotype and QST sensory phenotype for all sensory descriptors except for sensitivity to light touch, and these matches were statistically significant compared to HC data. The FM group demonstrated discrepancies between the PD-Q and QST sensory phenotypes for all sensory descriptors, indicating that the self-reported somatosensory profile did not consistently match the QST somatosensory profile.

8.2   Introduction

The traditional approach to classification and management of musculoskeletal and neuropathic pain (NeP) according to the aetiological condition has its limitations (Baron 2006; Jensen and Baron 2003). A mechanism, or symptom based classification approach, (Baron 2006; Jensen and Baron 2003; Woolf et al. 1998) has been proposed. This approach is based on the hypothesis that different clinical signs and symptoms reflect different underlying pathophysiological mechanisms of pain generation (Hansson 2002; Jensen and Baron 2003), with the ultimate aim to target treatment to the underlying pain mechanisms. The assessment of symptoms can be attained by means of questionnaires such as the Neuropathic Pain Symptom Inventory (NPSI) (Attal et al. 2008; Bouhassira et al. 2004; Rüger et al. 2008) and the painDETECT questionnaire (PD-Q) (Baron et al. 2009; Freynhagen et al. 2006; Mahn et al. 2011) and signs by quantitative sensory testing (QST) (Haanpää et al. 2011).

QST is a valuable research tool used to investigate clinical sensory phenotypes and to help interpret the pain mechanisms underlying associated clinical pain presentations (Aasvang et al. 2008; Chien et al. 2008; Taylor et al. 2010; Treede et al. 2008). As one specific symptom may be generated by several different underlying mechanisms (Woolf and Salter 2000), a combination of positive and negative sensory phenomena, namely a symptom profile, may better predict underlying pain mechanisms (Baron 2009; Cruccu and Truini 2009). In order to characterise the somatosensory profile of patients as precisely as possible, a sophisticated QST protocol has been developed comprising all of the somatosensory sub-modalities that are mediated by different primary afferents (C-, Aδ-, Aβ-) (Rolke et al. 2006a; Rolke et al. 2006b). Using this protocol, sub-groups of NeP patients with distinct somatosensory profiles within specific aetiologies have been identified (Maier et al. 2010; Rolke et al. 2006a) and attempts have been made to correlate the specific individual patterns with the likely underlying mechanisms (Baron 2006; Baron et al. 2010).

The PD-Q was originally developed and validated as a screening tool to identify patients with likely NeP (Freynhagen et al. 2006), and has been employed in this capacity in various patient populations (Gwilym et al. 2009; Jespersen et al. 2010; Steegers et al. 2008). Recently it has also been used, as a tool to identify somatosensory profiles in patients with lumbar radiculopathy/radicular pain (Mahn et al. 2011), in patients with diabetic neuropathy and postherpetic neuralgia (Baron et al. 2009) and in patients with fibromyalgia (FM) (Amris et al. 2010; Rehm et al. 2010). Patients with FM appear to demonstrate similarities to NeP patients in regard to their choice of sensory descriptors (Amris et al. 2010; Fishbain et al. 2008; Giske et al. 2009; Rehm et al. 2010) and their QST sensory phenotypes (Berglund et al. 2002; Hurtig et al. 2001; Klauenberg et al. 2008; Kosek et al. 1996; Pfau et al. 2009; Staud et al. 2003; Staud et al. 2001). However this does not mean that FM is a NeP condition (Hansson et al. 2007; Martinez-Lavin 2007; Treede et al. 2008). Based on the responses to verbal sensory descriptors in PD-Q, the four studies (Amris et al. 2010; Baron et al. 2009; Mahn et al. 2011; Rehm et al. 2010) were able to identify sub-groups of patients with distinct symptom profiles.

The PD-Q contains questions relating to evoked pain (light touch, pressure, cold/heat) and numbness. However, whilst a correlation between self-reported responses to evoked pain (brushing, pressure, cold) and QST has been demonstrated for the NPSI questionnaire (Attal et al. 2008), no study to date has documented if patients' subjective responses to sensory descriptors of PD-Q correspond with their sensory phenotypes as demonstrated using QST.

The aim of our study was to investigate if the self-reported somatosensory profile of patients with painful cervical radiculopathy and of patients with FM, as indicated by responses to verbal sensory descriptors items of PD-Q, corresponded with their sensory phenotype as demonstrated by QST, using QST data from healthy control subjects as reference criteria.

8.3 Materials and methods

8.3.1 Study population

This study included patients with painful cervical radiculopathy (n = 23), patients with FM (n = 22) and age matched healthy controls (HC) (n = 31) (Table 8.1). Patients were recruited from general private physiotherapy, medical, and neurosurgery practices; physiotherapy and pain management departments at five local hospitals; a neurosurgery outpatient department; a neurosurgery triage clinic at a large metropolitan hospital; from the local community via radio and newspaper advertising and from FM support groups. The study protocol and recruitment procedures were approved by the local Ethics Committee of all participating institutions and adhered to the ethical guidelines of the Declaration of Helsinki. Informed consent was obtained from each subject prior to participation.

The inclusion criteria for patients with cervical radiculopathy were: unilateral pain distribution consistent with specific radicular distributions (C6/C7), symptom duration of 3 to 18 months, pain intensity ≥ 2 on a visual analogue scale (VAS), signs of C6 or C7 nerve root dysfunction such as sensory impairment and motor impairment (either myotomal weakness and/or absent or diminished reflexes) and a demonstrable clinically relevant abnormality on imaging studies (Bono et al. 2011; Treede et al. 2008) indicating compromise of the exiting nerve root at the relevant spinal level. Exclusion criteria were: evidence of medical or metabolic disease, a history of cardiovascular disease, neurological or psychiatric disease and an insufficient level of English. Depending on the mode of recruitment, some of the potential subjects underwent an initial phone screening examination to ascertain they satisfied the inclusion and exclusion criteria. Prior to inclusion into the study, all patients underwent a comprehensive clinical examination in order to ascertain they met the inclusion criteria. As no gold standard exists for the diagnosis of painful cervical radiculopathy, the consensus of two clinical experts (a Fellow-trained neurosurgeon and a Fellow-qualified Specialist in Musculoskeletal Physiotherapy) was used to verify the diagnosis, as consistent with a previous study (Freynhagen et al. 2008). Using a blinded design, both experts reviewed the patient's clinical records, including the findings of the clinical examination and available

investigations. Where there was not consensus between the experts and clinical examiner, subjects were excluded from the data analyses.

Patients with FM underwent an initial phone screening examination to ascertain they fulfilled the inclusion and exclusion criteria. The diagnostic criteria for FM according to the 1990 American College of Rheumatology (ACR) (Wolfe et al. 1990) were used as inclusion criteria and were current at the time of recruitment. These criteria include widespread pain of at least 3 months duration in combination with tenderness at 11 or more of 18 specific anatomical sites. Although new diagnostic criteria now exist (Wolfe et al. 2010), the clinical profile of our FM group appears to also correspond with these new guidelines (Table 8.1). The exclusion criteria were the same as for the radiculopathy group. Of the participating 22 patients, 9 patients had been diagnosed with FM by a rheumatologist, 4 patients by a medical specialist (the patient could not remember what type of specialist), 8 patients by their general practitioner by exclusion (negative blood tests) and positive tender point count, and in one patient the origin of the diagnosis was not recorded. Prior to participation, tender point count was verified by means of a pressure algometer (probe size $1cm^2$) (Somedic AB, Farsta, Sweden), and assessing nine paired points as defined by the ACR Criteria (Wolfe et al. 1990) and two control points (at the centre of the right forearm and the right thumb nail). The algometer was placed on the examination site, and pressure was gradually increased by 1 kg/s. The participants were asked to press a button when the sensation at the examination site changed from pressure to pain. Pressure testing was stopped at that moment and the result recorded as positive if maximal pressure was $\leq 4kg$. If no pain was elicited at $\leq 4kg$, the test results were recorded as negative. The average number of tender point ratings of pain was 19 (+/- 0.9) from the possible 22. The patient's clinical history was taken, including pain location on a body chart and identification of the main pain area nominated as the site to be tested by QST. All patients were requested to refrain from non–steroidal anti-inflammatory drugs and analgesics on the day of examination.

HC were recruited from the local community and were excluded if they had a history of current pain or a chronic pain condition or fulfilled any of the exclusion criteria for the patients, including taking medications which influence pain perception.

Table 8.1

Demographics and profiles of healthy control (HC) subjects, patients with cervical radiculopathy (CxRAD) and patients with fibromyalgia (FM).

	HC (n = 31)	CxRAD (n = 23)	FM (n = 22)	p-value ANOVA
Age (years), (SD)	45.6 (12.5)	46.3 (9.6)	46.1 (11.5)	0.968
Gender (female, n)	15	8	20	
Symptom duration (months)*		7.6 (4.1)	124.9 (83.1)[c]	
Average pain intensity during last week (VAS)*		5.2 (2.0)	7.3 (1.2)[c]	
Maximal pain intensity during last 4 weeks (NRS 0-10)*		7.2 (2.2)	8.3 (1.2)	
Average pain intensity during last 4 weeks (NRS 0-10)*		5.0 (2.1)	6.2 (1.3)[d]	
Sleep quality during last week (VAS)*	2.9 (2.6)	5.3 (2.7)[b]	6.8 (2.3)[a]	<0.001
Sleep disturbance (n)				<0.001[###]
Negative	26	11	1	
Positive	5	12	21	
Fatigue (n)				<0.001[###]
Negative	25	9	2	
Positive	6	14	20	
SF-36				
Physical Component[#]	57.7 (3.7)	40.6 (12.6)[a]	36.4 (11.9)[a,]	<0.001[##]
Mental Component[#]	56.0 (7.6)	52.3 (17.4)[b]	30.8 (21.5)[a, d]	<0.001[##]

Table 8.1 continued

	HC (n = 31)	CxRAD (n = 23)	FM (n = 22)	p-value ANOVA
Hospital Anxiety and Depression Scale				
Anxiety score (HADS)[#]	3.0 (5.0)	6.0 (5.0)[b]	12.0 (6.2)[a, c]	<0.001[##]
Within normal range (≤ 10), n	29 (93%)	21(91%)	7 (32%)	
Depression score (HADS)[#]	1.0 (1.0)	3.0 (4.0)[a]	6.0 (4.2)[a, d]	<0.001[##]
Within normal range (≤ 10), n	31 (100%)	21 (91%)	19 (86%)	
Patients with medication, n		15 (65.2%)	12 (54.5%)	
Current medication[e]				
Selective serotonin reuptake inhibitor, n		1 (4.3%)	7 (31.8%)	
Serotonin-norepinephrine reuptake inhibitor, n		2 (8.7%)	2 (9.1%)	
Tricyclic antidepressant, n		1 (4.3%)	3 (13.6%)	
Tetracyclic antidepressant, n			1 (4.5%)	
Antiepileptics, n		2 (8.7%)		
Opioids, n		4 (17.4%)	1 (4.5%)	
Benzodiazepine, n		2 (8.7%)		
Analgesics, n		7 (30.4%)	3 (13.6%)	
Non-steroidal anti-inflammatories, n		7 (30.4%)		

*Data are mean (SD); [#]Data are median (IQR); [##]Kruskal –Wallis Test; [###]Fisher's Exact Test.
[a]Significantly different to HC (p < 0.001); [b]Significantly different to HC (p < 0.05); [c]Significantly different to CxRAD (p < 0.001);
[d]Significantly different to CxRAD (p < 0.05) ; [e]Multiple answers possible

8.3.2 Questionnaires

All patients completed the PD-Q. The following questionnaires were employed in order to characterise the patients and HC group. Patients and HC subjects completed the short form-36 health questionnaire (SF-36) to assess quality of life (Ware 2000) and the Hospital Anxiety and Depression Scale (HADS) to screen for the presence of psychological factors (Zigmond and Snaith 1983). Individual scores for anxiety and depression are generated with a maximum score of 21 for each parameter. Scores of ≤ 10 for each are considered within normal range. In addition, sleep quality over the last week was rated by all subjects on a 100-cm VAS with the end points 0 cm (good sleep) and 10 cm (bad sleep) (Hurtig et al. 2001). Sleep disturbance was assessed by asking whether the subject awakened tired or non-refreshed; fatigue was assessed by asking: "Are you fatigued?" (Wolfe et al. 1990). Both questions allowed for answers: "never", "seldom", "often or usually", "always". "Often or usually" or "always" was scored as positive, and other replies as negative. In all patients, average pain intensity over the last week was determined with a VAS with the end points 0 cm (no pain) and 10 cm (maximum tolerable pain) (Jensen et al. 1989). The strongest and average pain intensity over the last four weeks were documented on a numeric rating scale (NRS) as part of the PD-Q (0 = no pain, 10 = maximum pain). All questionnaires were administered before the QST testing was performed.

8.3.3 Quantitative sensory testing

Standardised QST measures were recorded according to the QST protocol of the German Research Network on Neuropathic Pain (DFNS) (Rolke et al. 2006a; Rolke et al. 2006b). This protocol comprises a battery of standardised tests in the following order: thermal detection thresholds for the perception of cold and warm and paradoxical heat sensation, cold and heat pain thresholds (CPT, HPT), mechanical detection threshold for touch (MDT), mechanical pain threshold for pinprick, a stimulus-response-function for pinprick sensitivity and dynamic mechanical allodynia (DMA), wind-up ratio to repetitive pinprick stimuli, mechanical detection thresholds for vibration (VDT) and pain thresholds to blunt pressure (PPT). Good test/retest- and inter-observer-reliability of this protocol has been demonstrated (Geber et al. 2011). In our laboratory the Intraclass-Correlation Coefficients (ICC) for triplicate measurements on the same day for all measurements of interest were >

0.9 (ICC [95% CI] for CPT 0.94 [0.85 - 0.98]; HPT 0.94, [0.85 - 0.98]; VDT 0.93 [0.84 - 0.98]; PPT 0.92 [0.80 - 0.97]). Measurements were taken from the main pain area, as nominated by the patients (upper trapezius muscle n = 18; paravertebral cervical spine n = 4, paravertebral thoracic spine n = 11; above and below spine scapula n = 3; upper arm n = 6; forearm n = 2, just above the elbow n = 1). HC reference data from a parallel study of ours were used for comparison. Measurements in the upper trapezius muscle had been obtained in 26 HC and measurements in all other pain areas in 8 HC, the latter including 3 HC in the upper trapezius group, consistent with established methodology in a previous QST study (Blankenburg et al. 2010). QST was conducted on each subject by the same investigator in a laboratory with a constant room temperature. The investigator was not aware of the patient's responses to the PD-Q. The full QST protocol as outlined above was performed on all subjects as part of another concurrent study. However, for the purpose of this study, only the following recordings were used to assess the patient's responses to the PD-Q.

PainDETECT question: Is light touching (clothing, a blanket) in this area painful?
QST test: Pain in response to stroking light touch (DMA) was assessed using a cotton wisp (3 mN), a cotton wool tip fixed to an elastic strip (100 mN) and a brush exerting a force of 200-400 mN. Subjects were asked to give a pain rating for each stimulus on a NRS (0 = no pain, 100 = most intense pain imaginable). This assessment forms part of the stimulus-response-function for pinprick sensitivity and DMA. Pinprick and light stroking applications were performed five times in a randomised sequence. DMA was calculated as the geometric mean of all numerical ratings across all three different types of light touch stimuli.

PainDETECT question: Is cold or heat (bath water) in this area occasionally painful?
QST test: CPT and HPT were measured using the MSA Thermotest system (Somedic AB, Farsta, Sweden). All thresholds were obtained with ramped stimuli (1° C/s) which were terminated when the subject pressed a button. The baseline temperature was set at 32°C; cut-off temperatures were 5°C and 50°C. The mean threshold temperature of three consecutive measurements was calculated.

PainDETECT question: Do you suffer from a sensation of numbness in the areas that you marked?

QST test: The MDT was measured with a standardised set of modified von Frey hairs (Optihari2-Set, Marstock Nervtest, Germany) that exert forces upon bending between 0.25 and 512 mN. The final threshold was the geometric mean of five series of ascending and descending stimulus intensities (Rolke et al. 2006b). A Rydel-Seiffer tuning fork (64Hz, 8/8 scale) was used to obtain the vibration detection threshold (VDT). VDT was measured over bony prominences unless the maximal pain area did not exhibit a bony surface (n = 11), in which case, measurements were taken over adjacent soft tissue. The threshold was determined as a disappearance threshold with three stimulus repetitions (Rolke et al. 2006b).

PainDETECT question: Does slight pressure in this area, e.g., with a finger, trigger pain?

QST test: PPTs were recorded using a pressure algometer with a probe size of $1cm^2$ and application rate of 50 kPa/s (Somedic AB, Farsta, Sweden). The subjects were asked to push a button when the sensation changed from one of pressure alone to one of pressure and pain. Triplicate recordings were taken and the mean values used for analysis.

8.3.4 Statistical analysis

Data were analysed using the statistical package SPSS vs 17. Each question of the PD-Q has five possible scores listed as: never = 0; hardly noticed = 1; slightly = 2; moderately = 3; strongly = 4; very strongly = 5 (Freynhagen et al. 2006). We defined a score of ≥ 3 (moderately, strongly, very strongly) as a clinically relevant sensory disturbance and a positive response and scores of < 3 as a negative response.

QST data were log-transformed prior to statistical analysis except HPT and VDT which were normally distributed as raw data (Rolke et al. 2006a; Rolke et al. 2006b). To compare and illustrate the patients' QST data with control data, independently of the different units of measurement, the log data of CPT, MDT and PPT and raw data of HPT and VDT were z-transformed using the following expression: Z-score = $(X_{single\ proband} - Mean_{healthy\ controls})/SD_{healthy\ controls}$ (Rolke et al. 2006b). Z-values were calculated based on the included HC group data.

To assess any difference in z-score QST parameters between positive and negative responders compared to healthy control data, a univariate analysis was performed for each patient group. Post hoc comparisons were calculated using LSD-post hoc tests for

    (i)   all patients giving positive responses and matched HC,

    (ii)   all patients giving negative responses and HC

    (iii)   patients giving positive responses and patients giving negative responses.

As CPT, HPT and PPT measurements have been reported to be significantly lower in females than males (Rolke et al. 2006a), gender was included in the model for analysis of all QST parameters. Measurements of MDT were not affected by gender in our study.

Data are presented as mean and standard deviation (SD). Age and sleep quality were compared between groups using one-way ANOVA. Post hoc comparisons were calculated using LSD-post hoc tests. The frequency of sleep disturbances was determined using Fisher's exact test. Anxiety and depression scores and the physical and mental components of the SF-36 were compared between groups using the Kruskal-Wallis Test. If there was a difference between groups, further pairwise analyses were performed using the Mann-Whitney-U Test. Symptom duration and pain intensity were compared between patient groups using an independent-samples T-Test. Significance was accepted at $p < 0.05$ for all analyses.

8.4   Results

8.4.1   Clinical profiles

A summary of the demographics is presented for each group in Table 8.1. Compared to patients with radiculopathy, patients with FM demonstrated significantly longer symptom duration and higher average pain intensity during the last week ($p < 0.001$) and the last 4 weeks prior to testing ($p = 0.026$). Both patient groups had significantly poorer sleep quality compared to HC and more frequently reported signs of increased sleep disturbance and fatigue. Both patient groups scored significantly higher anxiety and depression scores on the HADS than HC (for radiculopathy: anxiety $p = 0.002$, depression $p < 0.001$; for FM: anxiety $p < 0.001$, depression $p < 0.001$). Compared to patients with radiculopathy, patients with FM

scored significantly higher on both parameters (anxiety p < 0.001; depression p = 0.004). The depression scores were within the normal range for over 85% of patients in both groups. Anxiety scores were within the normal range in 91% of patients with radiculopathy, but in only 32% of patients with FM. Both patient groups demonstrated significantly lower SF-36 physical (radiculopathy p < 0.001; FM p < 0.001) and mental component summary scores (radiculopathy p = 0.027; FM p < 0.001) than HC. There was no significant difference in the physical component summary score between both patient groups. Patients with FM scored significantly lower on the mental component summary score than patients with radiculopathy (p < 0.001).

8.4.2 Sensory phenotypes

The z-score QST sensory profiles for CPT, HPT, MDT, VDT and PPT in patients with cervical radiculopathy are illustrated in Figure 8.1. There was a significant gain in cold, heat and pressure sensitivity in those patients with cervical radiculopathy who indicated being sensitive to these QST parameters and a sensory loss in patients who indicated feeling numbness. QST parameters of patients responding negative to the PD-Q questions were within one SD of the HC data.

The z-score QST sensory profiles of patients with FM are illustrated in Figure 8.2. All patients with FM demonstrated a significant gain in cold, heat and pressure sensitivity, irrespective of their responses to PD-Q.
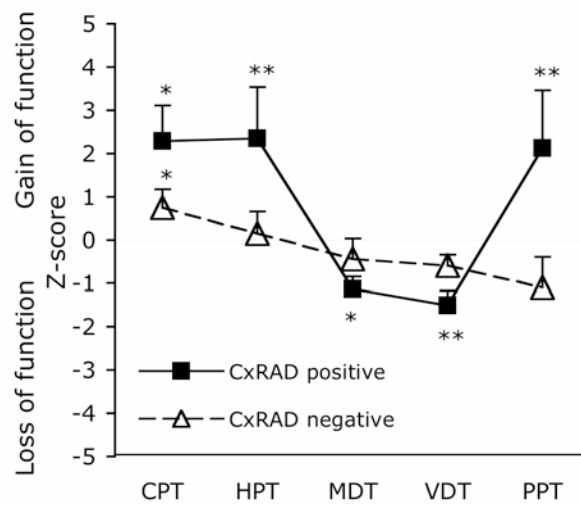
Figure 8.1 Sensory profiling of patients with cervical radiculopathy (CxRAD). The z-score sensory profiles are shown for cold pain threshold (CPT), heat pain thresholds (HPT), mechanical detection threshold (MDT), vibration detection threshold (VDT), pressure pain threshold (PPT) in patients responding positive (filled square) and negative to verbal descriptors (empty triangle). Healthy control subjects are represented by a z-score of "zero". Data are shown as the mean. Error bars indicate thestandard error of measurement.
*Significantly different from HC ($p < 0.05$).
**Significantly different from HC ($p < 0.001$).
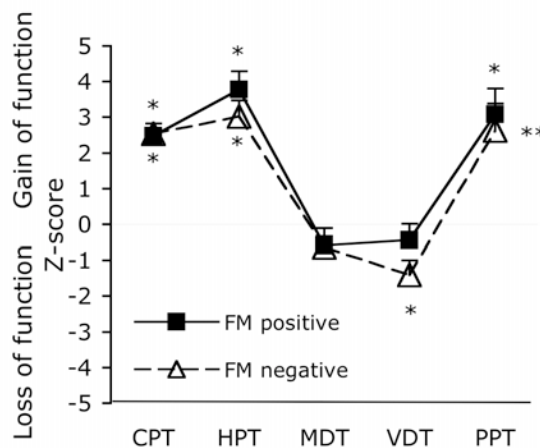
Figure 8.2 Sensory profiling of patients with fibromyalgia (FM). The z-score sensory profiles are shown for cold pain threshold (CPT), heat pain thresholds (HPT), mechanical detection threshold (MDT), vibration detection threshold (VDT), pressure pain threshold (PPT) in patients responding positive (filled square) and negative to verbal descriptors (empty triangle). Healthy control subjects are represented by a z-score of "zero". Data are shown as the mean. Error bars indicate the standard error of measurement.
*Significantly different from HC ($p < 0.05$).
**Significantly different from HC ($p < 0.001$).

8.4.3 Patients with cervical radiculopathy

Sensitivity to light touch

The PD-Q report indicated sensitivity to light touch in four patients with cervical radiculopathy (Table 8.2), and one of these patients demonstrated DMA on QST testing. Nineteen patients reported not being sensitive to light touch on PD-Q. None of these demonstrated DMA and no HC demonstrated DMA. We did not conduct statistical comparisons between groups for DMA due to the small number of subjects in some cells.

Sensitivity to cold/heat

Patients responding being sensitive to cold or heat demonstrated a significantly increased sensitivity to cold and heat ($p = < 0.001$) compared to HC subjects (Table 8.2). Patients who indicated not being sensitive to cold/heat also demonstrated significantly increased cold sensitivity ($p = 0.030$), but they did not differ in their heat pain thresholds when compared to HC.

Sensation of numbness

Patients who indicated feeling numbness in the area of pain demonstrated a loss of sensation, manifesting as a significantly elevated MDT ($p = 0.001$) and VDT ($p < 0.001$) compared to HC data (Table 8.2). Patients who responded as not feeling numbness, did not differ in their mechanical detection sensitivity compared to HC data.

Sensitivity to slight pressure

Patients responding being sensitive to pressure demonstrated significantly increased pressure sensitivity ($p = 0.001$) compared to HC (Table 8.2). Patients reporting not being sensitive demonstrated a loss of function with significantly reduced pressure sensitivity compared to HC ($p = 0.036$).

Table 8.2

Comparison of each QST parameter between healthy controls (HC), patients with cervical radiculopathy (CxRAD) who responded on painDETECT as being sensitive to a QST parameter (positive), and patients who responded on painDETECT as being not sensitive to a QST parameter (negative). Data are shown as mean (SD) for untransformed data and retransformed mean for log-normally distributed data (CPT, MDT, PPT).

	HC (n = 31)	CxRAD positive	CxRAD negative	p-value$^{\Diamond}$
Is light touching in this area painful?		n = 4	n = 19	
DMA	0 had DMA	1 had DMA	0 had DMA	
Is cold or heat in this area occasionally painful?		n = 5	n = 18	
CPT (°C)	7.0	18.8$^{a, c}$	9.6^{b}	0.001
HPT (°C)	46.7 (1.9)	41.2 (5.6)$^{b, c}$	46.5 (3.3)	0.003
Do you suffer from a sensation of numbness in the area that you marked?		n = 19	n = 4	
MDT (mN)	1.9	4.5^{b}	1.7	0.006
VDT (x/8)	6.1 (0.9)	5.3 (1.2)^{a}	5.8 (0.2)	0.001
Does slight pressure in this area trigger pain?		n = 7	n = 16	
PPT (kPa)	439	303$^{b, c}$	457^{b}	<0.001

DMA: dynamic mechanical allodynia, CPT: cold pain threshold, HPT: heat pain threshold, MDT: mechanical detection threshold, VDT: vibration threshold, PPT: pressure pain threshold.
[a]Significantly different to HC (p < 0.001).
[b]Significantly different to HC (p < 0.05).
[c]Significantly different to CxRAD negative (p < 0.001).
[◊]Univariate analysis.

8.4.4　Patients with fibromyalgia

Sensitivity to light touch

The PD-Q report indicated sensitivity to light touch in four patients with FM (Table 8.3), and none of these patients demonstrated DMA on QST testing. Eighteen patients reported not being sensitive to light touch on PD-Q. Three of these patients demonstrated DMA on QST testing.

Sensitivity to cold/heat

Regardless of PD-Q responses to cold/heat sensitivity, all patients with FM demonstrated a significantly increased sensitivity to both thermal stimuli ($p < 0.001$) (Table 8.3). There was no significant difference in CPT and HPT between patients responding on PD-Q as being sensitive to these thermal stimuli and those responding as not being sensitive.

Sensation of numbness

Patients responding as feeling numbness in their maximal pain area did not demonstrate a significant difference in MDT or VDT compared to HC (Table 8.3). Patients responding as not feeling numbness, demonstrated a loss of sensation with a significant difference in VDT ($p = 0.002$) compared to HC, but not in MDT (Table 8.3).

Sensitivity to slight pressure

All patients with FM demonstrated a significantly increased sensitivity to pressure ($p < 0.001$) compared to HC, regardless of a positive or negative PD-Q response (Table 8.3).

Table 8.3

Comparison of each QST parameter between healthy controls (HC), patients with fibromyalgia (FM) who responded on painDETECT as being sensitive to a QST parameter (positive), and patients who responded on painDETECT as being not sensitive to a QST parameter (negative). Data are shown as mean (SD) for untransformed data and retransformed mean for log-normally distributed data (CPT, MDT, PPT).

	HC (n = 31)	FM positive	FM negative	p-value$^{\lozenge}$
Is light touching in this area painful?		n = 4	n = 18	
DMA	0 had DMA	0 had DMA	3 had DMA	
Is cold or heat in this area occasionally painful?		n = 10	n = 12	
CPT (°C)	7.0	21.9[a]	26.3[a]	<0.001
HPT (°C)	46.7 (1.9)	39.2 (3.2)[a]	39.8 (3.5)[a]	<0.001
Do you suffer from a sensation of numbness in the area that you marked?		n = 7	n = 15	
MDT (mN)	1.9	2.9	3.2	0.208
VDT (x/8)	6.1 (0.9)	6.1 (1.1)	5.2 (1.0)[b]	0.007
Does slight pressure in this area trigger pain?		n = 18	n = 4	
PPT (kPa)	439	182[a]	186[b]	<0.001

DMA: dynamic mechanical allodynia, CPT: cold pain threshold, HPT: heat pain threshold, MDT: mechanical detection threshold, VDT: vibration threshold, PPT: pressure pain threshold.
[a]Significantly different to HC (p < 0.001).
[b]Significantly different to HC (p < 0.05).
[$\lozenge$]Univariate analysis.

8.5 Discussion

We investigated if the self-reported somatosensory profile of patients with cervical radiculopathy and patients with FM, obtained through the PD-Q, corresponded with the somatosensory profile as demonstrated by QST, using HC QST data as reference criteria. Patients with cervical radiculopathy demonstrated a match between their self-reported sensory phenotype and their QST sensory phenotype for all the sensory descriptors except for sensitivity to light touch, and these matches were statistically significant compared to HC data. The FM group demonstrated discrepancies between the PD-Q and QST sensory phenotypes for all sensory descriptors, indicating that the self-reported somatosensory profile did not consistently match the QST somatosensory profile.

Clinical and QST somatosensory profile of study groups

The diagnosis of our patients with painful cervical radiculopathy was based on established clinical criteria (Bogduk 2009; Bono et al. 2011; Kuijper et al. 2009), including clinically relevant abnormalities on imaging studies as confirmatory test for a nerve lesion (Bono et al. 2011; Treede et al. 2008) and validation of diagnosis by two clinical experts. According to the newly proposed grading system for NeP (Treede et al. 2008), all these radiculopathy patients presented with probable NeP. Furthermore, patients responding positive to the PD-Q questions met the criteria for definite NeP, as they demonstrated sensory abnormalities in the area of their maximal pain. Negative sensory signs, as demonstrated by the elevated MDT and VDT, are core signs of NeP due to the reduction of afferent input caused by a nerve lesion (Hansson 2002; Jensen and Baron 2003). The majority of our patients (83%) reported the presence of numbness, in contrast to only 15% of patients with painful lumbar radiculopathy (Mahn et al. 2011). However the latter study did not employ specific inclusion criteria of nerve root dysfunction, hence it is possible that patients may just have presented with radicular pain, and without any associated nerve damage (Merskey and Bogduk 1994).

Besides negative signs, positive sensory symptoms were also identified in our patients, manifesting as increased sensitivity to thermal stimuli. Our patients

demonstrated cold hypersensitivity/hyperalgesia which is a common sequel of peripheral nerve injury (de Medinaceli et al. 1997; Kleggetveit and Jørum 2010; Landerholm et al. 2010; Taylor et al. 2010) and has been previously demonstrated in patients with cervical radiculopathy (Chien et al. 2008). While the difference in cold sensitivity between patients who indicated not being sensitive to cold and HC was statistically significant, the clinical significance is questionable as the mean value fell within the 95% confidence interval of our HC data and other reference data (Magerl et al. 2010) and below the defined value for cold hyperalgesia ($\geq 15°$) (Bennett 2006). To our knowledge, no published data exist on heat pain thresholds measured specifically in the maximal pain area for a patient cohort with cervical radiculopathy. Previously heat hyperalgesia was found in 23% of 121 patients with NeP (Maier et al. 2010), and 15 (12.4%) of these 121 patients had a radiculopathy (not specified if lumbar or cervical). No comparative QST data exist for the assessment of DMA either. DMA did not seem to be a dominant feature in our patient cohort, consistent with self-reported responses of the PD-Q in patients with lumbar radiculopathy/radicular pain (Mahn et al. 2011). The difference in the somatosensory profiles between our patients who responded as positive or negative to the PD-Q might reflect the heterogeneity of the clinical pain disorder (Mahn et al. 2011) and also reflect the mixed pain types evident in radiculopathies (Baron and Binder 2004; Pérez et al. 2007).

Our patients with FM fulfilled the diagnostic criteria according to the ACR (Wolfe et al. 1990) and also demonstrated sleep and fatigue disturbance and widespread pain, corresponding with the new diagnostic criteria for FM (Wolfe 2010). Their demographic features were consistent with previous data (Gormsen et al. 2010). All patients, irrespective of their answers to PD-Q, demonstrated increased sensitivity to pressure in their area of maximal pain, as documented previously (Blumenstiel et al. 2011; Klauenberg et al. 2008; Koroschetz et al. 2010; Kosek et al. 1996; Pfau et al. 2009) and increased cold and heat sensitivity, corresponding with others (Berglund et al. 2002; Blumenstiel et al. 2011; Hurtig et al. 2001; Kosek et al. 1996). In contrast, other studies did not report increased cold (Klauenberg et al. 2008) or heat sensitivity (Klauenberg et al. 2008; Pfau et al. 2009).

The differences in findings are indicative of the heterogeneity of FM. Sub-groups of patients demonstrating increased thermal sensitivity have been identified (Hurtig et al. 2001; Rehm et al. 2010). Our patient cohort might have incorporated a larger proportion of patients characterised by increased thermal sensitivity (Rehm et al. 2010) which may also explain the observed magnitude of thermal sensitivity (z-scores outside 95% confidence interval of HC data). The generalised enhanced sensitivity might be reflective of a more global sensory discriminative dysfunction in patients with FM. Further, irrespective of the patients' responses to the PD-Q question of numbness, there was a trend to increased MDT in all patients with FM, but this did not reach statistical significance. In comparison, Pfau et al (Pfau et al. 2009) found significantly increased MDT in patients with FM compared to HC, but others did not (Blumenstiel et al. 2011; Kosek et al. 1996). In this regard, tactile hypoaesthesia does not necessarily indicate structural damage to tactile pathways (Geber et al. 2008) and can be present in clinical pain disorders possibly consistent with changes in central nervous system plasticity. Hypoaesthesia was also documented by an increased VDT in patients who indicated not feeling numbness. It is unclear why this was only observed in these patients and not in patients who reported feeling numbness. Sensitivity to light touch is not a consistent feature in populations with FM, with a small proportion of our patients demonstrating DMA (3/22) as well as in other studies (2/14) (Pfau et al. 2009) and (6/21) (Blumenstiel et al. 2011). Klauenberg et al (Klauenberg et al. 2008) did not find any abnormalities for 35 subjects with FM, although DMA was not measured in the area of maximal pain.

PD-Q somatosensory profiles and QST somatosensory profiles
The self-reported somatosensory profile of patients with cervical radiculopathy corresponded with the somatosensory profile, as demonstrated by QST for all sensory descriptors, except for DMA. Therefore, compared to HC, patients who indicated sensitivity to a specific sensory parameter did in fact demonstrate that sensory alteration. Patients who indicated not being sensitive to a parameter did not demonstrate a sensory alteration except for pressure sensitivity. In the latter, the PPT was elevated, indicating less sensitivity to pressure, hence this finding still correlated with the patients' self-report response. In contrast, self-reported somatosensory profiles in the FM group did not consistently match the QST somatosensory profile.

Although all patients who indicated sensitivity to heat/cold and pressure demonstrated increased sensitivity for these parameters, those who responded as not being sensitive also showed these sensory alterations. Furthermore, compared to HC, patients with FM who indicated numbness in the area of their pain did not demonstrate significant hypoaesthesia. Patients who reported not feeling numbness had a significantly elevated VDT, again demonstrating a discrepancy between patients' self-reported profile and the associated QST sensory profile.

In interpreting our findings in patients with FM, consideration should be given to the fact that PD-Q has never been validated for use in this population. It is also possible that psychological factors (Giesecke et al. 2003) or altered cognitive function (Dick et al. 2008) may have influenced patients' responses to PD-Q. In addition, it is open to debate if the PD-Q, and possibly other NeP screening tools, are suitable for people with widespread pain (Bouhassira and Attal 2011; Mulvey and McBeth). Although the main pain area in our patients with FM was identified prior to completing the PD-Q, most of the patients (n = 20) drew their main area of pain, plus additional pain areas on the PD-Q body chart. It is therefore possible that patients answered the questions of verbal descriptors for all their pain areas. It is unclear if the indication of multiple pain areas on the body chart could explain the discrepancy between patients' perception of sensory stimuli and the associated QST findings, as QST parameters were only measured in the area of maximal pain. In contrast, all patients with cervical radiculopathy indicated correctly the area of their neck-arm pain and associated paraesthesia and also demonstrated good agreement between self-reported and QST sensory profiles.

Factors influencing QST outcome
The painDETECT has five possible scores (never to very strongly) for each question of verbal descriptors. As no criteria are currently available to indicate validated cut-offs defining what constitutes a clinically relevant sensory disturbance, we chose the score "moderately" (≥ 3) as our cut-off score. Other researchers defined a clinically relevant sensory disturbance if patients marked a score > 3 (strongly and very strongly) (Amris et al. 2010; Baron et al. 2009; Mahn et al. 2011; Rehm et al. 2010). Consequently, we re-analysed our data using the cut-off scores of slightly, strongly

and very strongly. The results remain overall consistent with our previous analyses (supplementary material Tables 8.4 – 8.9).

Table 8.4.

Comparison of each QST parameter$^{\infty}$ between healthy controls (HC), patients with cervical radiculopathy (CxRAD) who responded on painDETECT as being sensitive to a QST parameter (positive), and patients who responded on painDETECT as being not sensitive to a QST parameter (negative). The score"slightly" was used as the cut-off score for answers on the painDETECT. Data are shown as mean (SD) for untransformed data and retransformed mean for log-normally distributed data (CPT, MDT, PPT).

	HC (n = 31)	CxRAD positive	CxRAD negative	p-value$^{\Diamond}$
Is light touching in this area painful?		n = 6	n = 17	
DMA	0 had DMA	1 had DMA	0 had DMA	
Is cold or heat in this area occasionally painful?		n = 5	n = 18	
CPT (°C)	7.0	18.8$^{a,\,c}$	9.6^{b}	0.001
HPT (°C)	46.7 (1.9)	41.2 (5.6)$^{b,\,c}$	46.5 (3.3)	0.003
Do you suffer from a sensation of numbness in the area that you marked?		n = 22	n = 1	
MDT (mN)	1.9	3.7^{b}	8.0§	0.011
VDT (x/8)	6.1 (0.9)	5.4 (1.1)^{a}	5.8§	0.002
Does slight pressure in this area trigger pain?		n = 12	n = 11	
PPT (kPa)	439	455	353	0.056

DMA: dynamic mechanical allodynia, CPT: cold pain threshold, HPT: heat pain threshold, MDT: mechanical detection threshold, VDT: vibration threshold, PPT: pressure pain threshold.
[a]Significantly different to HC ($p < 0.001$); [b]Significantly different to HC ($p < 0.05$); [c]Significantly different to CxRAD negative ($p < 0.05$).
[§]No further analysis performed as only 1 person.
[◊]Univariate analysis.

Table 8.5.
Comparison of each QST parameter between healthy controls (HC), patients with fibromyalgia (FM) who responded on painDETECT as being sensitive to a QST parameter (positive), and patients who responded on painDETECT as being not sensitive to a QST parameter (negative). The score "slightly" was used as the cut-off score for answers on the painDETECT. Data are shown as mean (SD) for untransformed data and retransformed mean for log-normally distributed data (CPT, MDT, PPT).

	HC (n = 31)	FM positive	FM negative	p-value$^{\Diamond}$
Is light touching in this area painful?		n = 13	n = 9	
DMA	0 had DMA	2 had DMA	1 had DMA	
Is cold or heat in this area occasionally painful?		n = 14	n = 8	
CPT (°C)	7.0	22.8[a]	26.9[a]	< 0.001
HPT (°C)	46.7 (1.9)	39.2 (3.3)[a]	40.1 (3.3)[a]	< 0.001
Do you suffer from a sensation of numbness in the area that you marked?		n = 14	n = 8	
MDT (mN)	1.9	2.6	4.1	0.130
VDT (x/8)	6.1 (0.9)	5.5 (1.2)[b]	5.4 (0.9)	0.029
Does slight pressure in this area trigger pain?		n = 22	n = 0	
PPT (kPa)	439	183[a]		< 0.001

DMA: dynamic mechanical allodynia, CPT: cold pain threshold, HPT: heat pain threshold, MDT: mechanical detection threshold, VDT: vibration threshold, PPT: pressure pain threshold.
[a]Significantly different to HC ($p < 0.001$).
[b]Significantly different to HC ($p < 0.05$).
$^{\Diamond}$Univariate Analysis.

Table 8.6.
Comparison of each QST parameter between healthy controls (HC), patients with cervical radiculopathy (CxRAD) who responded on painDETECT as being sensitive to a QST parameter (positive), and patients who responded on painDETECT as being not sensitive to a QST parameter (negative). The score "strongly" was used as the cut-off score for answers on the painDETECT. Data are shown as mean (SD) for untransformed data and retransformed mean for log-normally distributed data (CPT, MDT, PPT).

	HC (n = 31)	CxRAD positive	CxRAD negative	p-value$^\lozenge$
Is light touching in this area painful?		n = 0	n = 23	
DMA	0 had DMA	0 had DMA	1 had DMA	
Is cold or heat in this area occasionally painful?		n = 1	n = 22	
CPT (°C)	7.0	26.2§	10.7^b	<0.001
HPT (°C)	46.7 (1.9)	36.6§	45.8 (4.0)	0.004
Do you suffer from a sensation of numbness in the area that you marked?		n = 11	n = 12	
MDT (mN)	1.9	4.5^b	3.3^b	0.012
VDT (x/8)	6.1 (0.9)	5.4 (1.2)^a	5.4 (1.1)^a	0.002
Does slight pressure in this area trigger pain?		n = 5	n = 18	
PPT (kPa)	439	335$^{a, c}$	424	<0.001

DMA: dynamic mechanical allodynia, CPT: cold pain threshold, HPT: heat pain threshold, MDT: mechanical detection threshold, VDT: vibration threshold, PPT: pressure pain threshold.
[a]Significantly different to HC ($p < 0.001$).
[b]Significantly different to HC ($p < 0.05$).
[c]Significantly different to CxRAD negative ($p < 0.001$).
[§]No further analysis performed as only1 person.
[◊]Univariate analysis.

Table 8.7.
Comparison of each QST parameter between healthy controls (HC), patients with fibromyalgia (FM) who responded on painDETECT as being sensitive to a QST parameter (positive), and patients who responded on painDETECT as being not sensitive to a QST parameter (negative). The score "strongly" was used as the cut-off score for answers on the painDETECT. Data are shown as mean (SD) for untransformed data and retransformed mean for log-normally distributed data (CPT, MDT, PPT).

	HC (n = 31)	FM positive	FM negative	p-value$^{\lozenge}$
Is light touching in this area painful?		n = 1	n = 21	
DMA	0 had DMA	0 had DMA	3 had DMA	
Is cold or heat in this area occasionally painful?		n = 5	n = 17	
CPT (°C)	7.0	17.4[a]	29.0[a, c]	< 0.001
HPT (°C)	46.7 (1.9)	40.5 (3.6)[a]	39.2 (3.3)[a]	< 0.001
Do you suffer from a sensation of numbness in the area that you marked?		n = 3	n = 19	
MDT (mN)	1.9	7.1	2.7	0.122
VDT (x/8)	6.1 (0.9)	6.6 (0.8)	5.3 (1.1)[b]	0.005
Does slight pressure in this area trigger pain?		n = 11	n = 11	
PPT (kPa)	439	201[b]	167[a]	< 0.001

DMA: dynamic mechanical allodynia, CPT: cold pain threshold, HPT: heat pain threshold, MDT: mechanical detection threshold, VDT: vibration threshold, PPT: pressure pain threshold.
[a]Significantly different to HC ($p < 0.001$).
[b]Significantly different to HC ($p < 0.05$).
$^{\lozenge}$Univariate analysis

Table 8.8.
Comparison of each QST parameter between healthy controls (HC), patients with cervical radiculopathy (CxRAD) who responded on painDETECT as being sensitive to a QST parameter (positive), and patients who responded on painDETECT as being not sensitive to a QST parameter (negative). The score "very strongly" was used as the cut-off score for answers on the painDETECT. Data are shown as mean (SD) for untransformed data and retransformed mean for log-normally distributed data (CPT, MDT, PPT).

	HC (n = 31)	CxRAD positive	CxRAD negative	p-value[◊]
Is light touching in this area painful?		n = 0	n = 23	
DMA	0 had DMA	0 had DMA	1 had DMA	
Is cold or heat in this area occasionally painful?		n = 0	n = 23	
CPT (°C)	7.0		11.2[a]	<0.001
HPT (°C)	46.7 (1.9)		45.4 (4.4)	0.033
Do you suffer from a sensation of numbness in the area that you marked?		n = 2	n = 21	
MDT (mN)	1.9	23.4[a]	3.2[a]	0.003
VDT (x/8)	6.1 (0.9)	5.1 (1.3)[a]	5.4 (1.1)[a]	0.002
Does slight pressure in this area trigger pain?		n = 1	n = 22	
PPT (kPa)	439	344[§]	406	0.024

DMA: dynamic mechanical allodynia, CPT: cold pain threshold, HPT: heat pain threshold, MDT: mechanical detection threshold, VDT: vibration threshold, PPT: pressure pain threshold
[a]Significantly different to HC ($p < 0.05$).
[b]Significantly different to CxRAD positive ($p < 0.05$).
[§]No further analysis performed as only 1 person.
[◊]Univariate analysis.

Table 8.9.

Comparison of each QST parameter between healthy controls (HC), patients with fibromyalgia (FM) who responded on painDETECT as being sensitive to a QST parameter (positive), and patients who responded on painDETECT as being not sensitive to a QST parameter (negative). The score "very strongly" was used as the cut-off score for answers on the painDETECT. Data are shown as mean (SD) for untransformed data and retransformed mean for log-normally distributed data (CPT, MDT, PPT).

	HC (n = 31)	FM positive	FM negative	p-value$^{\lozenge}$
Is light touching in this area painful?		n = 1	n = 21	
DMA	0 had DMA	0 had DMA	3 had DMA	
Is cold or heat in this area occasionally painful?		n = 1	n = 21	
CPT (°C)	7.0	28.6§	24.0$^{\lozenge a}$	< 0.001
HPT (°C)	46.7 (1.9)	38.5§	39.6 (3.4)$^{\lozenge a}$	< 0.001
Do you suffer from a sensation of numbness in the area that you marked?		n = 0	n = 22	
MDT (mN)	1.9		3.1	0.075
VDT (x/8)	6.1 (0.9)		5.5 (1.1)^{b}	0.008
Does slight pressure in this area trigger pain?		n = 1	n = 21	
PPT (kPa)	439	85§	190^{a}	< 0.001

DMA: dynamic mechanical allodynia, CPT: cold pain threshold, HPT: heat pain threshold, MDT: mechanical detection threshold, VDT: vibration threshold, PPT: pressure pain threshold.
[a]Significantly different to HC ($p < 0.001$).
[b]Significantly different to HC ($p < 0.05$).
[§]Not included in analysis as only 1 person.
[◊]Univariate analysis.

Clinical implications

Our data support the use of PD-Q as a tool to identify somatosensory profiles in patients with painful cervical radiculopathy. The questionnaire could possibly be applied in large epidemiological studies to classify patients with cervical radiculopathy based on sensory descriptors of PD-Q, as previously documented for patients with lumbar radicular pain (Mahn et al. 2011) and for patients with painful diabetic neuropathy and postherpetic neuralgia (Baron et al. 2009). However, bedside sensory examination would allow a comparison of sensory testing between symptomatic and asymptomatic body regions and side-to-side comparison enhances the sensitivity to detect sensory abnormalities (Maier et al. 2010; Rolke et al. 2006a).

Caution needs to be applied when making assumptions in the FM population about their sensory profiles based upon self-reported sensory descriptors of PD-Q alone. A recent cross-sectional cohort survey of 3035 patients with FM (Rehm et al. 2010) captured relevant sensory abnormalities, including pressure pain sensitivity (58.3%) and thermal hypersensitivity (24%). Amris et al (2010) reported 83% of 81 patients with FM indicated pressure sensitivity on PD-Q and 54% indicated thermal hypersensitivity. Both studies used a cut-off score > 3 for their analysis. In comparison, we had a lower percentage of patients with FM reporting pressure (50%) and thermal sensitivity (23%) (Table 8.7), but a larger percentage of patients with FM (100%) demonstrated these hypersensitivities as demonstrated by our QST data. Our data suggest that there is potential for misclassification if only patient reported outcomes are used for sub-grouping.

In conclusion, the data from our study demonstrate correspondence between the self-reported somatosensory profile of patients with cervical radiculopathy and their sensory phenotype as demonstrated by QST. The QST sensory phenotype of patients with FM was not consistently reflected by responses to verbal descriptors from the PD-Q. Clinicians and researchers should be cautious about relying on PD-Q as a stand-alone screening tool to determine sensory abnormalities in FM.

Acknowledgement

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Chapter 9 - Discussion

Nerve-related spinal neck-arm pain disorders are common musculoskeletal conditions that are associated with a negative impact on overall health status (Daffner et al. 2003). A neuropathic mechanism is implied in the genesis of some disorders such as painful cervical radiculopathies (Haanpää et al. 2009). NeP in musculoskeletal pain disorders leads to impaired quality of life and increased utilization of health care and is associated with more comorbidities such as anxiety, depression and sleep disturbances compared to nociceptive pain disorders (Freynhagen et al. 2006a; Saldaña et al. 2010; Schmidt et al. 2009).

The management of patients with NeP remains a challenge (Finnerup et al. 2010), indicated by the variability of treatment response among patients with pain related to lumbar (Baron et al. 2010b; Brötz et al. 2010) and cervical radiculopathy/radicular disorders (Saldaña et al. 2010). The variability may be due to the heterogeneity of nerve-related neck-arm pain disorders pertaining to differing aetiologies, clinical presentations or varying underlying pain types. Consequently, the characterisation of these patients with respect to the mix of NeP and nociceptive pain and the possible dominance of one pain type in mixed pain syndromes is of therapeutic relevance as NeP conditions require a different therapeutic approach than nociceptive pain conditions (Baron et al. 2010a; Harden and Cohen 2003). Furthermore, within one aetiology, recent research investigating somatosensory profiles has identified diverse sub-groups of patients with NeP (Baron et al. 2009; Maier et al. 2010). Differing somatosensory profiles may be associated with different underlying pain mechanisms, this providing another possible explanation for individual differences in responsiveness to anti-neuropathic drug treatment in patients with radiculopathy (Baron et al. 2010b; Saldaña et al. 2010).

Clinical classification systems have been proposed for the characterisation of patients with nerve-related neck-arm pain (Elvey 1997; Radhakrishnan et al. 1994), however their reliability has never been established in this population. Furthermore, various clinical tools such as a grading system of certainty for the presence of NeP (Treede et al. 2008); NeP screening questionnaires (Bennett et al. 2007); and laboratory tests

(QST) have been recommended for the assessment of NeP components in patients with chronic pain (Haanpää et al. 2011). In contrast to the literature investigating NeP components in low back and leg pain (Beith et al. 2011; Freynhagen et al. 2006a; Freynhagen et al. 2006b; Freynhagen et al. 2008; Kaki et al. 2005; Prout et al. 2010), there has been little research on the assessment of NeP in nerve-related spinal neck-arm pain (Chien et al. 2008; Sterling and Pedler 2009). The aim of this thesis was to add to the current understanding of neck-arm pain by characterising patients with nerve-related neck-arm pain, with a particular emphasis on the assessment of NeP in patients with painful cervical radiculopathy and patients with NSNAP. These groups were chosen as they have commonalities in their clinical presentation (pain characteristics), but may differ in the dominance of underlying pain types. The overall aim of the thesis was to investigate the characteristics of patients with nerve-related neck-arm pain and establish their somatosensory profile.

A series of 5 studies was conducted. The objective of the first study (Chapter 4) was to assess the inter-examiner agreement of two musculoskeletal physiotherapists in classifying patients with cervical radiculopathy and patients with NSNAP, using documented specific clinical classification systems (Elvey 1997; Radhakrishnan et al. 1994). Additionally, the diagnostic accuracy of these clinical examiners was determined, using the opinion and consensus of two experts (spinal neurosurgeon, Specialist in Musculoskeletal Physiotherapy) as the reference criterion. The cohort in this study consisted of patients with unilateral neck and arm pain. The pain areas may have been causally related or may have been independent from each other. The heightened nerve mechanosensitivity could have related to spinal mediated nerve sensitivity, as well as to clinically diagnosed distal/peripheral neuropathies, such as carpal tunnel syndrome. The findings of this study demonstrated a high percentage agreement between the clinical examiners and between these examiners and the two experts in identifying and classifying patients with cervical radiculopathy and patients with NSNAP.

The second study (Chapter 5) investigated the clinical application of the NeuPSIG grading system for the assessment of NeP (Treede et al. 2008) in 152 patients with neck-upper limb pain, and the level of agreement in detecting likely NeP between this model and two NeP questionnaires (LANSS, PD-Q). The application of the

grading system was found to be feasible in this patient cohort. However, its implementation required specific expertise and a considerable amount of clinical examination time due to the complexity of the patients' pain presentations. LANSS and PD-Q failed to identify a large number of patients clinically classified as having NeP, indicating limitations of the screening questionnaires for identifying NeP in patients with neck-arm pain of mixed aetiology and mixed pain type.

The third and fourth studies of this thesis were designed to characterise patients with cervical radiculopathy and patients with NSNAP using QST and to explore differences or commonalities in sensory parameters and underlying pain types. In contrast to patients with NSNAP in Study 1, additional inclusion criteria were required for patients with NSNAP in order to ensure more homogeneity. Patients with NSNAP had to present with a dermatomal C6/7 pain distribution and absence of clinical signs of radiculopathy. The specific dermatomal pain distribution was chosen to match closely the pain distribution of patients with C6 or C7 radiculopathy. Study 3 (Chapter 6) addressed the hypotheses that somatosensory profiles would differ between patients with cervical radiculopathy and patients with NSNAP, and that the sensory profiles of both groups would differ from a positive control group (patients with FM). HC data were used as reference data for all groups. The QST profile of patients with cervical radiculopathy was distinct from that of patients with NSNAP. Patients with cervical radiculopathy were characterised predominantly by a loss of function in non-nociceptive stimuli in their maximal pain area and affected dermatome, findings consistent with nerve root damage and the presence of NeP (Haanpää et al. 2011; Treede et al. 2008). In addition, patients with cervical radiculopathy demonstrated a gain of function (cold hypersensitivity) in their maximal pain area and ipsilateral foot. This gain in cold sensitivity was also evident in patients with NSNAP in their maximal pain area and foot and defined the sensory phenotype for this patient group. Patients with NSNAP were predominantly characterised by nociceptive pain. Both patient groups differed in their somatosensory profiles from patients with FM, the latter demonstrating a widespread gain of function in most nociceptive parameters.

In order to further characterise patients with cervical radiculopathy and patients with NSNAP and to determine the presence of NeP components for each group, a side comparison of QST data was performed and the PD-Q applied (Study 4, Chapter 7). The QST findings increased the evidence for the presence of nerve root damage in patients with cervical radiculopathy, indicated by a significant loss of function in cold, mechanical and vibration detection and pressure sensitivity in the affected dermatome. The QST findings further supported the presence of NeP in these patients, with evidence of lowered mechanical and vibration sense on the symptomatic side of their maximal pain area compared to the asymptomatic side. At a group level, the PD-Q score did not suggest the presence of NeP, but PD-Q identified 30% of individuals as having NeP components. In patients with NSNAP, side comparison of QST data and the PD-Q score did not provide evidence for the presence of NeP. The findings rather indicated nociceptive pain as the dominant pain type in this group.

The PD-Q has been used not only as a discriminative tool for NeP, but also for the characterisation of somatosensory profiles in patients with lumbar radiculopathy (Mahn et al. 2011) and other NeP conditions (Baron et al. 2009) as well as in patients with FM (Amris et al. 2010; Rehm et al. 2010). Hence the final study of this dissertation (Chapter 8) explored the correspondence between the self-reported somatosensory profiles established by responses to PD-Q, and sensory phenotypes demonstrated by QST in patients with cervical radiculopathy and patients with FM. Patients with radiculopathy demonstrated a match between their self-reported sensory phenotype and QST sensory phenotype for all sensory descriptors except for sensitivity to light touch, supporting its use for characterisation of this patient group. In patients with FM, the self-reported sensory phenotype did not consistently correspond with the QST sensory phenotype.

In this discussion chapter, the application and utility of the clinical and laboratory tools used in this thesis for the somatosensory characterisation of patients with nerve-related neck-arm pain, will be discussed. The strengths and limitations of this research; recommendations for future research; and the implications for clinical practice will also be presented.

9.1 Clinical classification systems

The fundamental method of identification of NeP is the clinical examination, which is aimed at recognising in patients the existence of NeP, localizing the lesion and diagnosing the causative disease or event. The latter two aspects were relevant in the first study of this thesis (Chapter 4), a study that investigated the inter-examiner agreement in classifying patients with cervical radiculopathy and NSNAP, using specific classification systems. It has to be emphasized that the presentation of heightened nerve mechanosensitivity is not a diagnosis in its own right, as it is not a disease entity like radiculopathy, rather it is a clinical feature seen in patients with neck-arm pain. It is well documented in the physiotherapy literature (Butler 2000; Elvey and Hall 1997; Hall and Elvey 2005; Shacklock 1995) and its assessment has been accepted as common clinical practice (Petty and Moore 2001). However, the identification of this clinical sign and its differentiation from cervical radiculopathy is important as it directs the treatment approach.

The research in this thesis demonstrated a high percentage agreement between the clinical examiners in classifying the two patient groups, consistent with findings from another classification study of patients with low back-related leg pain (Schäfer et al. 2009). Furthermore, high diagnostic accuracy of both examiners in identifying these two patient groups was demonstrated. Similarly, high diagnostic accuracy of one examiner was further demonstrated in the Studies 3 and 4 (Chapter 6, 7), with agreement in classification of 31 of 34 patients classification (91%) between the clinical examiner and clinical experts. These results are important as they demonstrate effective clinical diagnostic skills that are critical for physiotherapists as first contact practitioners and in extended scope of practice areas such as triaging patients in neurosurgery clinics or emergency departments (Anaf and Sheppard 2007; Lau et al. 2008). High diagnostic accuracy and the risk-benefit implications of making wrong diagnostic decisions are of particular significance for patients where the causative disease may warrant specific treatment such as surgical or pharmaceutical intervention instead of or in addition to physical therapies.

The classification systems for identifying patients with cervical radiculopathy and patients with NSNAP were shown to be clinically feasible and reliable in this patient

cohort. However, some limitations were identified in strictly applying these systems. Strict adherence as applied in the research setting can limit clinical reasoning which is an important aspect of clinical decision making (Christensen et al. 2005). For example, Category II of the classification system for radiculopathy (see Chapter 4, Table 4.1) specifies that, in the absence of any imaging results, three clinical signs of nerve root impairment have to be present for the diagnosis of radiculoapthy: a sensory dermatomal change, a myotomal change and a diminished reflex. Therefore, this category encompasses criteria for the presence of a combined motor and sensory radiculopathy, but does not allow for a differentiation between the two. This issue is clinically important as each condition is indicative of a nerve root lesion and may need specific intervention. An example would be a patient with a pure sensory radiculopathy (no motor impairment) who may present with NeP, requiring targeted treatment. In contrast, a patient with a pure motor radiculopathy may not experience any pain and may not need any intervention, as long as their function was not significantly impaired. Moreover, Category II of the classification system is compromised if muscle strength tests cannot be performed due to pain inhibition, negating one criterion for the presence of motor nerve root impairment. Furthermore, the presence of neck and/or arm pain should be listed in this category, if the system is used for the classification of *painful* radiculopathies.

To our knowledge, no comparative studies exist which assess inter-examiner agreement in the classification of patients with cervical radiculopathy or patients with NSNAP. To some extent, the findings can be compared to an inter-rater reliability study of a classification system for 40 patients with neural low back–related leg pain (Schäfer et al. 2009), although patients were classified into four groups: 1) *central sensitisation*, defined by the authors when patients demonstrated a score of ≥ 12 on the LANSS; 2) *denervation*, defined as a LANSS score < 12 and the presence of clinical signs of nerve root damage; 3) *peripheral nerve sensitisation,* where the first two classification did not apply and patients presented with increased peripheral nerve mechanosensitivity and 4) *musculoskeletal* (patients not meeting any of the above criteria). Group 2 in the Schäfer et al study (2009) equates to our patients with cervical radiculopathy, except that in our study the LANSS was not used for classification. Group 3 equates to patients with clinical signs of heightened nerve mechanosensitivity and group 4 equates to others (patients not fulfilling the

criteria for cervical radiculopathy or heightened nerve mechanosensitivity). Similarities between Schäfer et al's study and ours do exist, as both studies employed experienced clinical examiners, the classifications were applied in a hierarchical order and both studies reported 80% agreement between clinical examiners in classifying patient groups. However, while Schäfer et al (2009) commented that the ease of application of a hierarchical order is advantageous, this system has limitations as the categories were treated as being mutually exclusive. Such separation is not consistent with clinical pain presentations. For example, heightened nerve mechanosensitivity can coexist with pain presentation of denervation, as documented in patients with low back–related leg pain (Schäfer et al. 2009), in patients with cervical radiculopathies (Study 4) (Chien et al. 2008; Wainner et al. 2003) and in patients with carpal tunnel syndrome (Wainner et al. 2005). Although the differentiation between the clinical presentation of painful cervical radiculopathy and NSNAP is important, they should not be regarded as being mutually exclusive, as these could be viewed as disorders on a clinical continuum. For example, pathological conditions attacking the nerve from the outside might initially cause nociceptive nerve trunk pain and subsequently also cause nerve damage and therefore be associated with NeP (Marchettini et al. 2006). The patient would therefore present with co-existing nociceptive and NeP.

Considering that both clinical examiners in our study were highly skilled and experienced, it is unclear if less experienced physiotherapists would achieve similar agreements in classifying these patient groups, and this aspect of clinical application of classification warrants further research. Moreover, the sample size of patients with NSNAP classified by the expert was small (n = 9), and the implication of such small sample size is discussed in detail under section 9.3. Summarized, patients with cervical radiculopathy and patients with NSNAP can be reliably identified, using the two documented clinical classifications systems, although a combination of the two may increase the likelihood of accurate classification for less experienced clinicians.

Similar to the classification of the patients with cervical radiculopathy and patients with NSNAP, the recommended classification of patients with NeP relies on a combination of items (Treede et al. 2008). The NeuPSIG grading system of certainty for the presence of NeP, is based on pain distribution and a history suggesting a

relevant nerve lesion, the presence of sensory alterations in the innervation territory of the affected nerve structure and confirmative evidence of a nerve lesion/disease from diagnostic tests (Treede et al. 2008). Study 2 (Chapter 5) is the first study to demonstrate the application of this grading system in a large cohort of patients with neck-upper limb pain, and applying this classification system proved to be feasible in this clinical cohort. However, several considerations have to be discussed, considering that this model has been recommended for use in primary care settings (Haanpää et al. 2009). The first criterion of this grading system relates to the presence of pain within a distinct neuroanatomically plausible distribution. In our Studies 3 and 4, patients with cervical radiculopathy as well as patients with NSNAP both met this criterion. Both groups presented with pain following a C6 or C7 dermatomal distribution, however the dominant underlying pain types differed between groups. Additionally, the pain distribution in patients with radiculopathy may not always follow a dermatomal pattern (Murphy et al. 2009; Slipman et al. 1998). Furthermore, coexisting musculoskeletal disorders are common in patients with suspected cervical radiculopathy (Cannon et al. 2007) and can mimic nerve lesions (Lauder 2002). Thus, the pain distribution alone does not necessarily indicate the presence of NeP.

It has been suggested that the assessment of sensory alterations is the most important part of the clinical examination of NeP (Haanpää et al. 2011). While the sensory testing in the patient's maximal pain area is not difficult to perform, the interpretation of the findings of sensory aberrations can be challenging for the following reasons:

1) The presence of a sensory alteration is not necessarily indicative of NeP, as sensory changes can be present in non-NeP conditions, as documented in patients with FM in Study 3 and 5 (Chapter 6, 8) and other patient populations (Blumenstiel et al. 2011; Leffler et al. 2000; Westermann et al. 2011).

2) Sensory aberrations have been reported in referred pain areas in patients with musculoskeletal pain (Leffler et al. 2000), thus symptoms and signs may to some extent mimic NeP states. As for patients with neck-arm pain, musculoskeletal conditions are common in patients with suspected cervical radiculopathy (Cannon et al. 2007) and can mimic cervical radiculopathy

(Lauder 2002). The patient cohort in Study 2 gives an example, as 54% of patients indicated the neck/trapezius/scapula/shoulder area as their main area of pain and these areas also correlate with specific cervical nerve root distributions (Tanaka et al. 2006). Further, a musculoskeletal pain disorder and a non-painful nerve lesion may coexist (for example nociceptive neck pain coexisting with a non-painful motor radiculopathy), and the pain distribution of nociceptive pain may be located in the same area as the innervation territory of the affected nerve structure. Thus, sensory alterations may be misinterpreted as a sign of the presence of NeP.

3) It has been recommended that findings in the painful area should be compared with findings on the contralateral mirror side in unilateral pain conditions (Haanpää et al. 2011). However, limitations to this approach are also evident as sensory changes may exist bilaterally, as seen in patients with cervical radiculopathy (Chien et al. 2008), in patients with trigeminal neuropathy (Jääskeläinen et al. 2005; Leffler and Hansson 2008) and also in patients with non-NeP (Leffler et al. 2003). Hence, the asymptomatic side may be misleading as a true control (Baron 2006). Our patients with cervical radiculopathy (Study 4, Chapter 7) presented with bilateral reduced thermal detection in the maximal pain area, therefore the asymptomatic side was not a true control for the side comparison of thermal detection. However, the asymptomatic area was effective as a control for identifying differences in mechanical and vibration detection between sides.

4) Sensory alterations may occur without any tissue damage. The presence of cold hypersensitivity is an example. While cold hypersensitivity is a common sequel of nerve injuries (Landerholm et al. 2010; Taylor et al. 2010), it has also been documented in patients with no identifiable underlying pathology such as FM, as documented in Studies 3 and 5 and by others (Berglund et al. 2002; Blumenstiel et al. 2011; Hurtig et al. 2001). Furthermore, patients with depression and without pain presented with cold hypersensitivity (Klauenberg et al. 2008).

Summarized, the findings of sensory aberrations in patients with suspected NeP have to be interpreted in light of the overall clinical examination findings. The frequency of sensory aberrations tends to increase with the likelihood of the presence of NeP,

as evident in the patient cohort with neck-arm pain in Study 2 and in others (Rasmussen et al. 2004). Hence, clinicians may use this information as a further hint for the determination of the predominant underlying pain type, as patients with NeP are likely to demonstrate more than one sensory alteration.

Another important element in the determination of the presence of NeP in patients with neck-arm pain is the evidence for the presence of a nerve lesion/disease. Imaging studies such as a CT scan or MRI are accepted as diagnostic tests to confirm nerve root compression (Treede et al. 2008). However, degenerative changes of the cervical spine are common and can be easily interpreted as false positive findings (Matsumoto et al. 1998) if not put into the context of the overall clinical examination findings. For example, our patients with NSNAP presented with a C6/7 dermatomal pain distribution, but no clinical signs of a radiculopathy. If imaging studies for these patients revealed any abnormality indicating compression of the C6 or C7 nerve root on the symptomatic side, this finding may be misinterpreted as a confirmation of a radiculopathy. Likewise, false negative findings may also be misleading, as for example in the case of Parsonage Turner Syndrome associated with NeP. This pain condition mimicked cervical radiculopathy, but in this case MRI findings were negative (Feinberg et al. 2007). The clinician should be aware of these limitations of diagnostic tests in order to correctly classify NeP.

Identification of a NeP component in mixed pain presentations may be more difficult than identification of 'typical' NeP conditions such as postherpetic neuralgia as various degrees of neuropathic components may be present, also referred to as pain 'being more or less neuropathic' (Attal and Bouhassira 2004; Bennett et al. 2006). The diagnosis of NeP and application of this grading system to patient pain disorders can be straight forward, as in the case of postherpetic neuralgia after shingles or NeP after a known surgical nerve lesion. In both cases, the history provides information on the cause of the pain disorder, plus the pain is localized to a single body area. However, this diagnostic approach does require a considerable time allocation and specific expertise for the classification of patients with complex and mixed pain presentations as seen in the current study. Applicability in primary care settings for such patient populations may be limited, given the time-constraints in general practice (Bindman et al. 2007; Campbell 2007) and possible lack of adequate skills

(Bennett et al. 2007). Furthermore, the identification of NeP does not exclude the coexistence of nociceptive pain.

There is a challenge for clinicians to identify the dominant underlying pain type. The assessment of self-reported pain descriptors may aid in the determination of the predominant pain type. In both Studies 2 and 4, the descriptor 'electric shock' was only used by patients with NeP and the descriptor of 'spontaneous' pain was most common in patients with NeP. However, single descriptors are not discriminative for NeP and nociceptive pain (Behrman et al. 2007; Hansson et al. 2007), rather a combination of items can discriminate between the two, as demonstrated with the use of various NeP screening tools (Bennett 2001; Bennett et al. 2005; Bouhassira et al. 2005; Krause and Backonja 2003). Nevertheless, these clusters of sensory verbal descriptors were obtained in patients with 'classical' NeP conditions. Using descriptors of two NeP questionaires (Galer and Jensen 1997; Krause and Backonja 2003), Behrman et al (2007) demonstrated that patients with mixed pain presentations (radiculopathies) were much more difficult to classify than patients with NeP polyneuropathies. Similarly, our patients in Study 2 and 4 (Chapter 5, 7) would be difficult to classify purely based on their sensory descriptors, as an overlap of NeP and nociceptive pain descriptors was demonstrated between the patient groups. While further questionnaires were developed to assess pain qualities related to NeP as well as non-NeP pain (Dworkin et al. 2009; Jensen et al. 2006), these questionnaires are not screening tools to identify NeP. Before NeP questionnaires can be generalised to all types of NeP, it has to be determined if the NeP component in the population studied has similar pain descriptors to the NeP in the original validation study of the questionnaire (Bouhassira et al. 2005). This issue will be further discussed in section 9.2.

In Studies 3 and 4, common NeP descriptors were more frequently used for the description of patients' arm pain than patients' neck pain, suggesting that where multiple symptom areas exist, the assessment of pain descriptors for each symptom area may further assist in identification of pain types. This approach was employed in a recent study on patients with low back and leg pain (Attal et al. 2011) in which the DN4 questionnaire was applied independently to both the patient's back and leg pain. Based on the DN4 score, 52% of patients with lumbar radiculopathy presented

with nociceptive back pain and neuropathic leg pain while others presented with neuropathic back pain and nociceptive leg pain. These results demonstrate well the coexistence of two pain types within separate body regions in patients with radiculopathy. However, mixed neuropathic and nociceptive mechanisms may also account for pain in the same body area (Baron and Binder 2004). Therefore, while it has to be noted that pain descriptors would never be used in isolation for the diagnosis of NeP, more data on the usefulness of pain descriptors in the determination of dominant pain types in patients with mixed pain presentations is needed.

It is unclear how confident health professionals in primary care are in identifying NeP in patients with chronic pain disorders. Data from a general practice research database in the UK suggest sub-optimal NeP management for patients with predominantly NeP and for patients with mixed pain disorders (including back/neck pain) (Gore et al. 2007). It has not been established whether the sub-optimal management occurs as a result of lack of knowledge on how to identify patients with NeP or lack of knowledge on how to manage patients with NeP. In a survey amongst European neurologists (n = 745) participants frequently mentioned that NeP in patients with radiculopathy remains undiagnosed because of a lack of knowledge. Similarly, few data exist on physiotherapists' knowledge in the identification of NeP in musculoskeletal pain disorders. A recent Delphi survey of 103 expert clinicians (31 pain physicians and 72 musculoskeletal physiotherapists) established clinical indicators of nociceptive, peripheral neuropathic and central mechanisms of musculoskeletal pain (Smart et al. 2010). Based on these clinical indicators and using the statistical method of logistic regression analysis, a discriminatory cluster of symptoms and signs predictive of each mechanism was identified in patients with low back (±) leg pain. According to this analysis, a cluster of three criteria was predictive of the dominance of peripheral NeP: 'history of nerve injury/pathology'; 'pain referral in a dermatomal or cutaneous nerve distribution'; and 'pain/symptom provocation with movement tests that move/load/compress neural tissue' (Smart et al. 2011, p5). The predictive value of this cluster approach was 86.3%. The first two criteria, a history of nerve injury and pain referral in a dermatomal or cutaneous nerve distribution, are consistent with the first two criteria of the NeuPSIG grading system for NeP (Treede et al. 2008).

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In this thesis, the results of Study 4 do not necessarily support the argument that pain referral in a dermatomal distribution and pain provocation in response to a nerve provocation test are indicative of NeP, as patients with NSNAP (and these two clinical features) were characterised by mainly nociceptive pain. However, a few considerations apply to the studies by Smart et al (2010; 2011). Firstly, the former definition for NeP, that is "pain initiated or caused by a primary lesion or dysfunction of the nervous system" (Merskey and Bogduk 1994, p212), was used in developing the clinical indicators. Under this definition, clinical signs of heightened nerve mechanosensitivity could be interpreted as a *dysfunction* of the nervous system because neural tissues demonstrate lowered compliance to movement tests. However, this criterion does not meet the new definition of NeP that requires a nerve lesion or disease of the somatosensory nervous system to be present. More data are needed to investigate how prevalent the feature of heightened nerve mechanosensitivity is in patients with painful nerve lesions and NeP. Secondly, mixed pain presentations (for example mixed nociceptive/neuropathic, mixed neuropathic/central sensitisation) were excluded in the Smart et al (2011) regression analysis. Hence, similar to the classification study of Schäfer et al (2009), pain disorders were classified as being mutually exclusive and this does not reflect the clinical spectrum of patients with low back pain disorders (or with nerve-related neck-arm pain).

Furthermore, a sensory deficit in the innervation territory of a lesioned nerve structure is a diagnostic criterion of NeP (Haanpää et al. 2011; Treede et al. 2008), but this criterion did not get any mention in this classification system for peripheral NeP. In contrast, using logistic regression analysis, Scholz et al (2009) documented a cluster of physical examination discriminative indicators for the differentiation of lumbar radicular pain (radicular pain being defined in this context as NeP with clinical signs of nerve root impairment) and lumbar axial pain, which incorporated a deficit in the detection of cold sensation and pinprick hypoalgesia. Interestingly, a positive straight leg raise test was also included in this cluster, for this clinical sign has not been mentioned before as a criterion for the presence of NeP. However, the diagnostic accuracy of the developed standardised evaluation of pain (combination of interview items and physical examination items) was still high when the straight-leg-raising test was excluded from the analysis (area under the curve 0.85 compared to

0.98), indicating that the straight-leg-raising test is not that important as a single discriminative factor in this cohort. The Scholz et al (2009) study demonstrated that a combination of pain-related symptoms and signs is useful in differentiating axial and radicular low back pain and this approach is consistent with the NeuPSIG grading system comprising neuroanatomically related pain distribution and sensory aberrations.

Summarized, the NeuPSIG grading system was feasible for the identification of NeP in patients with neck-arm pain of mixed aetiologies and mixed pain types. However, for our study population this diagnostic approach required a considerable time allocation and specific skills, both of which may not be available in primary care settings. Clinician's lack of time or skill has been acknowledged (Bennett et al. 2007) and NeP screening tools, for example the LANSS and PD-Q, have been developed in order to assist health professionals in identifying potential patients with NeP.

9.2 Neuropathic pain screening tools

NeP screening tools are recommended for the use by non-specialists and in primary care (Bennett et al. 2007; Haanpää et al. 2011). However, our results (Chapter 5) suggest that the LANSS and PD-Q may not be suitable tools for the identification of NeP in patients with neck-arm pain of mixed aetiology and mixed pain types. We found LANSS had a sensitivity of 22% and PD-Q a sensitivity of 64% in patients with neck-arm pain, much lower than those sensitivities reported in the original developmental studies (Bennett 2001; Freynhagen et al. 2006a).

One explanation for the lowered sensitivity of both questionnaires may be the differences in clinical characteristics of the studied patient cohorts. Both questionnaires were validated in specific pain clinic patient populations with and without NeP. Importantly, patients with mixed pain presentations were excluded from both studies (Bennett 2001; Freynhagen et al. 2006a). Patients with NeP included those with 'typical' NeP conditions such as postherpetic neuralgia, painful neuropathy and nerve traumas. In the LANSS study, 7 out of 30 patients with NeP had a radiculopathy (lumbar radiculopathy n = 5, cervical radiculopathy n = 2)

(Bennett 2001). In the PD-Q study, the number of patients with NeP radiculopathy was not mentioned (Freynhagen et al. 2006a). In fact, the latter study did not provide any information on the proportion of patients in each group or each group's pain characteristics. In contrast to the validation studies, our 152 patients with neck-arm pain in Study 2 presented with a wide spectrum of pain presentations of mixed aetiology. Some conditions, such as radiculopathies and carpal tunnel syndrome were likely to include NeP, whereas others were predominantly nociceptive musculoskeletal conditions, such as mechanical neck pain.

Our patients' choice of pain descriptors to some extent differed to the defined pain descriptors listed in the NeP screening tools. In the validation study of LANSS (Bennett 2001), a significant association between allodynia and hyperalgesia was noted for patients with NeP. In contrast, in our neck-arm pain study (Study 2), hyposensitivity occurred more frequently than hypersensitivity. Our data are consistent with findings in patients with lumbar radiculopathy (Scholz et al. 2009), and in patients with various chronic suspected NeP conditions (Rasmussen et al. 2004), and in our patients with cervical radiculopathy (Chapters 6, 7). In the LANSS tool, only allodynia is scored as a relevant sensory alteration in response to light touch, but not hypoaesthesia. Allodynia was demonstrated in only 5 of our 152 patients. Furthermore, only 6 of our patients reported symptoms of possible autonomic nervous system dysfunction, such as color changes of the skin in the painful area. These observations suggest that allodynia and autonomic dysfunction are not frequently- reported characteristics for these patients with nerve-related neck-arm pain. Both items (allodynia and autonomic dysfunction) yield the highest score (score = 5) that is obtainable for a question in LANSS. The high score associated with a relatively rare characteristic is consistent with the low sensitivity of LANSS in our patient population. This finding demonstrates the limitation associated with validation of a questionnaire in a dichotomous patient sample (NeP/non-NeP) and the application to a heterogeneous sample. Splitting patients into two categories may limit the ability to generalise results to a mixed pain clinical population.

The LANSS may be most useful for the identification of NeP in patient cohorts who demonstrate mainly positive sensory signs rather than negative sensory signs. Heterogeneity of patients with NeP in regard to their sensory characteristics

/somatosensory profiles has been demonstrated by use of QST (Maier et al. 2010; Rolke et al. 2006a) and the PD-Q (Baron et al. 2009; Mahn et al. 2011). In the two latter studies, in patients with NeP due to diabetic neuropathy and postherpetic neuralgia and in patients with lumbar radiculopathy, two sub-groups of patients were characterised by burning pain, paraesthesia, numbness and lack of hyperalgesia and allodynia. If this sensory profile was assessed by LANSS, a score ≥ 12 may not be reached, thus this patient group would be incorrectly classified as having predominantly nociceptive pain. Similarly, a patient with postherpetic neuralgia, characterised by the presence of mainly negative signs/loss of function (Rolke et al. 2006a), may score much lower on the LANSS than a patient with the same aetiology, but who is characterised by the presence of mainly positive signs manifesting as hyperalgesia and allodynia in various QST submodalities (Rolke et al. 2006a).

There are indications that the cut-off score of LANSS may have to be adjusted for identification of NeP components in differing populations from the original population studied. A recent study in patients with spinal cord injuries demonstrated that the appropriate cut-off value of LANSS, the PD-Q and NPQ for the population studied was lower than in the original studies (Hallström and Norrbrink 2011). The cut-off value of LANSS dropped from ≥ 12 to ≥ 4 and the cut-off value of PD-Q from ≥ 19 to ≥ 8. Interestingly, the cut-off score for the DN4 did not differ to its original study and DN4 was most sensitive out of all questionnaires (sensitivity: DN4 93%, LANSS 36%, PD-Q 68%, NPQ 50%; specificity: DN4 75%, LANSS 100%, PD-Q 83%, NPQ 100%). In our Study 2, there were 48 cases where results of LANSS and clinical classification were discordant. In 35 of these the clinical classification was definite NeP. The LANSS scores for 16 of the 35 were 10 or 11 points, just short of the published cut off of 12. With a cut-off score of 10, sensitivity of LANSS would have increased to 58%. However, at the same time, specificity would have reduced from 88% to 73%, thus a change in cut-off points may improve sensitivity, but compromise specificity.

Given the bias of LANSS towards identifying NeP components characterised by predominantly sensory gains, the validity of this questionnaire applied in patients with mixed pain may be limited. The inclusion of patients with mixed pain presentations has been reported to reduce the sensitivity of LANSS (from 85.9% to

81.8%) in a cohort of 156 patients with chronic pain (Rejas et al. 2006), whereby specificity did not alter much (from 90.3% to 89.4%). However the proportion of patients with mixed pain was small (14%) and unfortunately, the type of patient population/aetiologies was not mentioned in the study making a comparison with our data difficult.

The DN4 may be more suitable for the identification of NeP in mixed pain presentations than LANSS or PD-Q. The diagnostic accuracy of the LANSS and DN4 questionnaire was compared in a cohort of 180 patients of which 59 patients had clinically classified nociceptive pain and 121 patients had clinically classified definite or probable NeP (Treede et al. 2008; Unal-Cevik et al. 2010). Fifty-two percent of the latter comprised patients with cervical or lumbar radiculopathy. The sensitivities of LANSS and DN4 were 70% and 95% respectively, the specificity of both tests was 97%. However, the patients with radiculopathy demonstrated predominantly NeP, thus it is unclear if DN4 would perform better than LANSS in a mixed patient cohort similar to those in Study 2. Independent of the various patient populations studied, LANSS has demonstrated high specificity in all studies (Bennett 2001; Hallström and Norrbrink 2011; Mercadante et al. 2009; Potter et al. 2003; Unal-Cevik et al. 2010; Yucel et al. 2004), including Study 2 in this thesis, suggesting its usefulness in ruling out NeP in patients with chronic pain disorders.

The PD-Q was specifically designed to identify NeP components in patients with low back pain with and without referred pain (Freynhagen et al. 2006a). Hence it was anticipated that the questionnaire may be transferable to patients with neck-arm pain. One concerning factor of the PD-Q emerging from this thesis, is its openness to individual interpretation as a self-reported tool. Patients are asked to mark their maximal pain area on the body chart of the PD-Q and each item descriptor is supposed to relate to this marked body area. In Study 2, 35% of patients with neck-arm pain either didn't mark a pain area at all or marked multiple pain areas, some of which were unrelated to each other. Thus, it remains unclear which pain area these patients were referring to when they gave their responses in PD-Q. In addition, many patients experienced paraesthesia in their upper limb, but not in their pain area, thus creating confusion about how to answer the two questions about the presence of paraesthesia (tingling, numbness) in the area of pain. Other studies using the PD-Q

have not commented in regard to misinterpretations of PD-Q or the difficulty with multiple pain areas (Amris et al. 2010; Baron et al. 2009; Beith et al. 2011; Freynhagen et al. 2006a; Hallström and Norrbrink 2011; Jespersen et al. 2010; Prout et al. 2010; Rehm et al. 2010), except one study reporting missing data on the PD-Q (Junker et al. 2008). Thus, it is unknown if the study in this thesis is the only one observing these discrepancies, although this would seem unlikely. Then again, as documented in Chapter 8, patients with cervical radiculopathy correctly marked their pain/symptom area in the body chart of PD-Q without being given prior instructions. Perhaps the combination of: a) the fact that their pain areas were causally related; b) they did not have other/additional pain areas; and c) patients were in a research environment concentrating just on neck-arm pain yielded a better accuracy in matching responses to the item descriptors and the relevant pain areas.

One explanation why the PD-Q only identified 30% of patients with cervical radiculopathy as having NeP (Study 4), may relate to the discriminative ability of NeP screening tools, as it has been proposed that these tools are only reliable when applied to one specific painful area (Bouhassira and Attal 2011). It is possible, that the independent application of PD-Q to both pain areas (neck and arm pain) may increase the sensitivity of the PD-Q, as previously demonstrated for the DN4 in patients with lumbar radiculopathy (Attal et al. 2011). Additionally, a future study will have to investigate if the lowered sensitivity of PD-Q may be related to a mismatch between the pain descriptors reported by the patients and the pain descriptors included in PD-Q. For example, in patients with radicular leg pain, sub-groups with distinct sensory profiles were identified, and one sub-group presented with only one dominant sensory descriptor contained in the PD-Q (Mahn et al. 2011).

Another possible explanation may be the weighing of the item descriptors. In the study of patients with spinal cord injuries (Hallström and Norrbrink 2011), cut-off levels for discriminating NeP were low in the weighted items of PD-Q and it was suggested that the intensity of the sensory descriptor may not be that important for discrimination, but simply its presence or absence. Lastly, NeP screening tools are suggested to be less feasible in patients with multiple pain locations and with

widespread pain (Bouhassira and Attal 2011), consistent with our results in patients with neck-arm pain (Study 2) and in patients with FM (Study 5).

Reliability studies of PD-Q are scarce with only one study reporting moderate reliability (Kappa 0.59; 95% CI 0.34 to 0.85) of the Swedish version of the questionnaire in patients with central NeP (Hallström and Norrbrink 2011). No study documented reliability in other patient cohorts, using either the original German version of PD-Q (Hallström and Norrbrink 2011) or other translated versions, nor do reports on further validation studies exist, suggesting a possible compromise of the validity of the PD-Q outside the documented settings and cohorts. Hence, PD-Q outcomes have to be interpreted in light of these limitations.

In conclusion, the diagnostic accuracy of LANSS and PD-Q in identifying NeP was limited in our patients with neck-arm pain of mixed aetiology and mixed pain type(s) (Study 2) and in our patients with cervical radiculopathy (Study 4). Future research is recommended, aiming to define the pain descriptors and sensory characteristics that are able to better discriminate NeP from non-NeP in patients with neck-arm pain and to further analyse the appropriate cut-off values of LANSS and PD-Q for discriminating NeP in such patient cohorts. Furthermore, the reliability of PD-Q needs to be investigated in patients with peripheral NeP related to musculoskeletal conditions.

NeP screening tools are not meant to be used in isolation for the diagnosis of NeP, as they do fail to identify 10-20% of patients with NeP (Bennett et al. 2007) and do not provide information about the causal lesion or the location of the affected nerve structure(s). Furthermore, it has been demonstrated in patients with low back and leg pain that the exploration of sensory symptoms in interview format for the distinction between NeP and non-NeP, was less sensitive than the physical examination items (Scholz et al. 2009). Hence, the physical assessment of sensory profiles, using bedside examination, or more sophisticated QST, plays an important role in better discriminating pain types, as documented in section 9.4. For the interpretation of the findings from our QST studies (section 9.4), certain considerations are relevant.

9.3   The samples

Patient samples

Despite extensive recruitment efforts and numerous referring sources, it was not possible to recruit more subjects into the QST studies (Chapters 6 – 8), within the given timeframe of this thesis. The methods employed for the studies were robust and the inclusion/exclusion criteria for patients with cervical radiculopathy and patients with NSNAP were tight. Our strict selection criteria add strength to the studies as they ensured our study groups were homogenous. However, the strict inclusion criteria brought with them the compromise of obtaining smaller sample sizes than anticipated and also limit the generalisability of our findings. The patient cohort in Study 2 demonstrated that patients with neck-arm pain frequently present with co-morbidities, for example diabetes and thyroid dysfunction, that were not present in our patient cohorts in the QST studies. Thus, the patient cohorts in the QST studies may not reflect the clinical spectrum of patients with cervical radiculopathy and patients with NSNAP.

The sample size of patients with NSNAP was small, thus a type II error cannot be excluded from our studies. A post-hoc power analysis demonstrated ß values ≤ 0.65 for the comparison of QST parameters that did not differ between patients with NSNAP and HC and for the comparison of QST parameters that did not differ between sides in patients with NSNAP. The small sample size might reflect that NSNAP as a discrete disorder is far less prevalent than clinically reported and may occur more frequently in coexistence with nerve lesions including radiculopathy. Comparable data exist in patients with nerve-related low back and leg pain (Schäfer et al. 2009) where out of 40 patients, only 10% demonstrated features of heightened nerve mechanosensitivity as a discrete disorder (without any clinical signs of nerve root dysfunction), but in 57% heightened nerve mechanosensitivity coexisted with clinical signs of nerve damage.

Apart from patients not fulfilling the inclusion and exclusion criteria of the study, another limitation for recruitment was the time needed for the performance of the QST protocol. The QST of each body area tested typically required 30 minutes, thus in total the assessment time for 5 body regions came to 2.5 hours. In addition, the

questionnaires had to be completed prior to QST, which took 15 to 30 minutes, and the NPT$_{\text{MEDIAN}}$ was performed after the QST testing. Several patients fulfilling the inclusion criteria of the study were unable to participate due to time constraints.

HC sample

In addition to the patient groups recruited, we recruited a sample of healthy control subjects. QST data from these subjects were used to transform the patient data to standardise the values obtained in a variety of different units of measures into standard deviation units that can more readily be compared between parameters and body regions measured. The method of z-transformation used in this thesis was that proposed by Rolke et al (2006b). Prior to the commencement of data collection, based on clinical observations, it was anticipated that most patients would nominate the upper trapezius muscle as their main pain area. Consequently early in the data collection period, QST parameters were measured in 26 HC subjects in the upper trapezius muscle. However, during the course of the study it became apparent that patients indicated a variety of other body regions as their main pain area. Although some studies have calculated patient z-scores using HC reference data from different body regions it has been recognized as a limitation (Blumenstiel et al. 2011; Maier et al. 2010). The importance of this limitation was discussed with DFNS, who recommended site matched data should be collected from a minimum of 8 HC subjects for each site. Therefore additional HC subjects were recruited and QST data collected from the seven additional sites patients had indicated to be their maximal pain. Due to time constraints it was not possible to gender-match this additional HC data.

Ultimately, data for z-score transformation were available from at least 8 HC for every site measured in the patient groups. This sample size is in accordance with established methodology by DFNS for data standardisation (Blankenburg et al. 2010). However, in our opinion this sample size is small and caution should be applied in interpreting the findings from a sample of 8 subjects to be 'normative' or suggesting that values outside the 95% CI around the mean of such a small sample could be regarded as 'abnormal' (Krumova et al. 2010). Therefore, patient QST data in this thesis have to be interpreted in light of this caveat.

On a further note, some of our HC data measured over the dorsum of the foot and the

C6/7 dermatome(s) were different from the reference data obtained by DFNS over the foot and the dorsum of the hand (see Table 9.1), suggesting that our HC group was less sensitive to thermal pain, mechanical detection and vibration detection compared to the DFNS normative data. There was no obvious explanation for these differences. The differences in measured thermal sensitivity are unlikely due to the equipment as the thermostat was regularly calibrated, including trips to Sweden during the course of the study. We speculated the reduced sensitivity of our cohort may be a geographical effect as individuals in the southern hemisphere are more exposed to environmental influences such as sun light and UV radiation compared to individuals in the northern hemisphere. While speculative, such exposure may cause thickening of the epidermis resulting in reduced sensitivity. However, a CPT of 9º over the hand, similar to DFNS data, has been reported in another Australian HC group (Chien et al. 2008), suggesting variances in Australian HC cohorts and not supporting the concept of sun damaged skin reducing sensitivity. Mechanical detection was not measured in the latter study and the methodology of vibration detection differed from ours, limiting a comparison of findings for those parameters. Regardless of the reasons, these differences in the comparative HC data across laboratories and studies, highlights the importance of using HC data measured in the same laboratory as the patient data.

Table 9.1

A comparison of our healthy control QST data (foot/dermatome) and the data of the German Research Network on Neuropathic Pain (DFNS) (Rolke et al. 2006a)

	Current study	DFNS	
	Age 20 – 65 years 48% female	Female $\geq$ 40 years	Male $\geq$ 40 years
QST parameter	FOOT		
CDT (°C)	3.42	2.61	3.39
WDT (°C)	4.70	4.37	6.21
TSL (°C)	9.39	7.57	10.33
CPT (°C)	5.8	10.8	8.0
HPT (°C)	46.3	45.02	47.0
MDT (mN)	6.3	2.2	3.0
MPT (mN)	58	62	103
MPS (NRS_{100})	0.41	0.77	0.51
WUR (ratio)	3.30	2.51	2.59
VDT (x/8)	5.9	7.0	6.8
PPT (kPa)	584	535	570
	HAND		
CDT (°C)	1.57	1.44	1.35
WDT (°C)	2.94	2.01	2.08
TSL (°C)	4.71	3.22	3.05
CPT (°C)	6.11	10.43	7.29
HPT (°C)	47.3	44.1	45.8
MDT (mN)	2.24	1.17	0.90
MPT (mN)	73	71	116
MPS (NRS_{100})	0.36	0.63	0.50
WUR (ratio)	2.77	2.24	1.97
VDT (x/8)	7.0	7.7	7.6
PPT (kPa)	471	441	516

Differences between data of current study and DFNS data are highlighted in grey

9.4 Sensory profiling

The recognition of patients with differing pain syndromes presenting with similar clinical profiles is important because this directs the provision of targeted treatment. Our patients with cervical radiculopathy and our patients with NSNAP in Study 3 and 4, were similar in regard to demographics and clinical characteristics such as pain distribution, pain descriptors, degree of disability, impact of their pain on physical and mental status, sleep quality, fear avoidance behaviours and anxiety and depression scores. However, QST proved to be a useful adjunct in identifying the underlying pain type in each patient group and in identifying the difference between

the groups in regard to their underlying pain types. The use of QST profiling was important to distinguish groups because the presence of radiculopathy alone does not imply the presence of NeP, as a nerve lesion can be pain free (Landerholm et al. 2010).

Distinct somatosensory profiles were identified for patients with cervical radiculopathy and patients with NSNAP. Patients with cervical radiculopathy were characterised by a loss of function in non-nociceptive stimuli in their maximal pain area (thermal, mechanical and vibration detection) compared to HC, findings consistent with neural damage and the presence of NeP, and consistent with findings in patients with lumbar radicular pain (Scholz et al. 2009). In our patients, the presence of nerve root damage was further supported by the findings of a loss of function of thermal and vibration detection as well as pressure sensitivity in the affected dermatome compared to HC, and by a loss of function of mechanical detection, identified by the side difference in MDT between the symptomatic and asymptomatic side. The dermatomal loss of function in all sensory fibers tested is in accordance with previous findings using QST in patients with lumbar radiculopathy (Nygaard and Mellgren 1998). In contrast, Chien et al (Chien et al. 2008) using QST in patients with cervical radiculopathy, did not report reduced cold detection in tested dermatomes, however it is unclear if these dermatomal areas corresponded with each individual patient's area of sensory loss.

Considering the argument that our HC samples for z-transformation were quite small (section 9.3) and that the QST data of our patients were within the 95% confidence interval of our HC reference data, the side-to-side comparison of QST data was valuable in further establishing which sensory alterations on the symptomatic side were characteristic for the patient group with radiculopathy (Study 4, Chapter 7). The reduction in mechanical and vibration detection in the maximal pain area was further highlighted by the significant side difference in these parameters. Likewise, cold detection, mechanical and vibration detection and pressure sensitivity in the affected dermatome were significantly reduced compared to the asymptomatic side. Our data support the notion that a side comparison can enhance the sensitivity to detect sensory aberrations (Haanpää et al. 2011; Rolke et al. 2006a), and that such a side

comparison should be part of the standard clinical examination of patients with unilateral pain presentations.

However, side comparison is less meaningful in case of the presence of bilateral sensory aberrations, as already discussed under section 9.1, and evidenced by the bilateral thermal hypoaesthesia demonstrated in our patients with cervical radiculopathy (Study 4). The parameters of mechanical and vibration detection were more discriminative for the identification of sensory loss and of NeP components in our patient cohort than thermal detection thresholds. Hence, the assessment of MDT and VDT may be considered as first-line assessment in patients with cervical radiculopathy, consistent with the examination of touch hypoaesthesia employed in the DN4. Both tools, the DN4 and LANSS, do not incorporate the physical assessment of thermal sensitivity.

Patients with cervical radiculopathy were further characterised by the presence of cold hypersensitivity in their maximal pain area compared to HC, consistent with QST findings in patients with peripheral nerve injury (de Medinaceli et al. 1997; Kleggetveit and Jørum 2010; Landerholm et al. 2010; Taylor et al. 2010) and with findings at the cervical spine in patients with cervical radiculopathy (Chien et al. 2008). The significance of the cold hypersensitivity in our patients with cervical radiculopathy seemed unclear initially, as the group mean value for CPT was below the value of defined cold hyperalgesia ($\geq 15°$) and fell within our 95% CI HC reference data. However the side-difference for CPT was close to significant, consistent with a trend towards heightened sensitivity on the symptomatic side. Further evaluation of individual results revealed the presence of cold hyperalgesia in 48% of patients, suggesting that a sub-group of patients within the cohort was characterised by cold hypersensitivity. Moreover, a sub-group of patients with cold hyperalgesia was also identified in Study 5 (Chapter 8), as patients reporting cold sensitivity on the PD-Q also demonstrated an average CPT of 19° (i.e.; by definition these patients experienced a cold hypersensitivity).

Our data indicate the existence of sub-groups of patients with distinct sensory alterations within the same aetiology of cervical radiculopathy as reflected by the proportion of patients demonstrating increased pressure sensitivity in their maximal

pain area (z-score outside 95% CI of our HC data), while others demonstrated reduced pressure sensitivity (Study 3). Similarly, sub-groups with altered pressure sensitivity compared to HC were identified using the PD-Q (Study 5, Chapter 8). Patients who reported being sensitive to pressure, presented with a significantly lowered PPT compared to HC and compared to patients who reported not being sensitive to pressure. The self-reported somatosensory profiles of patients with cervical radiculopathy obtained through the PD-Q and confirmed by QST findings, demonstrated additional differences between patients in regards to measures of HPT, MDT and VDT. Patients indicating thermal sensitivity were significantly more sensitive to heat compared to HC. Patients indicating feeling numbness in their pain area demonstrated a loss in mechanical and vibration detection, but this was not the case for patients not reporting numbness. These data suggest heterogeneity in our patient group, consistent with data reported in other patient groups with NeP (Baron et al. 2009; Mahn et al. 2011; Maier et al. 2010). Somatosensory heterogeneity within a clinical disorder highlights the need for an individual patient assessment in order to determine sensory phenotypes and implement appropriately matched management.

The fact that the self-reported somatosensory profiles of our patients with cervical radiculopathy matched the QST sensory profile suggests that the PD-Q can be used as a tool to characterise these patients, and that the PD-Q is able to identify sub-groups based on sensory symptoms. These findings are consistent with previous data in patients with lumbar radiculopathy/radicular pain (Mahn et al. 2011) and in patients with postherpetic neuralgia and diabetic neuropathy (Baron et al. 2009). It has been proposed that the individual pattern of sensory symptoms may reflect the underlying pain-generating mechanisms and furthermore that the sensory profiling of patients may open up avenues to stratify patients in clinical trials (Baron et al. 2009). For example, in patients with thermal hypersensitivity, drugs that potentially act on thermosensitive transient receptor channels involved in mediating cold and heat sensitivity (Knowlton et al. 2010; Obata et al. 2005) may be useful. Our data may help to explain some of the variability in responsiveness to anti-neuropathic drug treatments in patients with radiculopathy (Baron et al. 2010b; Saldaña et al. 2010) and may direct clinicians in the most appropriately targeted choice of pharmaceutical intervention. The self-reported somatosensory profiles however included only

sensory descriptors that could be verified by QST, thus a future study would be valuable to investigate if all self-reported responses match with the clinical examination findings. For example, the presence of burning pain, tingling sensation and sudden pain attacks cannot be assessed by QST. Findings in this thesis suggest that the PD-Q should not be used for somatosensory profiling in patients with FM and the argument for this proposition is outlined in Chapter 5.

Patients with NSNAP were characterised by the presence of cold hypersensitivity in their maximal pain area compared to HC, however there was no difference in cold sensitivity between the symptomatic and asymptomatic side. No comparative data exists for this patient group. It is debatable whether the bilateral cold hypersensitivity evident in this group should be interpreted as satisfying a criterion for NeP as the NeuPSIG grading system does not specify which type of sensory alteration (loss or gain of function) is considered as a confirmatory test (Treede et al. 2008) although negative signs are reported as a hallmark for NeP (Dworkin 2002). As discussed already under section 9.1 (page 9-10), the finding of just one sensory alteration in the maximal pain area of our patients with NSNAP has to be interpreted in context of the overall examination findings. The factors that would argue against the presence of cold hypersensitivity as an indicator for NeP in our patients with NSNAP include: (i) no confirmative diagnostic test for the presence of nerve root compression; (ii) no sensory loss indicative of nerve damage; and (iii) cold hypersensitivity can be present in the absence of pain (Klauenberg et al. 2008) and tissue damage (Berglund et al. 2002; Hurtig et al. 2001; Klauenberg et al. 2008; Pfau et al. 2009).

Our data suggest that NeP components were unlikely in this patient group, although the small sample size may have limited the power to detect significant differences. For example, the VDT was lower in patients with NSNAP compared to HC. However, hypoaesthesia to vibration occurred bilaterally and has been demonstrated in patients with non-NeP such as in our patients with FM, and also by others (Blumenstiel et al. 2011; Koroschetz et al. 2010). Additionally, tactile hypoaesthesia has also been documented in patients with nociceptive pain (Geber et al. 2008; Voerman et al. 2000; Westermann et al. 2011).

Neuropathic components have been investigated in patient groups similar to our patients with NSNAP (Greening and Lynn 1998; Greening et al. 2003; Moloney et al. 2010; Tucker et al. 2007; Voerman et al. 2000). The studies by Greening et al (1998; 2003), Moloney et al (2010) and Tucker et al (2007) included patients with non-specific arm pain (office work-related upper limb disorders associated with repetitive movements) whereas the study by Voerman et al (2000) examined patients with dermatomal neck-arm pain in the absence of any neurological signs. Tactile hypoaesthesia (Voerman et al. 2000) and vibration hypoaesthesia (Greening and Lynn 1998; Greening et al. 2003) were found in the dermatomal areas tested. These sensory deficits are suggestive of nerve damage, however this does not necessarily equate to the presence of NeP. In contrast, our QST data recorded from the dermatome of patients with NSNAP did not suggest any signs of nerve root damage. Taking into account the clinical presentation of our patients with NSNAP, including clinical examination findings and QST findings, it is most likely that nociceptive pain was the predominant underlying pain type.

A novel finding in both our patient groups with nerve-related neck-arm pain was that of cold hypersensitivity in the foot. No comparative data exists as Chien et al (2008) did not measure CPT in the foot. Contrary to our patients with FM, who demonstrated widespread cold hyperalgesia in all three body regions tested, none of our patients demonstrated cold hypersensitivity in the dermatome, consistent with previous data (Chien et al. 2008). Only two of our patients with cervical radiculopathy recorded cold hyperalgesia in all body regions and only 4 patients recorded cold hyperalgesia in both the maximal pain area and foot. Hence, the presence of cold hyperalgesia was not consistent, and this was also the case for patients with NSNAP. As discussed in Chapter 6, the mechanisms underlying cold pain are not yet fully understood (Belmonte et al. 2009; Viana 2009) and may even not be associated with the presence of pain (Klauenberg et al. 2008). Therefore the significance of cold hypersensitivity in the foot in our patient cohorts with neck-arm pain remains unclear.

Underlying pain mechanisms in patients with nerve-related neck-arm pain differ from those in patients with FM. Patients with FM were characterised by predominantly increased pain sensitivity across nociceptive submodalities in almost

all the body regions tested. Such generalised enhanced sensitivity was not present in our patient groups with neck-arm pain and may be reflective of a more global sensory discriminative dysfunction in patients with FM. Alterations in pain inhibitory (Ingvar 2009; Julien et al. 2005; Lannersten and Kosek 2010) and pain facilitatory mechanisms (Lannersten and Kosek 2010) and central augmentation of sensory input (Banic et al. 2004; Desmeules et al. 2003; Staud et al. 2008) may all account for the enhanced pain sensitivity in patients with FM.

The clinical sign of heightened nerve mechanosensitivity may or may not be associated with NeP. The findings in our patients with NSNAP suggest that the clinical presentation of heightened nerve mechanosensitivity as a discrete disorder does not equate with NeP. However, as already described in section 9.1 (page 9-7), it can coexist with nerve lesions (Chien et al. 2008; Wainner et al. 2003; Wainner et al. 2005) and NeP, as observed in our patients with cervical radiculopathy. In fact, heightened nerve mechanosensitivity in the lower limb, as identified by the straight leg raise test, was reported to be part of a cluster of physical examination discriminative indicators for NeP in lumbar radiculopathy patients (Scholz et al. 2009). A future study will have to investigate, if the presence of heightened nerve mechanosensitivity in the upper limb in patients with cervical radiculopathy (and patients with other nerve-related upper limb pain) may also be identified as a discriminative factor for NeP.

Cluster analyses have been suggested to be useful in determining the positive predictive value of clinical examination findings for the diagnosis of NeP conditions (Scholz et al. 2009; Smart et al. 2011), as well as for clustering pain descriptors to discriminate between different pain types (Baron et al. 2009; Rehm et al. 2010; Scholz et al. 2009). Numerous literature (Haanpää et al. 2011; Hansson 2002; Scholz et al. 2009; Treede et al. 2008) including our findings in this dissertation support the concept that the identification of NeP is not based on single examination test, but on a combination of clinical findings. Combining patient interview and physical examination findings, Scholz et al (2009) developed a new assessment tool for the assessment of NeP in patients with lumbar radiculopathy and axial low back pain. This tool exceeded the diagnostic accuracy of the DN4 in the Scholz patient cohort. Similar to the study by Scholz et al (2009) and based on our findings in this

dissertation, a cluster analysis would be valuable to determine the most discriminative items in patients with nerve-related neck-arm pain, incorporating all criteria for the classification of NeP according to the NeuPSIG grading system, pain descriptors and physical examination findings such as sensory alterations and clinical signs of heightened nerve mechanosensitivity. Such an analysis was not possible in our studied cohorts due to small sample sizes and was considered beyond the scope of the current thesis. However, this is an approach that we will consider as a future research direction.

The significant impact of psychosocial factors on pain and disability in patients with persistent pain has been widely documented (Linton 2000; Linton et al. 2008; Linton et al. ; Vlaeyen et al. 1995). In our studies, the psychometric data were collected in order to better characterise the patient groups with neck-arm pain and to investigate their effect on pain measures (Rhudy and Meagher 2000). Our findings suggest that psychosocial factors did not play a significant role on QST pain measures in our patient cohorts with neck-arm pain. Although both groups demonstrated significantly higher anxiety and depression scores compared to HC, the scores were within the normal range for anxiety in over 75% of patients and for depression in over 91% of patients. Furthermore, the documented association between anxiety and heat sensitivity and depression and mechanical pain sensitivity was evident only for patients with FM, but not for patients with neck-arm pain. Patients with nerve related neck-arm pain did not differ statistically in their score of fear avoidance behaviours, although patients with cervical radiculopathy demonstrated a score of 40.9, just above the score of ≤ 40 that is considered to indicate significant kinesiophobia (Crombez et al. 1999). However, in this context fear avoidance behaviour is appropriate as these patients did demonstrate a nerve lesion and any aggravation of symptoms is may be provocative of further nerve damage and increased NeP. Comorbidities such as anxiety, depression and sleep disturbances are common in patients with nerve-related neck-arm pain and in patients with NeP (Freynhagen et al. 2006a; Saldaña et al. 2010; Starkweather). Recognition of these factors is important in order to provide a holistic approach to the management of these patients.

Considerations for QST measures

Participant's responses to QST may be influenced by factors such as cognitive deficits, fatigue, distraction or intention to deceive (Backonja et al. 2009). The latter was rather unlikely in our patient cohorts, as none of our patients were involved in a current compensation claim. Considering that intense pain can act as a distraction, the patients' pain levels were monitored throughout the testing and adequate breaks were provided. While all participants were able to complete the full QST session, our conclusion is, using the DFNS protocol, not to assess more than 5 body regions (equating to testing of 2.5 hours) to minimize the potential effect of fatigue and inattention on participants' responses. Although blinding of the QST examiner is recommended (Haanpää et al. 2011), for logistic reasons this was not possible in our studies.

9.5   Clinical implications

Evidence from this dissertation indicates that patients with nerve-related neck-arm pain are heterogeneous. Despite patients presenting with similar pain characteristics and sensory symptoms, the clinical presentation and the mix of nociceptive and NeP components varied between the two specific neck-arm pain groups studied and even between individuals within one group. Our patients with cervical radiculopathy were characterised by predominantly NeP components, whereas patients with NSNAP as a discrete disorder demonstrated predominantly nociceptive pain. This information is valuable for health care providers as this may assist in directing treatment to the underlying pain type(s) and ultimately translate as improved patient outcomes.

Our observations suggest that NSNAP as a discrete disorder is not as prevalent as may be commonly thought, and that clinical signs of heightened nerve mechanosensitivity may rather coexist with disorders of nerve lesions than exist in isolation. Similar observations have been reported in patients with low back-related leg pain (Schäfer et al. 2009). However, clinical signs of heightened nerve mechanosensitivity do not equate with NeP and they may or may not be associated with NeP.

In order to determine the aetiology/type of a clinical pain presentation and the dominant underlying pain type(s), each patient should be individually assessed with a comprehensive clinical examination comprising the assessment of musculoskeletal as well as neural structures and a neurological examination including sensory testing in the patient's maximal pain area. In patients with unilateral pain, examination findings should be compared between the symptomatic and asymptomatic side as this comparison will provide information on what is an 'abnormal' finding for the patient. The clinical classification systems for the identification of patients with cervical radiculopathy and patients with NSNAP were shown to be reliable tools and should be used in conjunction. Furthermore, the grading system of NeP (Treede et al. 2008) proved to be a useful guideline for the identification of NeP in patients with neck-arm pain. Although the application of this system may require specific skills, Musculoskeletal Physiotherapists may be well equipped for this task, based on their level of training and clinical reasoning skills.

Clinicians should not rely solely on the patient's pain descriptors, as they do not indicate the aetiology of a pain disorder (Attal et al. 2008) nor is any pain descriptor pathognomonic. Our findings indicate that patients with cervical radiculopathy and patients with NSNAP use pain descriptors common for nociceptive as well as NeP, reflecting the presence of a mixed pain syndrome.

Based on the lower diagnostic accuracy documented in our studies, the LANSS and PD-Q are not useful tools in identifying NeP in patients with neck-arm pain. However, the PD-Q may be used for establishing the somatosensory profile of patients with cervical radiculopathy provided the questionnaire is strictly applied to the patient's symptomatic main pain area.

Patients with nerve-related neck-arm pain do frequently present with comorbidities such as sleep disturbance, anxiety and depression and these factors need to be addressed in a multidimensional approach to the patient's pain management.

9.6   Directions for future research

In consideration of the research findings presented in this thesis and the acknowledged limitations of the studies, the following recommendations are made:

- A larger study with greater power is required to confirm the preliminary QST findings presented for patients with cervical radiculopathy, patients with NSNAP and HC. This should also include a larger sample size of HC subjects to allow generalisability. A greater number in each patient group will allow further determination of specific sub-groups within each patient cohort.

- A future study should consider a cluster analysis of clinical examination findings, incorporating pain characteristics/pain descriptors, physical examination findings including sensory testing and responses to neural provocation tests and possibly results of NeP screening tools, to determine the most discriminative items for the identification of NeP in patients with neck-arm pain.

- In order to determine further the usefulness of NeP screening tools in the identification of NeP in patients with neck-arm pain of mixed pain type, a future study should aim to define the pain descriptors that are able to discriminate NeP from non-NeP in these patient cohorts and to analyse the appropriate cut-off values of LANSS and PD-Q for discriminating NeP in this patient cohort.

- If the PD-Q is to be used in further studies, its reliability has to be established in order to strengthen its validity. It might be valuable to compare the outcome of PD-Q when patients are provided specific instructions on how to complete the questionnaire, compared to the current format which does not provide instruction.

- In order to support the use of the PD-Q as a tool for characterisation of somatosensory profiles, a future study should explore if self-reported responses match with clinical examination findings.

- To help inform the development of targeted interventions for patients with musculoskeletal conditions and NeP, further research should investigate the confidence of primary care health practitioners in identifying NeP and, in case of lack of confidence, establish what may be needed to improve the shortcoming.

9.7   Conclusion

The series of studies conducted in this doctoral thesis has highlighted the heterogeneity of patients with nerve-related neck-arm pain in regard to their clinical presentations as well as pain characteristics, somatosensory profiles and dominant underlying pain types. This heterogeneity exists, not only between patients with differing aetiology, such as patients with cervical radiculopathy and patients with NSNAP, but also in patients with the same aetiology. The enhanced knowledge gained about these pain presentations and their underlying pain mechanisms may assist clinicians in "matching" interventions to patients with the potential for better clinical outcome. Furthermore, the findings of this thesis have contributed to the reliability and validity of clinical classification systems used to identify patients with painful cervical radiculopathy and patients with NSNAP, and to identify NeP in patients with nerve-related neck-arm pain.

9.8   References

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APPENDIX 1

ETHICAL APPROVALS

Curtin
University of Technology

Office of Research and Development

memorandum

To	A/Prof Kathy Briffa, Physiotherapy
From	A/Professor Stephan Millett, Executive Officer, Human Research Ethics Committee
Subject	Protocol Approval **HR 117/2007**
Date	8 October 2007
Copy	Brigitte van der Heide, Physiotherapy Graduate Studies Officer, Faculty of Health Sciences

Human Research Ethics Committee

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin edu au

Thank you for your application submitted to the Human Research Ethics Committee (HREC) for the project titled "*Investigation of somatosensory characteristics in patients with neck/upper limb pain*". Your application has been reviewed by the HREC and is **approved**.

- You are authorised to commence your research as stated in your proposal.
- The approval number for your project is **HR 117/2007.** *Please quote this number in any future correspondence.*
- Approval of this project is for a period of twelve months **02-10-2007** to **02-10-2008.** To renew this approval a completed Form B (attached) must be submitted before the expiry date **02-10-2008**
- If you are a Higher Degree by Research student, data collection must not begin before your Application for Candidacy is approved by your Divisional Graduate Studies Committee.
- The following standard statement **must be** included in the information sheet to participants:

This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. Its main role is to protect participants. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au.

Applicants should note the following:

It is the policy of the HREC to conduct random audits on a percentage of approved projects. These audits may be conducted at any time after the project starts. In cases where the HREC considers that there may be a risk of adverse events, or where participants may be especially vulnerable, the HREC may request the chief investigator to provide an outcomes report, including information on follow-up of participants.

The attached **FORM B** should be completed and returned to the Secretary, HREC, C/- Office of Research & Development:
When the project has finished, or
- If at any time during the twelve months changes/amendments occur, or
- If a serious or unexpected adverse event occurs, or
- 14 days prior to the expiry date if renewal is required.
- An application for renewal may be made with a Form B three years running, after which a new application form (Form A), providing comprehensive details, must be submitted.

Regards,

A/Professor Stephan Millett
Executive Officer
Human Research Ethics Committee

Department of
Health

Sir Charles
Gairdner Hospital

Ethics Ref: 2007-185a
Ext 2999

7 February 2008

Dr Roger Goucke
Pain Management
Sir Charles Gairdner Hospital
Hospital Ave
NEDLANDS WA 6009

Dear Dr Roger Goucke

APPLICATION TO CONDUCT HUMAN RESEARCH AT SCGH:
TRIAL 2007-185 Investigation of Somatosensory Characteristics in Patients with Neck/Upper Limb Pain

I am happy to provide approval to conduct your research project at SCGH based on the favourable reviews provided to me by the Research Governance Unit and the Sir Charles Gairdner Hospital Human Research Ethics Committee.   This approval is granted until 30 January 2010, and on the basis of compliance with all requirements laid out in your application and with the provision of reports as required by the RGU and approving HREC in giving their favourable opinion (attached).

The responsibility for the conduct of this study remains with you as the Principle Investigator. You must notify the Research Governance Unit of any relevant issues arising during the conduct of the study that may affect continued favourable opinions by the hospital or by an HREC.

Please quote Study number 2007-185 on all correspondence associated with this study.

Yours sincerely

DR PETER BENTLEY
Acting Executive Director Medical Services
Sir Charles Gairdner Group
North Metropolitan Health Service

1 1 FEB 2008

A1-4

Department of
Health
Ethic Ref: QI Projects / 2109
Ext: 2999

Sir Charles
Gairdner Hospital

22 August 2008

Dr Roger Goucke
Pain Management
Lower Ground G Block
Sir Charles Gairdner Hospital
Hospital Ave
NEDLANDS   WA   6009

Dear Dr Goucke

QUALITY IMPROVEMENT No 2109:
**TITLE: Comparison of the LANSS Pain Scale and painDETECT questionnaires
in the diagnosis of neuropathic pain**

The above quality improvement project has been determined to be of negligible risk
by the Sir Charles Gairdner Hospital Human Research Ethics Committee. Therefore
the project, as per the National Statement on Ethical Conduct in Human Research
(5.1.22), is exempt from review. It was tabled at the HREC meeting on 21 August
2008.

Please quote number 2109 on all correspondence sent to the Human Research Ethics
Committee Office.

Yours sincerely

DR FELICITY FLACK
DELEGATE OF THE CHAIR
HUMAN RESEARCH ETHICS COMMITTEE

A1-4

Department of Health
Government of Western Australia

South Metropolitan Area Health Service
Human Research Ethics Committee

md
22 October 2008

Ms Brigitte Tampin
Musculoskeletal Physiotherapist
School of Physiotherapy
Curtin University of Technology
GPO Box U1987
Perth WA 6845

Dear Brigitte,

Re: Investigation of Somatosensory Characteristics in Patients with Neck/ Upper Limb Pain

Further to my correspondence dated 24th September 2008, I have now received a copy of the Patient Invitation Letter that will be used to recruit patients who have already attended the Pain Service at Fremantle Hospital.

I have perused the document provided and am happy to approve it on behalf of the SMAHS HREC using Chair's discretion.

Please quote the following reference number on any future correspondence with the Committee regarding this protocol: **C/08/414.**

Yours sincerely

DR WINTON BARNES
ACTING CHAIRMAN
HUMAN RESEARCH ETHICS COMMITTEE

cc: Dr S Davies (FHHS)
Executive Officer, Curtin University HREC (Ref No. HR 117/2007)

Department of Health
Government of Western Australia

South Metropolitan Area Health Service
Human Research Ethics Committee

Wk
C/08/414
23 December 2008

Ms Brigitte Tampin
Musculoskeletal Physiotherapist
School of Physiotherapy
Curtin University of Technology
GPO Box U1987
Perth WA 6845

Dear Brigitte,

Re: **Investigation of Somatosensory Characteristics in Patients with Neck/ Upper Limb Pain**

I am writing further to my correspondence dated 24 September 2008, approving the above study under the reciprocal agreement. The SMAHS HREC Office has recently received an email from Dr Reg Andrews, Deputy Director, Clinical Services at Bentley Health Service, advising that he is happy for patients to be recruited to the above study from the Bentley Physiotherapy Department and I understand that Kelly Simpson and Andrew Walton from that Department are happy to assist. You may, therefore, now commence recruitment at Bentley Hospital.

Please quote the following reference number on any future correspondence with the Committee regarding this protocol: **C/08/414.**
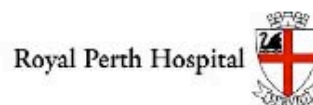
Yours sincerely

DR WINTON BARNES
ACTING CHAIRMAN
HUMAN RESEARCH ETHICS COMMITTEE

cc: Ms Kelly Simpson, Physiotherapy, BHS
Mr Andrew Walton, Physiotherapy, BHS
Executive Officer, Curtin University HREC (Ref No. HR 117/2007)

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Department of Health
Government of Western Australia
South Metropolitan Area Health Service

Royal Perth Hospital

ETHICS COMMITTEE

Prof F M Van Bockxmeer PhD, MHGSA, ARPCA, FAHA
Pathwest Laboratory Medicine
Tel: 9224 2322 Fax: 9224 2491
Email: Frank.VB@health.wa.gov.au

Room 4112 Level 4, Kirkman House
Tel: 9224 2292

Ref: EC RA-09/008
(This number must be quoted on all correspondence)

2nd April 2009

Dr Helen Slater
Pain Medicine Centre
Royal Perth Hospital

Brigitte Tampin
PhD Candidate
School of Physiotherapy
Curtin University

Dear Helen and Bri

EC RA-09/008 Investigation of somatosensory characteristics in patients with neck/upper limb pain

I am pleased to advise that the Ethics Committee at Royal Perth Hospital has approved the above project under its reciprocal agreement with the Sir Charles Gairdner Hospital (SCGH) Human Research Ethics Committee (HREC) (their Ref: **2007-185**). Under the reciprocal agreement, approval of protocol amendments and reporting of adverse events will be the responsibility of the parent committee providing approval, that is, the SCGH HREC.

The RPH Committee is obliged by the provisions of the revised "National Statement" of the NH&MRC (2007) to monitor progress of all studies until completion. Therefore, this approval is granted on the understanding that you will *advise of any protocol amendments and submit an annual report to the Committee.*

The study has been assigned the RPH reference number **RA-09/008** and this should be quoted on all future correspondence regarding the trial.

Yours sincerely

Prof Frank van Bockxmeer
Chairman, Royal Perth Hospital Ethics Committee

The Royal Perth Hospital Ethics Committee is constituted and operates in accordance with NHC & MRC Guidelines. An Annual Report on the progress of your trial will be required (see Committee explanatory notes available on Servio)

Copy: Felicity Flack (SCGH HREC)

APPENDIX 2

PATIENT INFORMATION SHEETS

AND

CONSENT FORMS

Curtin University

Division of Health Sciences
School of Physiotherapy

Telephone +61 8 9266 3618
Facsimile +61 8 9266 3699
Email physio@curtin.edu.au
Web www.physiotherapy.curtin.edu.au

PATIENT INFORMATION SHEET

Study A
Project title: Do physiotherapists agree on a diagnosis for patients with neck and arm pain?

Principal Investigator: Brigitte Tampin, PhD student
Project Supervisor: A/Prof Kathy Briffa
Co-Supervisor: Dr Helen Slater

Purpose of Research
There are a number of different reasons why people can have neck and arm pain. It is important to identify the cause of the pain so that treatment can be directed at the specific cause. Physiotherapists use certain examination protocols for the assessment of patients with neck/arm pain, but the interpretation of their findings might vary between therapists. The purpose of this study is to examine if two experienced physiotherapists come to the same conclusion about the cause of your pain.

Your role
You will be examined by two qualified and experienced physiotherapists (the principal investigator and one other) on two separate occasions. Each examination will take approximately one hour. Your medical history will be taken and a physical examination conducted. This will involve the assessment of movements of your neck and arm and a range of tests of sensation in the neck and arm. All tests will only be performed just to the point of pain onset.

Risks and Discomforts
You may experience some very momentary discomfort during the testing of sensations. You may also experience some minor increase of symptoms similar to what you might expect after a standard physiotherapy treatment.

Benefits
Physiotherapists need to diagnose patients with neck/arm pain accurately so that the correct treatment can be given to these patients. Although the results of this study will importantly add to the body of knowledge in diagnosing patients with neck/arm pain, the examination you will undertake and the results gained will probably not directly benefit you, but aim to benefit the

wider clinical population by assisting physiotherapists in making accurate diagnoses.

Confidentiality

You will be issued a study number instead of using your name, which will remain confidential to the principle investigator and the project supervisors. All the data (information) recorded will be stored on computer within the School of Physiotherapy, Curtin University of Technology. Access to this information will be via password only. This password will only be known to the principal investigator and to the project supervisors. The results of this study will be reported, but it will not be possible to identify individual subjects. Following the study period, the data will be held in a secure place for 7 years. After this time it will be destroyed. This is a requirement of Curtin University of Technology.

Refusal or Withdrawal

If you consent to participate in this study, you will be free to withdraw at any time, without fear of prejudice. If you do decide to withdraw from the study you would be asked to contact the Principle Investigators at the earliest opportunity. In the event that you withdraw, all of your data would be destroyed.

Further Information

This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. Its main role is to protect participants. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au

If you would like further information about the study, please feel free to contact me on 9266 3667 or 0409 883 548 or by email: brigitte.tampin@postgrad.curtin.edu.au. Alternatively, you can contact my supervisor A/Prof Kathy Briffa on 9266 3666 or by email: K.Briffa@exchange.curtin.edu.au or my co-supervisor Dr Helen Slater on 9266 3099, or by email: H.Slater@curtin.edu.au

Thank you very much for your involvement in this research, your participation is greatly appreciated.

Curtin University

Division of Health Sciences
School of Physiotherapy

Telephone **+61 8 9266 3618**
Facsimile **+61 8 9266 3699**
Email physio@curtin.edu.au
Web www.physiotherapy.curtin.edu.au

CONSENT SHEET

Investigation of somatosensory characteristics in patients with neck/upper limb pain.

This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007).

I _____ consent to participate in this study. I have read the Information Sheet and understand the consequences and risks associated with participation in the study. The Principal Investigators has answered my questions regarding all aspects of the study. I understand that all information provided is treated as confidential. I give my permission for any results from this study to be used in any report or research paper, on the understanding that anonymity will be preserved. I understand that I retain the right to withdraw from this study at any time, and without prejudice. I undertake to contact the Researcher (**Tel: 9266-3667**) at the earliest opportunity should I wish to exercise this right. On withdrawal of my consent I understand that my data will be destroyed.

Signature:_____Date:_____

Investigator:_____Signature_____

SIR CHARLES GAIRDNER HOSPITAL

Participant Information Sheet

Study title: Do physiotherapists agree on a diagnosis for patients with neck and arm pain?

Principal Investigator: Brigitte Tampin, PhD student
Project Supervisor: A/Prof Kathy Briffa
Co-Supervisor: Dr Helen Slater
SCGH Investigator: Dr Roger Goucke

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study?
Brigitte Tampin is supported in her study by a postgraduate scholarship from the National Health and Medical Research Council of the Australian Government

Contact persons:
Should you have questions about the study you may contact:

Brigitte Tampin   Phone No. 9266 3667, 0409 883 548
                              After hours: 0409 883 548
A/Prof Kathy Briffa   Phone No. 9266 3666
Dr Helen Slater   Phone No. 9266 3099
Dr Roger Goucke   Phone No.   9346 3263

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve.

Whatever your decision, this decision <u>will not</u> lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

The following information sheet will explain the study and will include details such as:
- o Why this study might be suitable for you;
- o The type, frequency and risks of any tests or procedures required by the study;
- o The nature of your participation including how many visits you will make to the hospital;
- o Your rights and responsibilities.

What is the purpose of the study?

There are a number of different reasons why people can have neck and arm pain. It is important to identify the cause of the pain so that treatment can be directed at the specific cause. Physiotherapists use certain examination protocols for the assessment of patients with neck/arm pain, but the interpretation of their findings might vary between therapists. The purpose of this study is to examine if two experienced physiotherapists come to the same conclusion about the cause of your pain and if their conclusion is supported by the judgement of a neurologist and a specialist in musculoskeletal therapy.

Why is this study suitable to me?

You have been experiencing neck and/or arm pain for a longer time and you have been referred to see a neurosurgeon at Sir Charles Gairdner Hospital. Your name has been registered on a waiting list, however waiting times for an appointment can amount to over a year. The hospital has set up a Comprehensive Spinal Care Clinic, comprising of a neurosurgeon, pain specialist and a physiotherapist, in order to reduce these long waiting periods. Patients are initially assessed by a highly qualified and experienced physiotherapist who will then discuss further management with the patient and refer them on to the medical specialists, if needed.

This research study will give you the opportunity to reduce your waiting time for an appointment. You will be examined by a physiotherapist as mentioned above. However you are under no obligation to take part in the study as outlined in the next paragraph.

How long will I be in this study?

You would have to attend the Department of Pain Management at Sir Charles Gairdner Hospital or the Physiotherapy Clinic at the School of Physiotherapy, Curtin University of Technology, whichever one is more convenient to you. You will be examined independently by two physiotherapists; each assessment will take about one hour. It might be possible to schedule your visit in such a way that your assessments will be performed on the same day, one after the other, which would mean you only have to attend once for two hours in total. Otherwise your assessments will be on two different days for one hour.

What will happen if I decide to be in this study?

You will be examined by two qualified and experienced physiotherapists (the principal investigator and one other) on two independent consultations. Each examination will take approximately one hour. Your medical history will be taken and a physical examination conducted. This will involve the assessment

of movements of your neck and arm and a range of tests of sensation in the neck and arm. All tests will only be performed just to the point of pain onset.

After your visit, the clinical notes which the physiotherapists took during your consultation, might be given to a neurologist and to a specialist in musculoskeletal therapy for further diagnostic opinion.

Are there any reasons I should not be in this study?:
The physiotherapy assessment is an examination which is standard clinical practice in any Physiotherapy department. The principal investigator will discuss with you any exclusion criteria in detail and will be directed at ensuring that the examination is both safe and appropriate for you.

What are the costs to me?
There will be no charge for the examination by the two physiotherapists. Transport to and from the clinic where examination will take place will not be provided.

What are the possible benefits of taking part?
Physiotherapists need to diagnose patients with neck/arm pain accurately so that the correct treatment can be given to these patients. Although the results of this study will importantly add to the body of knowledge in diagnosing patients with neck/arm pain, the results gained will probably not directly benefit you, but aim to benefit future patients by assisting physiotherapists in making accurate diagnoses.

However, the clinical examination which is performed by highly qualified physiotherapists would benefit you. By taking part in this study, you would reduce your waiting time for an appointment at the Department of Pain Management plus you will be given advice and direction on further management of your neck/arm pain.

What are the possible side effects, risks and discomforts of taking part?
You may experience some very momentary discomfort during the testing of sensations. You may also experience some minor increase of symptoms similar to what you might expect after a standard physiotherapy treatment.

Will my taking part in this study be kept confidential?
The researchers will need to collect personal data about you, which may be sensitive, e.g. date of birth and relevant health information. The researchers may also need to get some of your health information from other health service providers, e.g another hospital, pathology laboratory, radiographer, GP or other medical specialist.

Any personal or health information will be kept private and confidential. It will be stored securely and only authorised persons, who understand it must be kept confidential, will have access to it. Your study details will be given a number so that your identity will not be apparent. The clinical notes taken during your examination will be kept at the School of Physiotherapy at Curtin University of Technology during the study and in a locked archive for 5 years from the time the study is closed. After this time they will be destroyed. This is

a requirement of Curtin University of Technology. Some data/information will be stored on a computer at the School of Physiotherapy at Curtin University of Technology. Access to this information will be via password only. This password will only be known to the principal investigator and to the project supervisors.

Authorised representatives of the Hospital Human Research Ethics Committee, and Research Governance may require access to your study records to verify study procedures and/or data. In all cases when dealing with your information, these people are required to comply with privacy laws that protect you.

The results of the research will be made available to other health professionals through medical journals or meetings, but you will not be identifiable in these communications. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

Will I find out the results of the study?
A summary of the study findings will be forwarded to each participant.

Who has reviewed the study?
The Sir Charles Gairdner Hospital Human Research Ethics Committee has reviewed this study and has given its approval for the conduct of this research. In doing so this study conforms to the principles set out by the National Statement on Ethical Conduct in Research involving Humans and according to the Good Clinical Practice Guidelines.

This study has also been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au

CONSENT FORM

Do physiotherapists agree on a diagnosis for patients with neck and arm pain?

Investigators: Brigitte Tampin, A/Prof Kathy Briffa, Dr. Helen Slater, Dr Roger Goucke

Participant Name:_____

Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.
2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.
3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.
4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to your principal investigator before signing this Consent Form.

_____
Name of Participant   Signature of Participant   Date

_____
Name of Investigator   Signature of Investigator   Date

The Sir Charles Gairdner Hospital Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact the secretary of the Sir Charles Gairdner Hospital Human Research Ethics Committee on telephone No. (08) 9346.2999

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

FREMANTLE HOSPITAL

Participant Information Sheet

Study title: Do physiotherapists agree on a diagnosis for patients with neck and arm pain?

Principal Investigator: Brigitte Tampin, PhD student
Project Supervisor: A/Prof Kathy Briffa
Co-Supervisor: Dr Helen Slater
SMHAS Investigators: Dr Stephanie Davies
                        Stuart Waters

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study?
Brigitte Tampin is supported in her study by a postgraduate scholarship from the National Health and Medical Research Council of the Australian Government

Contact persons:
Should you have questions about the study you may contact:

Brigitte Tampin   Phone No.   9266 3667, 0409 883 548
                          After hours: 0409 883 548
A/Prof Kathy Briffa   Phone No. 9266 3666
Dr Helen Slater   Phone No.   9266 3099
Dr Stephanie Davies   Phone No. 9431 3296
Stuart Waters   Phone No. 9431 2533

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve.

Whatever your decision, this decision <u>will not</u> lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

The following information sheet will explain the study and will include details such as:
- o Why this study might be suitable for you;
- o The type, frequency and risks of any tests or procedures required by the study;
- o The nature of your participation including how many visits you will make to the hospital;
- o Your rights and responsibilities.

What is the purpose of the study?
There are a number of different reasons why people can have neck and arm pain. It is important to look for possible factors contributing to pain so that treatment can be directed at these factors. Physiotherapists use certain examination protocols for the assessment of patients with neck/arm pain, but the interpretation of their findings might vary between therapists. The purpose of this study is to examine if two experienced physiotherapists come to the same conclusion about the cause of your pain and if their conclusion is supported by the judgement of a neurosurgeon and a specialist in musculoskeletal therapy.

Why is this study suitable to me?
You are invited to take part in this study as you experience one sided neck and/or arm pain. Your participation would give you the opportunity to be examined by two very qualified and experienced physiotherapists who will give you feedback on their diagnosis and advice on further management of your neck/arm pain.

How long will I be in this study?
You would have to attend Fremantle Hospital or the School of Physiotherapy, Curtin University of Technology or the principal investigator's Physiotherapy Practice in Fremantle, whichever one is more convenient to you. You will be examined independently by two physiotherapists; each assessment will take about one hour. It might be possible to schedule your visit in such a way that your assessments will be performed on the same day, one after the other, which would mean you only have to attend once for two hours in total. Otherwise your assessments will be on two different days for one hour.

What will happen if I decide to be in this study?
You will be examined independently by two qualified and experienced physiotherapists (the principal investigator and one other). Each examination will take approximately one hour. Your medical history will be taken and a physical examination conducted. This will involve the assessment of movements of your neck and arm and a range of tests of sensation in the neck and arm. All tests will only be performed just to the point of pain onset. After your visit, the clinical notes which the physiotherapists took during your consultation, will be given to a neurosurgeon and to a specialist in musculoskeletal therapy for further diagnostic opinion.

Are there any reasons I should not be in this study?
The physiotherapy assessment is an examination which is standard clinical practice in any Physiotherapy department. The principal investigator will discuss with you any exclusion criteria in detail and will be directed at ensuring that the examination is both safe and appropriate for you.

What are the costs to me?
There will be no charge for the examination by the two physiotherapists. Transport to and from the clinic where examination will take place will not be provided, however your travel expenses will be reimbursed with a $20 voucher.

What are the possible benefits of taking part?
Physiotherapists need to diagnose patients with neck/arm pain accurately so that the correct treatment can be given to these patients. Although the results of this study will importantly add to the body of knowledge in diagnosing patients with neck/arm pain, the results gained will probably not directly benefit you, but aim to benefit future patients by assisting physiotherapists in making accurate diagnoses.

However, the clinical examination which is performed by highly qualified physiotherapists would benefit you. You will be given advice and direction on further management of your neck/arm pain.

What are the possible side effects, risks and discomforts of taking part?
You may experience some very momentary discomfort during the testing of sensations. You may also experience some minor increase of symptoms similar to what you might expect after a standard physiotherapy treatment.

Will my taking part in this study be kept confidential?
The researchers will need to collect personal data about you, which may be sensitive, e.g. date of birth and relevant health information. The researchers may also need to get some of your health information from other health service providers, e.g another hospital, pathology laboratory, radiographer, GP or other medical specialist.

Any personal or health information will be kept private and confidential. It will be stored securely and only authorised persons, who understand it must be kept confidential, will have access to it. Your study details will be given a number so that your identity will not be apparent. The clinical notes taken during your examination will be kept at the School of Physiotherapy at Curtin University of Technology during the study and in a locked archive for 5 years from the time the study is closed. After this time they will be destroyed. This is a requirement of Curtin University of Technology. Some data/information will be stored on a computer at the School of Physiotherapy at Curtin University of Technology. Access to this information will be via password only. This password will only be known to the principal investigator and to the project supervisors.

Authorised representatives of the Hospital Human Research Ethics Committee, and Research Governance may require access to your study records to verify study procedures and/or data. In all cases when dealing with your information, these people are required to comply with privacy laws that protect you.

The results of the research will be made available to other health professionals through medical journals or meetings, but you will not be identifiable in these communications. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

Will I find out the results of the study?
A summary of the study findings will be forwarded to each participant.

Who has approved the study?
The South Metropolitan Area Health Service Human Research Ethics
Committee has given approval for the conduct of this research. In doing so this study conforms to the principles set out by the National Statement on Ethical Conduct in Human Research and according to the Good Clinical Practice Guidelines.
This study has also been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au

CONSENT FORM

Do physiotherapists agree on a diagnosis for patients with neck and arm pain?

Investigators: Brigitte Tampin, A/Prof Kathy Briffa, Dr. Helen Slater, Dr Stephanie Davies, Stuart Waters

Participant Name:_____

Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.
2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.
3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.
4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to your principal investigator before signing this Consent Form.

_____
Name of Participant   Signature of Participant   Date

_____
Name of Investigator   Signature of Investigator   Date

The South Metropolitan Area Health Service Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact the Chair of the SMHAS Human Research Ethics Committee on telephone No. (08) 9431 2929.

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

Patient invitation letter Fremantle Hospital

Curtin University

Research on neck/arm pain of nerve origin

Dear…

The Pain Medicine Unit at Fremantle Hospital and Health Service is working with the School of Physiotherapy at Curtin University of Technology to conduct research in patients with neck and arm pain of nerve origin. We have identified that you experience neck and arm pain and therefore would like to invite you to take part in one of our research studies. Both studies have been approved by the South Metropolitan Area Health Service Human Research Ethics Committee and the Human Research Ethics Committee at Curtin University. They are supported by the National Health and Medical Research Council, by Arthritis Australia and the Physiotherapy Research Foundation.

Study A

There are a number of different reasons why people can have neck and arm pain. It is important to look for possible factors contributing to pain so that treatment can be directed at these specific factors. Physiotherapists use certain examination protocols for the assessment of patients with neck/arm pain, but the interpretation of their findings might vary between therapists. The purpose of this study is to examine if two experienced physiotherapists come to the same conclusion about the cause of your pain and if their conclusion is supported by the judgement of a neurosurgeon and a specialist in musculoskeletal therapy.

For this study we are seeking volunteers who experience one-sided neck and arm pain or neck pain with tingling/numbness in their arm/hand. Participants will be examined independently by two highly qualified and experienced physiotherapists; each assessment will take about one hour.

Study B

We are looking for people who have experienced one-sided neck pain with symptoms such as pain, numbness/tingling and/or weakness in their arm/hand for the last 3 to 12 months. Participants have to be between 18 and 65 years of age. Once they have been screened for specific inclusion criteria they will undergo a comprehensive protocol of sensation testing (testing sensitivity to heat and cold, to light touch and pressure, to pin–prick and vibration) which will be conducted at the School of Physiotherapy at Curtin University. The aim of this research is to examine how a pinched or irritated nerve may affect the nervous system and compare it to other conditions.

In the next few weeks, Brigitte Tampin from the School of Physiotherapy will call you and ask you if you might be interested to participate. While you are not obliged to participate, we hope that you choose to do so. The information collected aims to assist clinicians in diagnosing patients with pain of nerve origin so that appropriate treatment can be given.

If you would like to receive further information on the projects, or do not wish to be called, please contact Brigitte Tampin on 9266 3667 or email: brigitte.tampin@postgrad.curtin.edu.au. She will be happy to answer your questions.

We really appreciate your assistance.

Yours sincerely

Dr Stephanie Davies
Head of Service
Pain Medicine Unit
Fremantle Hospital Health Service

Brigitte Tampin
Musculoskeletal Physiotherapist
School of Physiotherapy
Curtin University of Technology

Funded by:

Australian Government
National Health and Medical Research Council

Arthritis
AUSTRALIA

Physiotherapy Research Foundation

BENTLEY HOSPITAL

Participant Information Sheet

Study title: Do physiotherapists agree on a diagnosis for patients with neck and arm pain?

Principal Investigator:	**Brigitte Tampin, PhD student**
Project Supervisor:	**A/Prof Kathy Briffa**
Co-Supervisor:	**Dr Helen Slater**
SMHAS Investigators:	**Andrew Walton**

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study?

Brigitte Tampin is supported in her study by a postgraduate scholarship from the National Health and Medical Research Council of the Australian Government

Contact persons:
Should you have questions about the study you may contact:

Brigitte Tampin	Phone No.	9266 3667, 0409 883 548
	After hours:	0409 883 548
A/Prof Kathy Briffa	Phone No.	9266 3666
Dr Helen Slater	Phone No.	9266 3099
Andrew Walton	Phone No.	93343777

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve.

Whatever your decision, this decision <u>will not</u> lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

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- o Your rights and responsibilities.

What is the purpose of the study?

There are a number of different reasons why people can have neck and arm pain. It is important to look for possible factors contributing to pain so that treatment can be directed at these factors. Physiotherapists use certain examination protocols for the assessment of patients with neck/arm pain, but the interpretation of their findings might vary between therapists. The purpose of this study is to examine if two experienced physiotherapists come to the same conclusion about the cause of your pain and if their conclusion is supported by the judgement of a neurosurgeon and a specialist in musculoskeletal therapy.

Why is this study suitable to me?

You are invited to take part in this study as you experience one sided neck and/or arm pain. Your participation would give you the opportunity to be examined by two very qualified and experienced physiotherapists who will give you feedback on their diagnosis and advice on further management of your neck/arm pain.

How long will I be in this study?

You would have to attend Fremantle Hospital or the School of Physiotherapy, Curtin University of Technology or the principal investigator's Physiotherapy Practice in Fremantle, whichever one is more convenient to you. You will be examined independently by two physiotherapists; each assessment will take about one hour. It might be possible to schedule your visit in such a way that your assessments will be performed on the same day, one after the other, which would mean you only have to attend once for two hours in total. Otherwise your assessments will be on two different days for one hour.

What will happen if I decide to be in this study?

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Are there any reasons I should not be in this study?
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Physiotherapists need to diagnose patients with neck/arm pain accurately so that the correct treatment can be given to these patients. Although the results of this study will importantly add to the body of knowledge in diagnosing patients with neck/arm pain, the results gained will probably not directly benefit you, but aim to benefit future patients by assisting physiotherapists in making accurate diagnoses.

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Will my taking part in this study be kept confidential?
The researchers will need to collect personal data about you, which may be sensitive, e.g. date of birth and relevant health information. The researchers may also need to get some of your health information from other health service providers, e.g another hospital, pathology laboratory, radiographer, GP or other medical specialist.

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This study has also been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au

CONSENT FORM

Do physiotherapists agree on a diagnosis for patients with neck and arm pain?

Investigators: Brigitte Tampin, A/Prof Kathy Briffa, Dr. Helen Slater, Andrew Walton

Participant Name:_____

Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.
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4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to your principal investigator before signing this Consent Form.

Name of Participant	Signature of Participant	Date

Name of Investigator	Signature of Investigator	Date

The South Metropolitan Area Health Service Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact the Chair of the SMHAS Human Research Ethics Committee on telephone No. (08) 9431 2929.

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records

ROCKINGHAM HOSPITAL

Participant Information Sheet

Study title: Do physiotherapists agree on a diagnosis for patients with neck and arm pain?

Principal Investigator: **Brigitte Tampin, PhD student**
Project Supervisor: **A/Prof Kathy Briffa**
Co-Supervisor: **Dr Helen Slater**
SMHAS Investigators: **David Veldman**

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study?
Brigitte Tampin is supported in her study by a postgraduate scholarship from the National Health and Medical Research Council of the Australian Government

Contact persons:
Should you have questions about the study you may contact:

Brigitte Tampin   Phone No.   9266 3667, 0409 883 548
                             After hours: 0409 883 548
A/Prof Kathy Briffa   Phone No.   9266 3666
Dr Helen Slater   Phone No.   9266 3099
David Veldman   Phone No.   9592 0762

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve.

Whatever your decision, this decision will not lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

The following information sheet will explain the study and will include details such as:
- o Why this study might be suitable for you;
- o The type, frequency and risks of any tests or procedures required by the study;
- o The nature of your participation including how many visits you will make to the hospital;
- o Your rights and responsibilities.

What is the purpose of the study?
There are a number of different reasons why people can have neck and arm pain. It is important to look for possible factors contributing to pain so that treatment can be directed at these factors. Physiotherapists use certain examination protocols for the assessment of patients with neck/arm pain, but the interpretation of their findings might vary between therapists. The purpose of this study is to examine if two experienced physiotherapists come to the same conclusion about the cause of your pain and if their conclusion is supported by the judgement of a neurosurgeon and a specialist in musculoskeletal therapy.

Why is this study suitable to me?
You are invited to take part in this study as you experience one sided neck and/or arm pain. Your participation would give you the opportunity to be examined by two very qualified and experienced physiotherapists who will give you feedback on their diagnosis and advice on further management of your neck/arm pain.

How long will I be in this study?
You would have to attend Fremantle Hospital or the School of Physiotherapy, Curtin University of Technology or the principal investigator's Physiotherapy Practice in Fremantle, whichever one is more convenient to you. You will be examined independently by two physiotherapists; each assessment will take about one hour. It might be possible to schedule your visit in such a way that your assessments will be performed on the same day, one after the other, which would mean you only have to attend once for two hours in total. Otherwise your assessments will be on two different days for one hour.

What will happen if I decide to be in this study?
You will be examined independently by two qualified and experienced physiotherapists (the principal investigator and one other). Each examination will take approximately one hour. Your medical history will be taken and a physical examination conducted. This will involve the assessment of movements of your neck and arm and a range of tests of sensation in the neck and arm. All tests will only be performed just to the point of pain onset. After your visit, the clinical notes which the physiotherapists took during your consultation, will be given to a neurosurgeon and to a specialist in musculoskeletal therapy for further diagnostic opinion.

Are there any reasons I should not be in this study?
The physiotherapy assessment is an examination which is standard clinical practice in any Physiotherapy department. The principal investigator will discuss with you any exclusion criteria in detail and will be directed at ensuring that the examination is both safe and appropriate for you.

What are the costs to me?
There will be no charge for the examination by the two physiotherapists. Transport to and from the clinic where examination will take place will not be provided, however your travel expenses will be reimbursed with a $20 voucher.

What are the possible benefits of taking part?
Physiotherapists need to diagnose patients with neck/arm pain accurately so that the correct treatment can be given to these patients. Although the results of this study will importantly add to the body of knowledge in diagnosing patients with neck/arm pain, the results gained will probably not directly benefit you, but aim to benefit future patients by assisting physiotherapists in making accurate diagnoses.

However, the clinical examination which is performed by highly qualified physiotherapists would benefit you. You will be given advice and direction on further management of your neck/arm pain.

What are the possible side effects, risks and discomforts of taking part?
You may experience some very momentary discomfort during the testing of sensations. You may also experience some minor increase of symptoms similar to what you might expect after a standard physiotherapy treatment.

Will my taking part in this study be kept confidential?
The researchers will need to collect personal data about you, which may be sensitive, e.g. date of birth and relevant health information. The researchers may also need to get some of your health information from other health service providers, e.g another hospital, pathology laboratory, radiographer, GP or other medical specialist.

Any personal or health information will be kept private and confidential. It will be stored securely and only authorised persons, who understand it must be kept confidential, will have access to it. Your study details will be given a number so that your identity will not be apparent. The clinical notes taken during your examination will be kept at the School of Physiotherapy at Curtin University of Technology during the study and in a locked archive for 5 years from the time the study is closed. After this time they will be destroyed. This is a requirement of Curtin University of Technology. Some data/information will be stored on a computer at the School of Physiotherapy at Curtin University of Technology. Access to this information will be via password only. This password will only be known to the principal investigator and to the project supervisors.

Authorised representatives of the Hospital Human Research Ethics Committee, and Research Governance may require access to your study records to verify study procedures and/or data. In all cases when dealing with your information, these people are required to comply with privacy laws that protect you.

The results of the research will be made available to other health professionals through medical journals or meetings, but you will not be identifiable in these communications. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

Will I find out the results of the study?
A summary of the study findings will be forwarded to each participant.

Who has approved the study?
The South Metropolitan Area Health Service Human Research Ethics
Committee has given approval for the conduct of this research. In doing so this study conforms to the principles set out by the National Statement on Ethical Conduct in Human Research and according to the Good Clinical Practice Guidelines.

This study has also been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au

CONSENT FORM

Do physiotherapists agree on a diagnosis for patients with neck and arm pain?

Investigators: Brigitte Tampin, A/Prof Kathy Briffa, Dr. Helen Slater,
David Veldman

Participant Name:_____

Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.
2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.
3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.
4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to your principal investigator before signing this Consent Form.

Name of Participant	Signature of Participant	Date

Name of Investigator	Signature of Investigator	Date

The South Metropolitan Area Health Service Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact the Chair of the SMHAS Human Research Ethics Committee on telephone No. (08) 9431 2929.

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal record.

ROYAL PERTH HOSPITAL

Do physiotherapists agree on a diagnosis for patients with neck and arm pain?

Principal Investigator: Brigitte Tampin, PhD student
RPH Investigator: Dr Helen Slater, Pain Medicine Centre, RPH
Project Supervisor: A/Prof Kathy Briffa

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study?
Brigitte Tampin is supported in her study by a postgraduate scholarship from the National Health and Medical Research Council of the Australian Government

Contact persons:
Should you have questions about the study you may contact:

Brigitte Tampin   Phone No. 9266 3667, 0409 883 548
                          After hours: 0409 883 548
Dr Helen Slater   Phone No. 9266 3099

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records. Participation is voluntary.

You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve. Whatever your decision, this decision will not lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

The following information sheet will explain the study and will include details such as:
- Why this study might be suitable for you;
- The type, frequency and risks of any tests or procedures required by the study;
- The nature of your participation including how many visits you will make to the hospital;
- Your rights and responsibilities.

What is the purpose of the study?
There are a number of different reasons why people can have neck and arm pain. It is important to look for possible factors contributing to pain so that treatment can be directed at these factors. Physiotherapists use certain examination protocols for the assessment of patients with neck/arm pain, but the interpretation of their findings might vary between therapists. The purpose of this study is to examine if two experienced physiotherapists come to the same conclusion about the cause of your pain and if their conclusion is supported by the judgement of a neurosurgeon and a specialist in musculoskeletal therapy.

Why is this study suitable to me?
You are invited to take part in this study as you experience one sided neck and/or arm pain. Your participation would give you the opportunity to be examined by two very qualified and experienced physiotherapists who will give you feedback on their diagnosis and advice on further management of your neck/arm pain.

How long will I be in this study?
If you agree to participate, we will ask you to attend the School of Physiotherapy, Curtin University of Technology or the principal investigator's Physiotherapy Practice in Fremantle, whichever one is more convenient to you. You will be examined independently by two physiotherapists; each assessment will take about one hour. It might be possible to schedule your visit in such a way that your assessments will be performed on the same day, one after the other, which would mean you only have to attend once for two hours in total. Otherwise your assessments will be on two different days for one hour.

What will happen if I decide to be in this study?
You will be examined independently by two qualified and experienced physiotherapists (the principal investigator and one other). Each examination will take approximately one hour. Your medical history will be taken and a physical examination conducted. This will involve the assessment of movements of your neck and arm and a range of tests of sensation in the neck and arm. All tests will only be performed just to the point of pain onset. After your visit, the clinical notes which the physiotherapists took during your consultation, will be given to a neurosurgeon and to a specialist in musculoskeletal therapy for further diagnostic opinion.

Are there any reasons I should not be in this study?
The physiotherapy assessment is an examination which is standard clinical practice in any Physiotherapy department. The principal investigator will discuss with you any exclusion criteria in detail and will be directed at ensuring that the examination is both safe and appropriate for you.

What are the costs to me?
There will be no charge for the examination by the two physiotherapists. Transport to and from the clinic where examination will take place will not be

provided, however your travel expenses will be reimbursed with a $20 voucher.

What are the possible benefits of taking part?
Physiotherapists need to diagnose patients with neck/arm pain accurately so that the correct treatment can be given to these patients. Although the results of this study will importantly add to the body of knowledge in diagnosing patients with neck/arm pain, the results gained will probably not directly benefit you, but aim to benefit future patients by assisting physiotherapists in making accurate diagnoses.

However, the clinical examination which is performed by highly qualified physiotherapists would benefit you. You will be given advice and direction on further management of your neck/arm pain.

What are the possible side effects, risks and discomforts of taking part?
You may experience some very momentary discomfort during the testing of sensations. You may also experience some minor increase of symptoms similar to what you might expect after a standard physiotherapy treatment.

What if something goes wrong during the study?
In the event that you suffer an adverse event or a medical accident during this study that arises from your participation in the study, you will be offered all full and necessary treatment by Royal Perth Hospital. The Ethics Committee has approved this study on the basis (amongst others) that the reported risk of such an event is either small or acceptable in terms of the risk you face as a result of your current illness. No provisions have been made in this trial to offer trial subjects who suffer an adverse reaction monetary compensation, but the absence of such a provision does not remove your rights to seek compensation under common law

Will my taking part in this study be kept confidential?
The researchers will need to collect personal data about you, which may be sensitive, e.g. date of birth and relevant health information. The researchers may also need to get some of your health information from other health service providers, e.g. another hospital, pathology laboratory, radiographer, GP or other medical specialist. The investigators will adhere to usual standards of confidentiality in the collection and handling of your personal information and the standards of the Privacy Act 1988 will apply to the way your information is handled.

Any personal or health information will be kept private and confidential. It will be stored securely and only authorised persons, who understand it must be kept confidential, will have access to it. Your study details will be given a number so that your identity will not be apparent. The clinical notes taken during your examination will be kept at the School of Physiotherapy at Curtin University of Technology during the study and in a locked archive for 5 years from the time the study is closed. After this time they will be destroyed. This is a requirement of Curtin University of Technology. Some data/information will be stored on a computer at the School of Physiotherapy at Curtin University of

Technology. Access to this information will be via password only. This password will only be known to the principal investigator and to the project supervisors.

Authorised representatives of the RPH Ethics Committee, and Research Governance may require access to your study records to verify study procedures and/or data. In all cases when dealing with your information, these people are required to comply with privacy laws that protect you.

The results of the research will be made available to other health professionals through medical journals or meetings, but you will not be identifiable in these communications. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

Will I find out the results of the study?
A summary of the study findings will be forwarded to each participant.

Who has approved the study?
This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007) and the Royal Perth Hospital Human Research Ethics Committee (EC RA-09/008). If you have any concerns about the conduct of the study or questions about your rights as a research participant, please contact the Chairman of the RPH Ethics Committee, Professor Frank van Bockxmeer on (08) 9224 2244.

CONSENT FORM

Do physiotherapists agree on a diagnosis for patients with neck and arm pain?

Investigators: Brigitte Tampin, Dr. Helen Slater, A/Prof Kathy Briffa

Participant Name:_____

Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.

2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.

3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.

4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.

5. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to your principal investigator before signing this Consent Form.

Name of Participant	Signature of Participant	Date

Name of Investigator	Signature of Investigator	Date

Curtin University

Division of Health Sciences
School of Physiotherapy

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PATIENT INFORMATION SHEET
Study B

Project title: Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Principal Investigator: Brigitte Tampin, PhD student
Project Supervisor: A/Prof Kathy Briffa
Co-Supervisor: Dr Helen Slater

Purpose of Research
Neck and upper limb pain can affect how your nerves interpret touch, movement, pressure and temperature sensations. This study will examine how your pain affects these sensations in both your painful and non-painful arm.

Your role
You will be required to attend the School of Physiotherapy on one occasion for approximately three hours. Firstly, you will be asked to fill out questionnaires which will ask you about your pain, loss of function due to pain, emotional stress, fear of movement and your overall quality of life. Secondly, you will undergo some sensation testing which will involve testing the sensitivity to heat and cold, to light touch and pressure, to pin-prick and vibration. During these testing procedures you will be asked to identify the presence (yes/no) and the quality of the stimulus, i.e. whether you feel touch, prick, pain etc. If you feel any pain, you will be asked to press a stop button immediately at the first painful sensation and the testing will be stopped. For vibration testing you will be asked to say when you stop to feel the vibration. All testing will be performed on the top of both of your hands, in the area where you feel most pain and its opposite side (for healthy controls bilaterally in the lower neck) and on one foot. In addition, the sensation of pressure over three nerves in your arms will be examined.

Finally, the movement of your elbow will be measured in both arms. You will be required to lie on your back. Your arm to be tested will be positioned comfortably away from your side, supported by the couch, and hold in this position by a frame. A splint will be attached to your hand which helps to control the wrist position. A measuring device called a goniometer will be attached to your forearm to allow for exact measurements of the elbow movement to be made. Your elbow will be initially bent at 90 degrees and then slowly straightened over 10 seconds by the examiner. You will be asked to press a trigger button when (1) you feel any onset of pain for the first time and (2) when you want the movement to be stopped. This process will be repeated 3 times. The testing procedure has been used in previous studies by the principal investigator.

Risks and Discomforts

You may experience some very momentary discomfort during the testing of sensations. You may also experience some post-assessment exacerbation of symptoms similar to what you might expect after a standard physiotherapy treatment.

Benefits

This project aims to help establish what sensations are affected by pain and what this might mean in terms of diagnosis. Although the results of this study will importantly add to the body of knowledge in the diagnosis of patients with neck/arm pain of nerve origin, the examination you will undertake and the results gained will probably not directly benefit you, but aim to benefit the wider clinical population by assisting physiotherapists in making accurate diagnoses.

Confidentiality

You will be issued a study number instead of using your name, which will remain confidential to the principle investigator and the project supervisors. All the data (information) recorded will be stored on computer within the School of Physiotherapy, Curtin University of Technology. Access to this information will be via password only. This password will only be known to the principal investigator and to the project supervisors. The results of this study will be reported, but it will not be possible to identify individual subjects. Following the study period, the data will be held in a secure place for 7 years. After this time it will be destroyed. This is a requirement of Curtin University of Technology.

Refusal or Withdrawal

If you consent to participate in this study, you will be free to withdraw at any time, without fear of prejudice. If you do decide to withdraw from the study you would be asked to contact the Principle Investigators at the earliest opportunity. In the event that you withdraw, all of your data would be destroyed.

Further Information

This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. Its main role is to protect participants. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au

If you would like further information about the study, please feel free to contact me on 9266 3667 or 0409 883 548 or by email: brigitte.tampin@postgrad.curtin.edu.au. Alternatively, you can contact my supervisor A/Prof Kathy Briffa on 9266 3666 or by email: K.Briffa@exchange.curtin.edu.au or my co-supervisor Dr Helen Slater on 9266 3099, or by email: H.Slater@curtin.edu.au

Thank you very much for your involvement in this research, your participation is greatly appreciated.

Curtin University

CONTROL SUBJECT INFORMATION SHEET

Study B

Project title: Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Principal Investigator: Brigitte Tampin, PhD student
Project Supervisor: A/Prof Kathy Briffa
Co-Supervisor: Dr Helen Slater

Purpose of Research
Neck and upper limb pain can affect how nerves interpret touch, movement, pressure and temperature sensations. This study will examine these sensations. Your participation in the study will allow us to compare the responses in people with pain with responses in people who have no neck and upper limb pain.

Your role
You will be required to attend the School of Physiotherapy on one occasion for approximately three hours. Firstly, you will be asked to fill out questionnaires which will ask you about pain, loss of function due to pain, emotional stress, fear of movement and your overall quality of life. Secondly, you will undergo some sensation testing which will involve testing the sensitivity to heat and cold, to light touch and pressure, to pin-prick and vibration. During these testing procedures you will be asked to identify the presence (yes/no) and the quality of the stimulus, i.e. whether you feel touch, prick, pain etc. If you feel any pain, you will be asked to press a stop button immediately at the first painful sensation and the testing will be stopped. For vibration testing you will be asked to say when you stop to feel the vibration. All testing will be performed on the top of both of your hands, on both sides of your lower neck and on one foot. In addition, the sensation of pressure over three nerves in your arms will be examined.

Finally, the movement of your elbow will be measured in both arms. You will be required to lie on your back. Your arm to be tested will be positioned comfortably away from your side, supported by the couch, and hold in this position by a frame. A splint will be attached to your hand which helps to control the wrist position. A measuring device called a goniometer will be attached to your forearm to allow for exact measurements of the elbow movement to be made. Your elbow will be initially bent at 90 degrees and then slowly straightened over 10 seconds by the examiner. You will be asked to press a trigger button when (1) you feel any onset of pain for the first time and (2) when you want the movement to be stopped. This process will be repeated 3 times. The testing procedure has been used in previous studies by the principal investigator.

Risks and Discomforts
You may experience some very momentary discomfort during the testing of sensation

Benefits
This project aims to help establish what sensations are affected by pain and what this might mean in terms of diagnosis. Although the results of this study will importantly add to the body of knowledge in the diagnosis of patients with neck/arm pain of nerve origin, the examination you will undertake and the results gained will not directly benefit you as you do not have any pain. However, the results will benefit people with pain by assisting physiotherapists in making accurate diagnoses.

Confidentiality
You will be issued a study number instead of using your name, which will remain confidential to the principle investigator and the project supervisors. All the data (information) recorded will be stored on computer within the School of Physiotherapy, Curtin University of Technology. Access to this information will be via password only. This password will only be known to the principal investigator and to the project supervisors. The results of this study will be reported, but it will not be possible to identify individual subjects. Following the study period, the data will be held in a secure place for 7 years. After this time it will be destroyed. This is a requirement of Curtin University of Technology.

Refusal or Withdrawal
If you consent to participate in this study, you will be free to withdraw at any time, without fear of prejudice. If you do decide to withdraw from the study you would be asked to contact the Principle Investigators at the earliest opportunity. In the event that you withdraw, all of your data would be destroyed.

Further Information
This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. Its main role is to protect participants. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au. If you would like further information about the study, please feel free to contact me on 9266 3667 or 0409 883 548 or by email: brigitte.tampin@postgrad.curtin.edu.au. Alternatively, you can contact my supervisor A/Prof Kathy Briffa on 9266 3666 or by email: K.Briffa@exchange.curtin.edu.au or my co-supervisor Dr Helen Slater on 9266 3099, or by email: H.Slater@curtin.edu.au
Thank you very much for your involvement in this research, your participation is greatly appreciated.

Sir Charles Gairdner Hospital

Participant Information Sheet

Study title: Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Principal Investigator:	**Brigitte Tampin, PhD student**
Project Supervisor:	**A/Prof Kathy Briffa**
Co-Supervisor:	**Dr Helen Slater**
SCGH Investigator:	**Dr Roger Goucke**

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study?
Brigitte Tampin is supported in her study by a postgraduate scholarship from the National Health and Medical Research Council of the Australian Government

Contact persons:
Should you have questions about the study you may contact:

Brigitte Tampin	Phone No.	9266 3667, 0409 883 548
	After hours:	0409 883 548
A/Prof Kathy Briffa	Phone No.	9266 3666
Dr Helen Slater	Phone No.	9266 3099
Dr Roger Goucke	Phone No.	9346 3263

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve.
Whatever your decision, this decision will not lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

The following information sheet will explain the study and will include details such as:
- o Why this study might be suitable for you;
- o The type, frequency and risks of any tests or procedures required by the study;
- o The nature of your participation including how many visits you will make to the hospital;
- o Your rights and responsibilities.

What is the purpose of the study?
Neck and upper limb pain can affect how your nerves interpret touch, movement, pressure and temperature sensations. This study will examine how your pain affects these sensations in both your painful and non-painful arm.

Why is this study suitable to me?
You are invited to take part in this study as you experience neck and/or arm pain relating to specific nerve in the neck. The study aims to help establish what sensations are affected by pain and what this might mean in terms of diagnosis.

How long will I be in this study?
You would have to attend the School of Physiotherapy, Curtin University of Technology, on one occasion for approximately three hours.

What will happen if I decide to be in this study?
Firstly, you will be asked to fill out questionnaires which will ask you about your pain, loss of function due to pain, emotional stress, fear of movement and your overall quality of life. Secondly, you will undergo some sensation testing which will involve testing the sensitivity to heat and cold, to light touch and pressure, to pin-prick and vibration. During these testing procedures you will be asked to identify the presence (yes/no) and the quality of the stimulus, i.e. whether you feel touch, prick, pain etc. If you feel any pain, you will be asked to press a stop button immediately at the first painful sensation and the testing will be stopped. For vibration testing you will be asked to say when you stop to feel the vibration. All testing will be performed on the top of both of your hands, in the area where you feel most pain and its opposite side and on one foot. In addition, the sensation of pressure over three nerves in your arms will be examined.

Finally, the movement of your elbow will be measured in both arms. You will be required to lie on your back. Your arm to be tested will be positioned comfortably away from your side, supported by the couch, and hold in this position by a frame. A splint will be attached to your hand which helps to control the wrist position. A measuring device called a goniometer will be attached to your forearm to allow for exact measurements of the elbow movement to be made. Your elbow will be initially bent at 90 degrees and then slowly straightened over 10 seconds by the examiner. You will be asked to press a trigger button when (1) you feel any onset of pain for the first time and (2) when you want the movement to be stopped. This process will be repeated

3 times. The testing procedure has been used in previous studies by the principal investigator.

Are there any reasons I should not be in this study?
Each potential participant will undergo a clinical examination (see paragraph below: "What are the possible benefits of taking part?") which will serve to establish if your pain condition fits the inclusion criteria for the study. Only persons who present with a pain condition that is related to nerves coming from a specific segment in the neck (between the 5th and 7th neck bone) could be included in the study. Further to this, participants should not have diabetes or a history of any vascular disease (impaired blood circulation). The principal investigator will discuss with you after the clinical examination if you fulfil the inclusion criteria.

What are the costs to me?
There will be no charge for the examination by the principal investigator. Transport to and from Curtin University will not be provided, however a free parking permit will be given to you.

What are the possible benefits of taking part?
You have been experiencing neck and/or arm pain for a longer time and you have been referred to see a neurosurgeon at Sir Charles Gairdner Hospital. The hospital has set up a Comprehensive Spinal Care Clinic at the Department of Pain Management, comprising of a neurosurgeon, pain specialist and physiotherapist, in order to reduce these long waiting periods. Patients are initially assessed by a highly qualified and experienced physiotherapist who will then discuss further management with the patient and refer them on to the medical specialists, if needed.

This research study will give you the opportunity to reduce your waiting time for an appointment. You will be examined by a physiotherapist as mentioned above. However, you are under no obligation to take part in the study of sensitivity testing.

This project of sensitivity testing aims to help establish what sensations are affected by pain and what this might mean in terms of diagnosis. Although the results of this study will importantly add to the body of knowledge in the diagnosis of patients with neck/arm pain of nerve origin, the examination you will undertake and the results gained will probably not directly benefit you, but aim to benefit future patients by assisting physiotherapists in making accurate diagnoses.

What are the possible side effects, risks and discomforts of taking part?
You may experience some very momentary discomfort during the testing of sensations. You may also experience some post-assessment exacerbation of symptoms similar to what you might expect after a standard physiotherapy treatment.

How will my safety by ensured?

The equipment which is used to measure your heat and cold pain threshold has a safety cut off temperature. This means when a certain temperature has been reached, the temperature goes automatically back to the starting temperature of 32°C which is like your body temperature. Therefore no harm can be done to you. In addition you will be asked to press a stop button immediately at the first painful sensation and the testing will be stopped.

Will my taking part in this study be kept confidential?

The principal investigator will need to collect personal data about you, which may be sensitive, e.g. date of birth and relevant health information. She may also need to get some of your health information from other health service providers, e.g. another hospital, pathology laboratory, radiographer, GP or other medical specialist.

Any personal or health information will be kept private and confidential. It will be stored securely and only authorised persons, who understand it must be kept confidential, will have access to it. Your study details will be given a number so that your identity will not be apparent. All data/information will be recorded on a computer at the School of Physiotherapy at Curtin University of Technology. Access to this information will be via password only. This password will only be known to the principal investigator and to the project supervisors. Any hard copies as well as backed up electronic copies will be kept at the School of Physiotherapy at Curtin University of Technology during the study and in a locked archive for 5 years from the time the study is closed. After this time they will be destroyed. This is a requirement of Curtin University of Technology.

Authorised representatives of the Hospital Human Research Ethics Committee, and Research Governance may require access to your study records to verify study procedures and/or data. In all cases when dealing with your information, these people are required to comply with privacy laws that protect you.

The results of the research will be made available to other health professionals through medical journals or meetings, but you will not be identifiable in these communications. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

Will I find out the results of the study?

A summary of the study findings will be forwarded to each participant.

Who has reviewed the study?

The Sir Charles Gairdner Hospital Human Research Ethics Committee has reviewed this study and has given its approval for the conduct of this research. In doing so this study conforms to the principles set out by the National Statement on Ethical Conduct in Research involving Humans and according to the Good Clinical Practice Guidelines.

This study has also been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au

CONSENT FORM

Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Investigators: Brigitte Tampin, A/Prof Kathy Briffa, Dr. Helen Slater, Dr Roger Goucke

Participant Name:_____

Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.
2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.
3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.
4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to the principal investigator before signing this Consent Form.

_____
Name of Participant   Signature of Investigator   Date

_____
Name of Investigator   Signature of Investigator   Date

The Sir Charles Gairdner Hospital Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact the secretary of the Sir Charles Gairdner Hospital Human Research Ethics Committee on telephone No. (08) 9346.2999

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

FREMANTLE HOSPITAL

Participant Information Sheet

Study title: Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Principal Investigator:	**Brigitte Tampin, PhD student**
Project Supervisor:	**A/Prof Kathy Briffa**
Co-Supervisor:	**Dr Helen Slater**
SMHAS Investigators:	**Dr Stephanie Davies**
	Stuart Waters

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study?
Brigitte Tampin is supported in her study by a postgraduate scholarship from the National Health and Medical Research Council of the Australian Government

Contact persons:
Should you have questions about the study you may contact:

Brigitte Tampin	Phone No.	9266 3667, 0409 883 548
	After hours:	0409 883 548
A/Prof Kathy Briffa	Phone No.	9266 3666
Dr Helen Slater	Phone No.	9266 3099
Dr Stephanie Davies	Phone No.	9431 3296
Stuart Waters	Phone No.	9431 2533

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.
You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve.

Whatever your decision, this decision will not lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

The following information sheet will explain the study and will include details such as:
- o Why this study might be suitable for you;
- o The type, frequency and risks of any tests or procedures required by the study;
- o The nature of your participation including how many visits you will make to the hospital;
- o Your rights and responsibilities.

What is the purpose of the study?
Pain can affect how your nerves interpret touch, movement, pressure and temperature sensations. This study will examine how your pain affects these sensations in your upper body.

Why is this study suitable to me?
You are invited to take part in this study as you experience neck and/or arm pain relating to a specific nerve in the neck or you have been diagnosed with fibromyalgia. The study aims to help establish what sensations are affected by pain and what this might mean in terms of diagnosis.

How long will I be in this study?
You would have to attend the School of Physiotherapy, Curtin University of Technology, on one occasion for approximately three hours.

What will happen if I decide to be in this study?
Firstly, you will be asked to fill out questionnaires which will ask you about your pain, loss of function due to pain, emotional stress, fear of movement and your overall quality of life. Secondly, you will undergo some sensation testing which will involve testing the sensitivity to heat and cold, to light touch and pressure, to pin-prick and vibration. During these testing procedures you will be asked to identify the presence (yes/no) and the quality of the stimulus, i.e. whether you feel touch, prick, pain etc. If you feel any pain, you will be asked to press a stop button immediately at the first painful sensation and the testing will be stopped. For vibration testing you will be asked to say when you stop to feel the vibration. All testing will be performed on the top of both of your hands, in the area where you feel most pain and its opposite side and on one foot. In addition, the sensation of pressure over three nerves in your arms will be examined.

Finally, the movement of your elbow will be measured in both arms. You will be required to lie on your back. Your arm to be tested will be positioned comfortably away from your side, supported by the couch, and hold in this position by a frame. A splint will be attached to your hand which helps to control the wrist position. A measuring device called a goniometer will be attached to your forearm to allow for exact measurements of the elbow movement to be made. Your elbow will be initially bent at 90 degrees and then slowly straightened over 10 seconds by the examiner. You will be asked to press a trigger button when (1) you feel any onset of pain for the first time and (2) when you want the movement to be stopped. This process will be repeated

3 times. The testing procedure has been used in previous studies by the principal investigator.

Are there any reasons I should not be in this study?
Each potential participant will undergo a clinical examination which will serve to establish if your pain condition fits the inclusion criteria for the study. Only persons who present with a pain condition that is related to nerves coming from a specific segment in the neck (between the 5th and 7th neck bone) and persons with fibromyalgia could be included in the study. Further to this, participants should not have diabetes or a history of any vascular disease (impaired blood circulation). The principal investigator will discuss with you after the clinical examination if you fulfil the inclusion criteria.

What are the costs to me?
There will be no charge for the examination by the principal investigator. Transport to and from Curtin University will not be provided, however a free parking permit will be given to you. Your travel expenses will be reimbursed with a $20 voucher.

What are the possible benefits of taking part?
This project of sensitivity testing aims to help establish what sensations are affected by pain and what this might mean in terms of diagnosis. Although the results of this study will importantly add to the body of knowledge in the diagnosis of patients with neck/arm pain of nerve origin, the examination you will undertake and the results gained will probably not directly benefit you, but aim to benefit future patients by assisting physiotherapists in making accurate diagnoses. However, if you wish, the results of your individual assessment can be given to you for further discussion with your doctor or other health professionals.

What are the possible side effects, risks and discomforts of taking part?
You may experience some very momentary discomfort during the testing of sensations. You may also experience some post-assessment exacerbation of symptoms similar to what you might expect after a standard physiotherapy treatment.

How will my safety be ensured?
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Will my taking part in this study be kept confidential?
The principal investigator will need to collect personal data about you, which may be sensitive, e.g. date of birth and relevant health information. She may also need to get some of your health information from other health service providers, e.g. another hospital, pathology laboratory, radiographer, GP or other medical specialist.

Any personal or health information will be kept private and confidential. It will be stored securely and only authorised persons, who understand it must be kept confidential, will have access to it. Your study details will be given a number so that your identity will not be apparent. All data/information will be recorded on a computer at the School of Physiotherapy at Curtin University of Technology. Access to this information will be via password only. This password will only be known to the principal investigator and to the project supervisors. Any hard copies as well as backed up electronic copies will be kept at the School of Physiotherapy at Curtin University of Technology during the study and in a locked archive for 5 years from the time the study is closed. After this time they will be destroyed. This is a requirement of Curtin University of Technology.

Authorised representatives of the Hospital Human Research Ethics Committee, and Research Governance may require access to your study records to verify study procedures and/or data. In all cases when dealing with your information, these people are required to comply with privacy laws that protect you.

The results of the research will be made available to other health professionals through medical journals or meetings, but you will not be identifiable in these communications. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

Will I find out the results of the study?
A summary of the study findings will be forwarded to each participant.

Who has approved the study?
The South Metropolitan Area Health Service Human Research Ethics Committee has given approval for the conduct of this research In doing so this study conforms to the principles set out by the National Statement on Ethical Conduct in Human Research and according to the Good Clinical Practice Guidelines.

This study has also been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au

CONSENT FORM

Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Investigators: Brigitte Tampin, A/Prof Kathy Briffa, Dr. Helen Slater, Dr Stephanie Davies, Stuart Waters

Participant Name:_____

Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.
2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.
3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.
4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to the principal investigator before signing this Consent Form.

_____

Name of Participant   Signature of Participant   Date

_____

Name of Investigator   Signature of Investigator   Date

The South Metropolitan Area Health Service Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact the Chair of the SMHAS Human Research Ethics Committee on telephone No. (08) 9431 2929.

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

BENTLEY HOSPITAL
PARTICIPANT INFORMATION SHEET

Study title: Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Principal Investigator:	**Brigitte Tampin, PhD student**
Project Supervisor:	**A/Prof Kathy Briffa**
Co-Supervisor:	**Dr Helen Slater**
SMHAS Investigators:	**Andrew Walton**

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study?
Brigitte Tampin is supported in her study by a postgraduate scholarship from the National Health and Medical Research Council of the Australian Government

Contact persons:
Should you have questions about the study you may contact:

Brigitte Tampin	Phone No.	9266 3667, 0409 883 548
	After hours:	0409 883 548
A/Prof Kathy Briffa	Phone No.	9266 3666
Dr Helen Slater	Phone No.	9266 3099
Andrew Walton	Phone No.	93343777

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve.

Whatever your decision, this decision will not lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

The following information sheet will explain the study and will include details such as:
- o Why this study might be suitable for you;
- o The type, frequency and risks of any tests or procedures required by the study;
- o The nature of your participation including how many visits you will make to the hospital;
- o Your rights and responsibilities.

What is the purpose of the study?
Pain can affect how your nerves interpret touch, movement, pressure and temperature sensations. This study will examine how your pain affects these sensations in your upper body.

Why is this study suitable to me?
You are invited to take part in this study as you experience neck and/or arm pain relating to a specific nerve in the neck or you have been diagnosed with fibromyalgia. The study aims to help establish what sensations are affected by pain and what this might mean in terms of diagnosis.

How long will I be in this study?
You would have to attend the School of Physiotherapy, Curtin University of Technology, on one occasion for approximately three hours.

What will happen if I decide to be in this study?
Firstly, you will be asked to fill out questionnaires which will ask you about your pain, loss of function due to pain, emotional stress, fear of movement and your overall quality of life. Secondly, you will undergo some sensation testing which will involve testing the sensitivity to heat and cold, to light touch and pressure, to pin-prick and vibration. During these testing procedures you will be asked to identify the presence (yes/no) and the quality of the stimulus, i.e. whether you feel touch, prick, pain etc. If you feel any pain, you will be asked to press a stop button immediately at the first painful sensation and the testing will be stopped. For vibration testing you will be asked to say when you stop to feel the vibration. All testing will be performed on the top of both of your hands, in the area where you feel most pain and its opposite side and on one foot. In addition, the sensation of pressure over three nerves in your arms will be examined.

Finally, the movement of your elbow will be measured in both arms. You will be required to lie on your back. Your arm to be tested will be positioned comfortably away from your side, supported by the couch, and hold in this position by a frame. A splint will be attached to your hand which helps to control the wrist position. A measuring device called a goniometer will be attached to your forearm to allow for exact measurements of the elbow movement to be made. Your elbow will be initially bent at 90 degrees and then slowly straightened over 10 seconds by the examiner. You will be asked to press a trigger button when (1) you feel any onset of pain for the first time and (2) when you want the movement to be stopped. This process will be repeated

3 times. The testing procedure has been used in previous studies by the principal investigator.

Are there any reasons I should not be in this study?
Each potential participant will undergo a clinical examination which will serve to establish if your pain condition fits the inclusion criteria for the study. Only persons who present with a pain condition that is related to nerves coming from a specific segment in the neck (between the 5th and 7th neck bone) and persons with fibromyalgia could be included in the study. Further to this, participants should not have diabetes or a history of any vascular disease (impaired blood circulation). The principal investigator will discuss with you after the clinical examination if you fulfil the inclusion criteria.

What are the costs to me?
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What are the possible benefits of taking part?
This project of sensitivity testing aims to help establish what sensations are affected by pain and what this might mean in terms of diagnosis. Although the results of this study will importantly add to the body of knowledge in the diagnosis of patients with neck/arm pain of nerve origin, the examination you will undertake and the results gained will probably not directly benefit you, but aim to benefit future patients by assisting physiotherapists in making accurate diagnoses. However, if you wish, the results of your individual assessment can be given to you for further discussion with your doctor or other health professionals.

What are the possible side effects, risks and discomforts of taking part?
You may experience some very momentary discomfort during the testing of sensations. You may also experience some post-assessment exacerbation of symptoms similar to what you might expect after a standard physiotherapy treatment.

How will my safety be ensured?
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Will my taking part in this study be kept confidential?
The principal investigator will need to collect personal data about you, which may be sensitive, e.g. date of birth and relevant health information. She may also need to get some of your health information from other health service providers, e.g. another hospital, pathology laboratory, radiographer, GP or other medical specialist.

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Authorised representatives of the Hospital Human Research Ethics Committee, and Research Governance may require access to your study records to verify study procedures and/or data. In all cases when dealing with your information, these people are required to comply with privacy laws that protect you.

The results of the research will be made available to other health professionals through medical journals or meetings, but you will not be identifiable in these communications. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

Will I find out the results of the study?
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Who has approved the study?
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This study has also been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au

CONSENT FORM

Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Investigators: Brigitte Tampin, A/Prof Kathy Briffa, Dr. Helen Slater, Andrew Walton

Participant Name:_____

Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.
2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.
3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.
4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to the principal investigator before signing this Consent Form.

_____
Name of Participant   Signature of Participant   Date

_____
Name of Investigator   Signature of Investigator   Date

The South Metropolitan Area Health Service Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact the Chair of the SMHAS Human Research Ethics Committee on telephone No. (08) 9431 2929.

All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

ROCKINGHAM HOSPITAL

Participant Information Sheet

Study title: Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Principal Investigator: **Brigitte Tampin, PhD student**
Project Supervisor: **A/Prof Kathy Briffa**
Co-Supervisor: **Dr Helen Slater**
SMHAS Investigators: **David Veldman**

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study?

Brigitte Tampin is supported in her study by a postgraduate scholarship from the National Health and Medical Research Council of the Australian Government

Contact persons:
Should you have questions about the study you may contact:

Brigitte Tampin   Phone No.   9266 3667, 0409 883 548
                                After hours: 0409 883 548
A/Prof Kathy Briffa   Phone No.   9266 3666
Dr Helen Slater   Phone No.   9266 3099
David Veldman   Phone No.   9592 0762

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Whatever your decision, this decision <u>will not</u> lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

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- o Why this study might be suitable for you;
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What is the purpose of the study?
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You may experience some very momentary discomfort during the testing of sensations. You may also experience some post-assessment exacerbation of symptoms similar to what you might expect after a standard physiotherapy treatment.

How will my safety be ensured?
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Will my taking part in this study be kept confidential?
The principal investigator will need to collect personal data about you, which may be sensitive, e.g. date of birth and relevant health information. She may also need to get some of your health information from other health service providers, e.g. another hospital, pathology laboratory, radiographer, GP or other medical specialist.

Any personal or health information will be kept private and confidential. It will be stored securely and only authorised persons, who understand it must be kept confidential, will have access to it. Your study details will be given a number so that your identity will not be apparent. All data/information will be recorded on a computer at the School of Physiotherapy at Curtin University of Technology. Access to this information will be via password only. This password will only be known to the principal investigator and to the project supervisors. Any hard copies as well as backed up electronic copies will be kept at the School of Physiotherapy at Curtin University of Technology during the study and in a locked archive for 5 years from the time the study is closed. After this time they will be destroyed. This is a requirement of Curtin University of Technology.

Authorised representatives of the Hospital Human Research Ethics Committee, and Research Governance may require access to your study records to verify study procedures and/or data. In all cases when dealing with your information, these people are required to comply with privacy laws that protect you.

The results of the research will be made available to other health professionals through medical journals or meetings, but you will not be identifiable in these communications. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

Will I find out the results of the study?
A summary of the study findings will be forwarded to each participant.

Who has approved the study?
The South Metropolitan Area Health Service Human Research Ethics Committee has given approval for the conduct of this research In doing so this study conforms to the principles set out by the National Statement on Ethical Conduct in Human Research and according to the Good Clinical Practice Guidelines.

This study has also been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007). If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au

CONSENT FORM

Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Investigators: Brigitte Tampin, A/Prof Kathy Briffa, Dr. Helen Slater, David Veldman

Participant Name:_____

Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.
2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.
3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.
4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to the principal investigator before signing this Consent Form.

_____

Name of Participant   Signature of Participant   Date

_____

Name of Investigator   Signature of Investigator   Date

The South Metropolitan Area Health Service Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact the Chair of the SMHAS Human Research Ethics Committee on telephone No. (08) 9431 2929. All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records

ROYAL PERTH HOSPITAL

Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Principal Investigator: Brigitte Tampin, PhD student
RPH Investigator: Dr Helen Slater, Pain Medicine Centre, RPH
Project Supervisor: A/Prof Kathy Briffa

Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.

Who is funding this study?
Brigitte Tampin is supported in her study by a postgraduate scholarship from the National Health and Medical Research Council of the Australian Government

Contact persons:
Should you have questions about the study you may contact:

Brigitte Tampin   Phone No.   9266 3667, 0409 883 548
                              After hours: 0409 883 548
Dr Helen Slater   Phone No.   9266 3099
All study participants will be provided with a copy of the Information Sheet and Consent Form for their personal records.

Participation is voluntary
You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve. Whatever your decision, this decision <u>will not</u> lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

The following information sheet will explain the study and will include details such as:
  o Why this study might be suitable for you;
  o The type, frequency and risks of any tests or procedures required by the study;
  o The nature of your participation including how many visits you will make to the hospital;
  o Your rights and responsibilities.

What is the purpose of the study?
Pain can affect how your nerves interpret touch, movement, pressure and temperature sensations. This study will examine how your pain affects these sensations in your upper body.

Why is this study suitable to me?
You are invited to take part in this study as you experience neck and/or arm pain relating to a specific nerve in the neck. The study aims to help establish what sensations are affected by pain and what this might mean in terms of diagnosis.

How long will I be in this study?
If you agree to participate, we will ask you to attend the School of Physiotherapy, Curtin University of Technology, or Sir Charles Gairdner Hospital on one occasion for approximately three hours.

What will happen if I decide to be in this study?
Firstly, you will be asked to fill out questionnaires which will ask you about your pain, loss of function due to pain, emotional stress, fear of movement and your overall quality of life. Secondly, you will undergo some sensation testing which will involve testing the sensitivity to heat and cold, to light touch and pressure, to pin-prick and vibration. During these testing procedures you will be asked to identify the presence (yes/no) and the quality of the stimulus, i.e. whether you feel touch, prick, pain etc. If you feel any pain, you will be asked to press a stop button immediately at the first painful sensation and the testing will be stopped. For vibration testing you will be asked to say when you stop to feel the vibration. All testing will be performed on the top of both of your hands, in the area where you feel most pain and its opposite side and on one foot. In addition, the sensation of pressure over three nerves in your arms will be examined.

Finally, the movement of your elbow will be measured in both arms. You will be required to lie on your back. Your arm to be tested will be positioned comfortably away from your side, supported by the couch, and hold in this position by a frame. A splint will be attached to your hand which helps to control the wrist position. A measuring device called a goniometer will be attached to your forearm to allow for exact measurements of the elbow movement to be made. Your elbow will be initially bent at 90 degrees and then slowly straightened over 10 seconds by the examiner. You will be asked to press a trigger button when (1) you feel any onset of pain for the first time and (2) when you want the movement to be stopped. This process will be repeated 3 times. The testing procedure has been used in previous studies by the principal investigator.

Are there any reasons I should not be in this study?
Each potential participant will undergo a clinical examination which will serve to establish if your pain condition fits the inclusion criteria for the study. Only persons who present with a pain condition that is related to nerves coming from a specific segment in the neck (between the 5th and 7th neck bone) could be included in the study. Further to this, participants should not have diabetes

or a history of any vascular disease (impaired blood circulation). The principal investigator will discuss with you after the clinical examination if you fulfil the inclusion criteria.

What are the costs to me?
There will be no charge for the examination by the principal investigator. Transport to and from Curtin University or Sir Charles Gairdner Hospital will not be provided, however parking fees will be reimbursed plus, your travel expenses will be reimbursed with a $20 voucher.

What are the possible benefits of taking part?
This project of sensitivity testing aims to help establish what sensations are affected by pain and what this might mean in terms of diagnosis. Although the results of this study will importantly add to the body of knowledge in the diagnosis of patients with neck/arm pain of nerve origin, the examination you will undertake and the results gained will probably not directly benefit you, but aim to benefit future patients by assisting physiotherapists in making accurate diagnoses. However, if you wish, the results of your individual assessment can be given to you for further discussion with your doctor or other health professionals.

What are the possible side effects, risks and discomforts of taking part?
You may experience some very momentary discomfort during the testing of sensations. You may also experience some post-assessment exacerbation of symptoms similar to what you might expect after a standard physiotherapy treatment.

How will my safety be ensured?
The equipment which is used to measure your heat and cold pain threshold has a safety cut off temperature. This means when a certain temperature has been reached, the temperature goes automatically back to the starting temperature of 32°C which is like your body temperature. Therefore no harm can be done to you. In addition you will be asked to press a stop button immediately at the first painful sensation and the testing will be stopped.

What if something goes wrong during the study?
In the event that you suffer an adverse event or a medical accident during this study that arises from your participation in the study, you will be offered all full and necessary treatment by Royal Perth Hospital. The Ethics Committee has approved this study on the basis (amongst others) that the reported risk of such an event is either small or acceptable in terms of the risk you face as a result of your current illness No provisions have been made in this trial to offer trial subjects who suffer an adverse reaction monetary compensation, but the absence of such a provision does not remove your rights to seek compensation under common law.

Will my taking part in this study be kept confidential?
The principal investigator will need to collect personal data about you, which may be sensitive, e.g. date of birth and relevant health information. She may also need to get some of your health information from other health service providers, e.g. another hospital, pathology laboratory, radiographer, GP or other medical specialist. The investigators will adhere to usual standards of confidentiality in the collection and handling of your personal information and the standards of the Privacy Act 1988 will apply to the way your information is handled.

Any personal or health information will be kept private and confidential. It will be stored securely and only authorised persons, who understand it must be kept confidential, will have access to it. Your study details will be given a number so that your identity will not be apparent. All data/information will be recorded on a computer at the School of Physiotherapy at Curtin University of Technology. Access to this information will be via password only. This password will only be known to the principal investigator and to the project supervisors. Any hard copies as well as backed up electronic copies will be kept at the School of Physiotherapy at Curtin University of Technology during the study and in a locked archive for 5 years from the time the study is closed. After this time they will be destroyed. This is a requirement of Curtin University of Technology.

Authorised representatives of the RPH Ethics Committee, and Research Governance may require access to your study records to verify study procedures and/or data. In all cases when dealing with your information, these people are required to comply with privacy laws that protect you.

The results of the research will be made available to other health professionals through medical journals or meetings, but you will not be identifiable in these communications. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

Will I find out the results of the study?
A summary of the study findings will be forwarded to each participant.

Who has approved the study?
This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 117/2007) and the Royal Perth Hospital Human Research Ethics Committee (EC RA-09/008). If you have any concerns about the conduct of the study or questions about your rights as a research participant, please contact the Chairman of the RPH Ethics Committee, Professor Frank van Bockxmeer on (08) 9224 2244.

CONSENT FORM

Investigating your sensitivity to touch, movement, pressure and temperature sensations in the neck and upper limbs

Investigators: Brigitte Tampin, Dr. Helen Slater, A/Prof Kathy Briffa

Participant Name:_____

Date of Birth: _____

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.
2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.
3. I have been able to have a member of my family or a friend with me while I was told about the study. I have been able to ask questions and all questions have been answered satisfactorily.
4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.
5. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

If you are unclear about anything you have read in the Participant Information Sheet or this Consent Form, please speak to the principal investigator before signing this Consent Form.

_____
Name of Participant   Signature of Investigator   Date

_____
Name of Investigator   Signature of Investigator   Date

APPENDIX 3

PATIENT SCREENING FORMS AND

CLINICAL ASSESSMENT FORMS

SCREENING FORM FOR PATIENTS WITH NECK/ARM PAIN

A3-2

Name:

Tel:

Address:
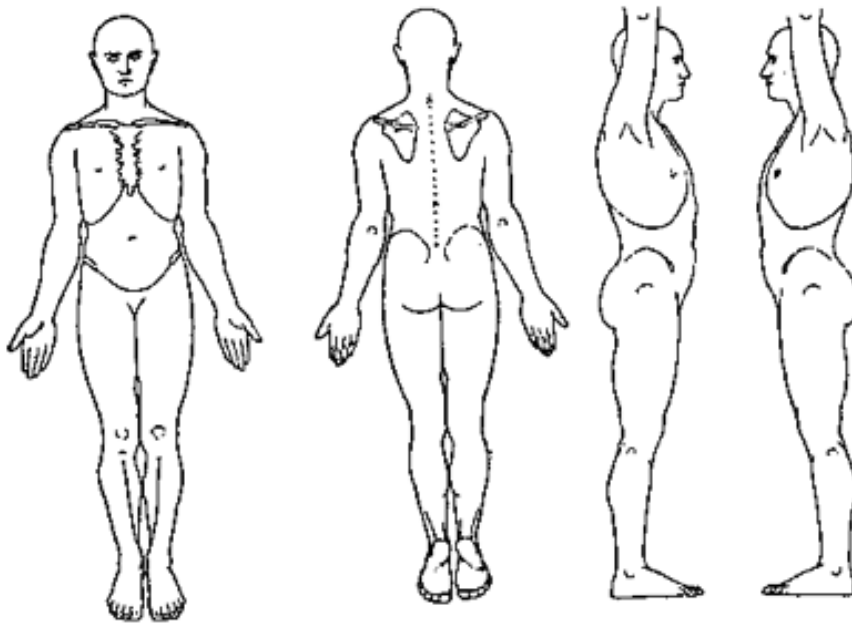
Hx:

Aggr factors:

Investigations:

Interventions:

Age 18-65	
Only one sided neck/arm pain	
Tingling/numbness in arm/hand	
Weakness in arm or hand	
Symptom duration 3-18 months	
VAS ≥ 2 maximal pain area	
Diagnostic imaging tests	
Other diagnostic tests	
Polyneuropathy/ nerve injuries (carpal tunnel, sciatica etc)	
Upper and lower limb injuries	
Back injury with sciatica/ back surgery	
Thyroid dysfunction	
Endocrine or allergic disorders, diabetes	
Inflammatory joint disease	
Cardiovascular or pulmonary disease	
Morbid obesity	
Cardiac or peripheral vascular disease	
Central nervous system disease (stroke, epilepsy etc)	
Psychiatric disorder (Bipolar depression, psychosis etc)	
Medication	

CLINICAL ASSESSMENT FORM FOR PATIENTS WITH NECK/ARM PAIN

ID:
NAME:
ADDRESS:
TEL: **DOB:**

DATE: **AGE:**   **Gender:**   **Profession:**

Main problem:
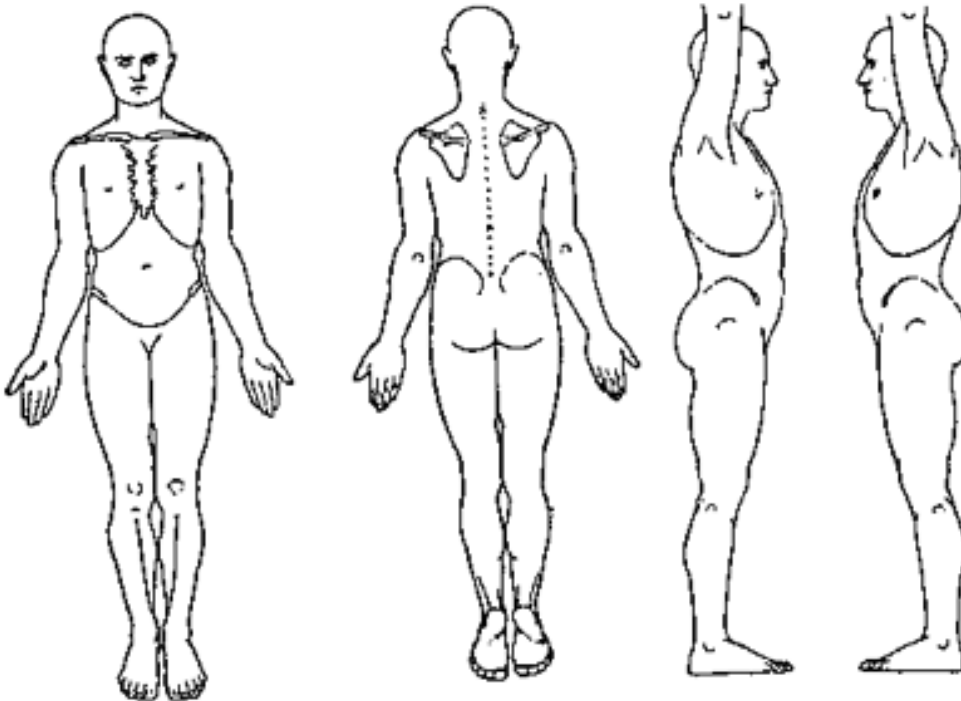
VASCULAR SYMPTOMS:

Current History:

Past History:

24 HOUR Hx

NIGHT:

A.M.:

DAY:

AGG:

SIT:

STAND:

WALK:

EASE:

MECHANICALLY PATTERNED:

SPONTANEOUS PAIN:

SENSITIVITY TO COLD:

G.H:

Diabetes: Insulin dependent:

Thyroid disturbances:
Endocrine instability:
B12 insufficiency:
Exposure to toxins:

INVESTIGATIONS:

W.L (Weight loss):

C/CE (Cord, cauda equina signs):   STER (steroid intake):

V.A. (signs of vertebral artery insufficiency):

C/SN (cough/sneeze):

MEDICATION:

Name	Dosage	Duration	Effect

PHYSICAL ACTIVITIES:

PSYCHO-SOCIAL

OBJECTIVE EXAMINATION

Pain Intensity:

Observation:

Functional activities:

ACTIVE MOVEMENTS

CERVICAL :	**SHOULDER:**
FLEX:	FLEX:
EXT:	ABD:
RROT:	ABD with Cx CLLF
LROT:	(slight shoulder girdle fix):
RLF:	ABD with wrist Ext
LLF:	(slight shoulder girdle fix):

SPURLING'S TEST (LF, ROT, COMPR):

NPT_{MEDIAN}

	ABD	**ER**	**SUP**	**WE**	**EL EXT**	**REL WE**
LEFT						
RIGHT						

NPT_{RADIAL}

	DEP	**WF**	**PRON**	**IR**	**EL EXT**	**ABD**	**REL WF**
LEFT							
RIGHT							

NPT_{ULNAR}

	DEP	**ABD**	**ER**	**PRON**	**WE**	**EL FLE**	**REL WE**
LEFT							
RIGHT							

NERVE TRUNK PALPATION: N = Normal, H=Hyperalgesia, Hypo =Hypoalgesia

Median nerve

	Axilla: sup brachial artery	Pronator tunnel	Carpal tunnel
LEFT			
RIGHT			

Radial nerve

	Intermuscular septum	Supinator tunnel	Wrist: Snuff box
LEFT			
RIGHT			

Ulnar nerve

	Axilla (inf brachial artery)	Cubital tunnel	Guyons canal
LEFT			
RIGHT			

OTHER as applicable

	Spinal nerves exit TP C4-6	Brachial Plexus trunks	Neurovascular bundle beneath coracoid process	Suprascapular, axillary nerve
LEFT				
RIGHT				

MOTION PALPATION TESTING PIVMS Cx

		C4/5	C5/6	C6/7	C7/T1
Up Slope	**L**				
	R				
Down Slope	**L**				
	R				

PAIVMs

PA	C4	C5	C6	C7
Unilateral L				
Unilateral R				
Central				

AP	C4	C5	C6	
Unilateral L				
Unilateral R				

OTHER TESTS

NEUROLOGICAL EXAMINATION

REFLEXES	Normal: ++ Hyper: +++	Diminished: + Absent: -
	LEFT	RIGHT
BICEPS		
TRICEPS		
BRACHIORADIAL		
PRONATOR		
ACHILLES		
KNEE JERK		

OTHER	LEFT	RIGHT
BABINSKI		
CLONUS		
GAIT		
BALANCE Single leg stand Romberg Test Tandem walking		
COORDINATION Buttoning shirt Other		

STRENGTH Rating 5/5=√	LEFT	RIGHT
SCAP ELEV (C4)		
SHOULD ABD (C5)		
ELB FLEX (C5/6)		
ELB EXT (C6/7)		
WRIST EXT (C6/7)		
EXT POLL.L. (C7/8) LONG FINGER FLEX (C8)		
INTRINS. (T1)		
OTHER		

SENSATION	INTENSITY	QUALITY
	N = normal	N = Normal
	Less = Hypoaesthesia	Other (paraesthesia,
	Loss = Analgesia	dysaesthesia, allodynia)
	More = Hyperaesthesia	

	DERMATOME			
	LEFT		**RIGHT**	
	INTENSITY	QUALITY	INTENSITY	QUALITY
COTTON WOOL				
PIN PRICK				
VIBRATION				
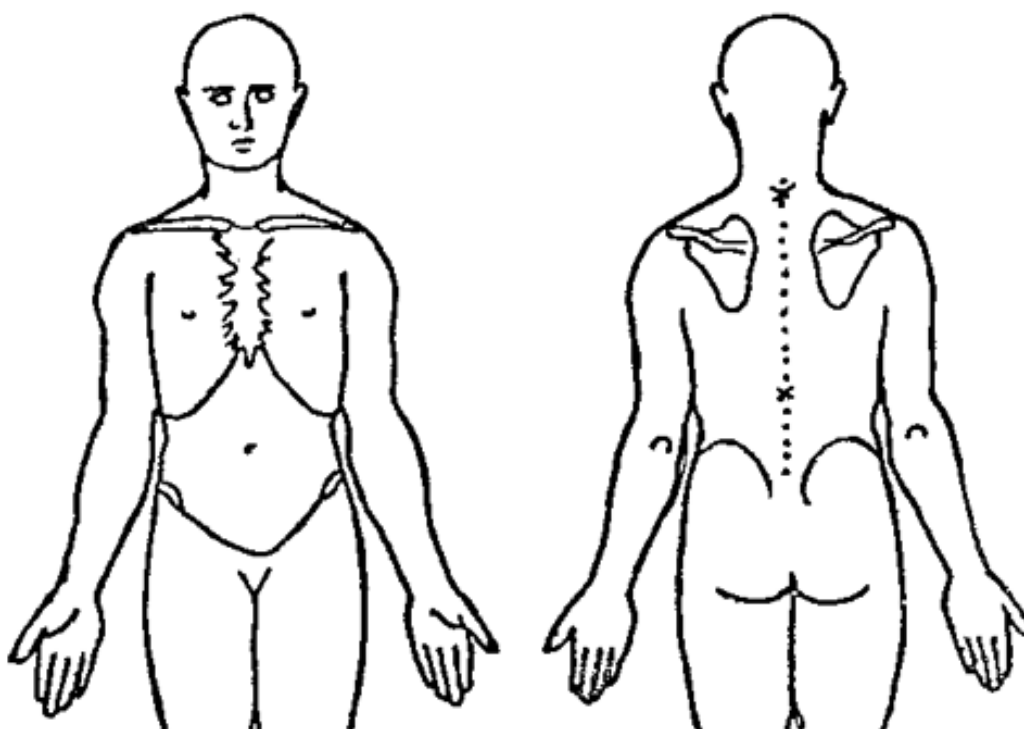
SCREENING FORM FOR PATIENTS WITH FIBROMYALGIA

Name:

Tel:

Age:

Address:

Onset of symptoms:

Diagnosed by:

Current Medication:

Pain upper/lower quarter, left and right	
Blood tests	
Erythrocyte sedimentation rate EST	
Hematology count	
Liver enzymes	
Creatinine kinase	
Rheumatoid factor	
Antinuclear antibodies	
Thyroid dysfunction	
Cardiovascular or pulmonary disease	
Chronic asthma	
Morbid obesity	
Cardiac or peripheral vascular disease	
Endocrine or allergic disorders, diabetes	
Inflammatory joint disease	
Upper limb injuries	
Polyneuropathy/ nerve injuries (carpal tunnel, sciatica etc)	
Central nervous system disease (stroke, epilepsy etc)	
Psychiatric disorder (Bipolar Depression, psychosis etc)	
Back injury with sciatica/ back surgery	
Hypertension	

Comments:

CLINICAL ASSESSMENT FORM FOR PATIENTS WITH FIBROMYALGIA

ID:
NAME:
ADDRESS:

TEL: **DOB:**
DATE: **AGE:**   **Gender:**   **Profession:**
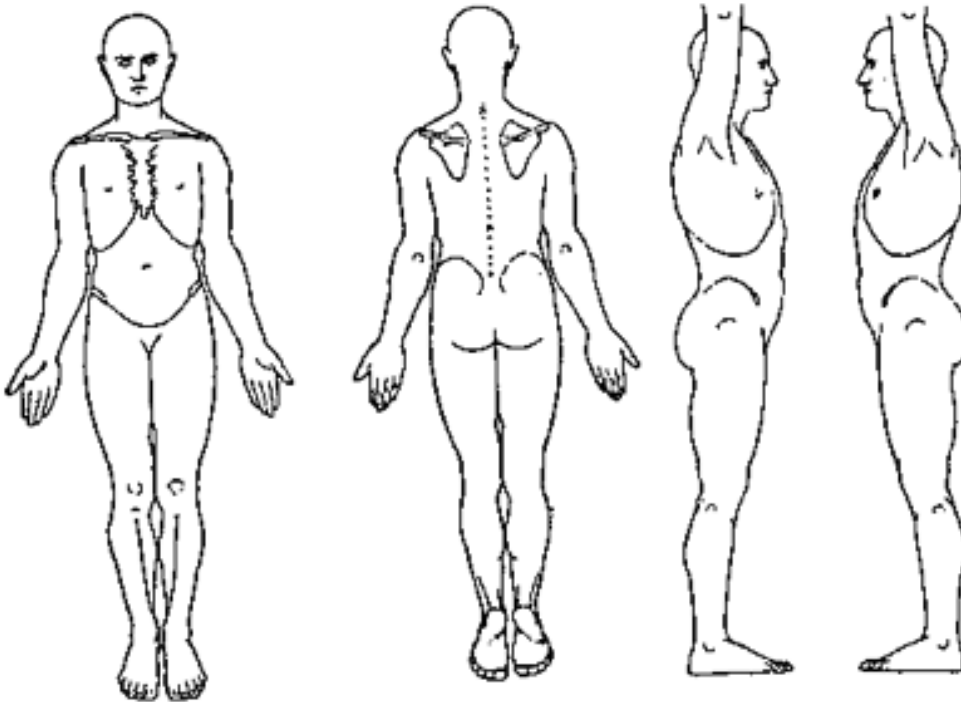
Main problem:

VASCULAR SYMPTOMS:

Current History:

Past History:

A3-13

24 HOUR Hx

NIGHT:

A.M.:

DAY:

AGG:

SIT:

STAND:

WALK:

EASE:

G.H:

A3-14

Cardiac or peripheral vascular disease	
Endocrine or allergic disorders (diabetes, hyper/hypothyroidism)	
Inflammatory joint disease	
Upper limb injuries	
Polyneuropathy/ nerve injuries	

INVESTIGATIONS:

W.L (Weight loss):

C/CE (Cord, cauda equina signs):   STER (steroid intake):

V.A. (signs of vertebral artery insufficiency) :

MEDICATION:

Name	Dosage	Duration	Effect

PHYSICAL ACTIVITIES:

OBJECTIVE EXAMINATION

Tender points Fibromyalgia

Tender points	Left	≥4kg	Right	≥4kg
Occiput: suboccipital muscle insertion				
Trapezius: midpoint of the upper border				
Supraspinatus: origins, above scapula spine near the medial border				
Gluteal: upper outer quadrants of buttocks in anterior fold of muscle				
Greater trochanter: posterior to trochanteric prominence				
Lower cervical: anterior aspects of the intertransverse spaces at C5-7				
Second rib: at second costochondral junctions, just lateral to the junctions on upper surfaces				
Lateral epicondyle: 2 cm distal to epicondyle				
Knee: medial fat pad proximal to the joint line				
Control points				
Right thumb nail				
At the center of right forearm				

Total tender points:

APPENDIX 4

QUESTIONNAIRES

LANSS PAIN SCALE
Leeds Assessment of Neuropathic Symptoms and Signs

NAME_____DATE_____

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A.   PAIN QUESTIONNAIRE

- Think about how your pain has felt over the last week.
- Please say whether any of the descriptions match your pain exactly.

1) Does your pain feel like strange, unpleasant sensations in your skin? Words like pricking, tingling, pins and needles might describe these sensations.

    a)   NO - My pain doesn't really feel like this.................................   (0)

    b)   YES - I get these sensations quite a lot...   (5)

2) Does your pain make the skin in the painful area look different from normal? Words like mottled or looking more red or pink might describe the appearance.

    a)   NO - My pain doesn't affect the colour of my skin.....................   (0)

    b)   YES - I've noticed that the pain does make my skin look different from normal (5)

3) Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.

    a)   NO - My pain doesn't make my skin abnormally sensitive in that area..........   (0)

    b)   YES - My skin seems abnormally sensitive to touch in that area.....................   (3)

4) Does your pain come on suddenly and in bursts for no apparent reason when you're still. Words like electric shocks, jumping and bursting describe these sensations.

    a)   NO - My pain doesn't really feel like this ....   (0)

    b)   YES - I get these sensations quite a lot ....   (2)

5) Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations

    a)   NO - I don't really get these sensations...   (0)

    b)   YES - I get these sensations quite a lot ....   (1)

B.   SENSORY TESTING

Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pin-prick threshold (PPT).

1) ALLODYNIA
Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

a)   NO, normal sensation in both areas ....   (0)

b)   YES, allodynia in painful area only ....   (5)

2)   ALTERED PIN-PRICK THRESHOLD
Determine the pin-prick threshold by comparing the response to a 23 gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently on to the skin in a non-painful and then painful areas.

If a sharp pin prick is felt in the non-painful area, but a different sensation is experienced in the painful area e.g. none / blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

a)   NO, equal sensation in both areas ....   (0)

b)   YES, altered PPT in painful area ....   (3)

SCORING:

Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE (maximum 24) ....

If score < 12, neuropathic mechanisms are **unlikely** to be contributing to the patient's pain
If score ≥ 12, neuropathic mechanisms are **likely** to be contributing to the patient's pain

painDETECT™ — PAIN QUESTIONNAIRE

Date: _____ **Patient:** **Last name:** _____ **First name:** _____

How would you assess your pain **now**, at this moment?

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

none — max.

How strong was the **strongest** pain during the past 4 weeks?

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

none — max.

How strong was the pain during the past 4 weeks **on average**?

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

none — max.

Mark the picture that best describes the course of your pain:

- Persistent pain with slight fluctuations ☐
- Persistent pain with pain attacks ☐
- Pain attacks without pain between them ☐
- Pain attacks with pain between them ☐

Please mark your main area of pain

Does your pain radiate to other regions of your body? yes ☐ no ☐

If yes, please draw the direction in which the pain radiates.

Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?

never ☐   hardly noticed ☐   slightly ☐   moderately ☐   strongly ☐   very strongly ☐

Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?

never ☐   hardly noticed ☐   slightly ☐   moderately ☐   strongly ☐   very strongly ☐

Is light touching (clothing, a blanket) in this area painful?

never ☐   hardly noticed ☐   slightly ☐   moderately ☐   strongly ☐   very strongly ☐

Do you have sudden pain attacks in the area of your pain, like electric shocks?

never ☐   hardly noticed ☐   slightly ☐   moderately ☐   strongly ☐   very strongly ☐

Is cold or heat (bath water) in this area occasionally painful?

never ☐   hardly noticed ☐   slightly ☐   moderately ☐   strongly ☐   very strongly ☐

Do you suffer from a sensation of numbness in the areas that you marked?

never ☐   hardly noticed ☐   slightly ☐   moderately ☐   strongly ☐   very strongly ☐

Does slight pressure in this area, e.g., with a finger, trigger pain?

never ☐   hardly noticed ☐   slightly ☐   moderately ☐   strongly ☐   very strongly ☐

(To be filled out by the physician)

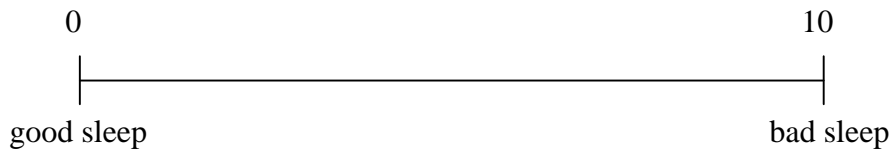| never	hardly noticed	slightly	moderately	strongly	very strongly
x 0 = 0	x 1 =	x 2 =	x 3 =	x 4 =	x 5 =

Total score ☐ out of 35

SLEEP/FATIGUE

A4-6

ID:

Do you awake tired or non refreshed? 'Never'   'seldom' 'often or usually' 'always'

FATIGUE: Are you fatigued?   'Never'   'seldom'   'often or usually'   always'

SLEEP QUALITY (over last week)

```
0                                    10
├─────────────────────────────────────┤

good sleep                        bad sleep
```

PAIN (over last week)
How was your pain on average over the last week?

```
0                                    10
├─────────────────────────────────────┤

no pain                  maximum tolerable pain
```
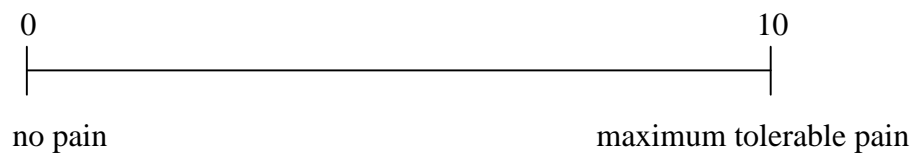
NECK DISABILITY INDEX

Office Use Only

Name _____

Date _____

This questionnaire has been designed to give us information as to how your neck pain has affected your ability to manage in everyday life. Please answer every section and **mark in each section only the one box that applies to you.** We realise you may consider that two or more statements in any one section relate to you, but please just mark the box that most closely describes your problem.

Section 1: Pain Intensity
- ☐ I have no pain at the moment
- ☐ The pain is very mild at the moment
- ☐ The pain is moderate at the moment
- ☐ The pain is fairly severe at the moment
- ☐ The pain is very severe at the moment
- ☐ The pain is the worst imaginable at the moment

Section 2: Personal Care (Washing,Dressing,etc.)
- ☐ I can look after myself normally without causing extra pain
- ☐ I can look after myself normally but it causes extra pain
- ☐ It is painful to look after myself and I am slow and careful
- ☐ I need some help but can manage most of my personal care
- ☐ I need help every day in most aspects of self care
- ☐ I do not get dressed, I wash with difficulty and stay in bed

Section 3: Lifting
- ☐ I can lift heavy weights without extra pain
- ☐ I can lift heavy weights but it gives extra pain
- ☐ Pain prevents me lifting heavy weights off the floor, but I can manage if they are conveniently placed, for example on a table
- ☐ Pain prevents me from lifting heavy weights but I can manage light to medium weights if they are conveniently positioned
- ☐ I can only lift very light weights
- ☐ I cannot lift or carry anything

Section 4: Reading
- ☐ I can read as much as I want to with no pain in my neck
- ☐ I can read as much as I want to with slight pain in my neck
- ☐ I can read as much as I want with moderate pain in my neck
- ☐ I can't read as much as I want because of moderate pain in my neck
- ☐ I can hardly read at all because of severe pain in my neck
- ☐ I cannot read at all

Section 5: Headaches
- ☐ I have no headaches at all
- ☐ I have slight headaches which come infrequently
- ☐ I have moderate headaches which come infrequently
- ☐ I have moderate headaches which come frequently
- ☐ I have severe headaches which come frequently
- ☐ I have headaches almost all the time

Section 6: Concentration
- ☐ I can concentrate fully when I want to with no difficulty
- ☐ I can concentrate fully when I want to with slight difficulty
- ☐ I have a fair degree of difficulty in concentrating when I want to
- ☐ I have a lot of difficulty in concentrating when I want to
- ☐ I have a great deal of difficulty in concentrating when I want to
- ☐ I cannot concentrate at all

Section 7: Work

☐ I can do as much work as I want to
☐ I can only do my usual work, but no more
☐ I can do most of my usual work, but no more
☐ I cannot do my usual work
☐ I can hardly do any work at all
☐ I can't do any work at all

Section 8: Driving

☐ I can drive my car without any neck pain
☐ I can drive my car as long as I want with slight pain in my neck
☐ I can drive my car as long as I want with moderate pain in my neck
☐ I can't drive my car as long as I want because of moderate pain in my neck
☐ I can hardly drive at all because of severe pain in my neck
☐ I can't drive my car at all

Section 9: Sleeping

☐ I have no trouble sleeping
☐ My sleep is slightly disturbed (less than 1 hr sleepless)
☐ My sleep is mildly disturbed (1-2 hrs sleepless)
☐ My sleep is moderately disturbed (2-3 hrs sleepless)
☐ My sleep is greatly disturbed (3-5 hrs sleepless)
☐ My sleep is completely disturbed (5-7 hrs sleepless)

Section 10: Recreation

☐ I am able to engage in all my recreation activities with no neck pain at all
☐ I am able to engage in all my recreation activities, with some pain in my neck
☐ I am able to engage in most, but not all of my usual recreation activities because of pain in my neck
☐ I am able to engage in a few of my usual recreation activities because of pain in my neck
☐ I can hardly do any recreation activities because of pain in my neck
☐ I can't do any recreation activities at all

Score: __/50   **Transform to percentage score   x 100 =   %points**

Scoring: For each section the total possible score is 5: if the first statement is marked the section score = 0, if the last statement is marked it = 5. If all ten sections are completed the score is calculated as follows: Example: 16 (total scored)
50 (total possible score) x 100 = 32%

If one section is missed or not applicable the score is calculated: 16 (total scored)
45 (total possible score) x 100 = 35.5%

Minimum Detectable Change (90% confidence): 5 points or 10 %points

ID:

Tampa scale for kinesiophobia

Here are some of the things which other patients have told us about their pain. For each statement please circle any number from 1 to 4 to signify whether you agree or disagree with the statement.

	Strongly disagree	Somewhat disagree	Somewhat agree	Strongly agree
1. I'm afraid that I might injure myself if I exercise.	1	2	3	4
2. If I were to try to overcome it, my pain would increase.	1	2	3	4
3. My body is telling me I have something dangerously wrong.	1	2	3	4
4. My pain would probably be relieved if I were to exercise.	1	2	3	4
5. People aren't taking my medical condition seriously.	1	2	3	4
6. My accident has put my body at risk for the rest of my life.	1	2	3	4
7. Pain always means I have injured my body.	1	2	3	4
8. Just because something aggravates my pain does not mean it is dangerous.	1	2	3	4
9. I am afraid that I might injure myself accidentally.	1	2	3	4
10. Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening.	1	2	3	4
11. I wouldn't have this much pain if there weren't something potentially dangerous going on in my body.	1	2	3	4
12. Although my condition is painful, I would be better off if I were physically active.	1	2	3	4
13. Pain lets me know when to stop exercising so that I do not injure myself.	1	2	3	4
14. It's really not safe for a person with a condition like mine to be physically active.	1	2	3	4
15. I can't do all the things normal people do because it's too easy for me to get injured.	1	2	3	4
16. Even though something is causing me a lot of pain, I don't think it's actually dangerous.	1	2	3	4
17. No one should have to exercise when he/she is in pain.	1	2	3	4

SF-36v2® Health Questionnaire

Your Health and Well-Being

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ⊠ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐₁	☐₂	☐₃	☐₄	☐₅

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
☐₁	☐₂	☐₃	☐₄	☐₅

3 **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot ▼	Yes, limited a little ▼	No, not limited at all ▼
a <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐₁	☐₂	☐₃
b <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐₁	☐₂	☐₃
c Lifting or carrying groceries	☐₁	☐₂	☐₃
d Climbing <u>several</u> flights of stairs	☐₁	☐₂	☐₃
e Climbing <u>one</u> flight of stairs	☐₁	☐₂	☐₃
f Bending, kneeling, or stooping	☐₁	☐₂	☐₃
g Walking <u>more than a kilometre</u>	☐₁	☐₂	☐₃
h Walking <u>several hundred metres</u>	☐₁	☐₂	☐₃
i Walking <u>one hundred metres</u>	☐₁	☐₂	☐₃
j Bathing or dressing yourself	☐₁	☐₂	☐₃

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time ▼	Most of the time ▼	Some of the time ▼	A little of the time ▼	None of the time ▼
a Cut down on the amount of time you spent on work or other activities	□ 1	□ 2	□ 3	□ 4	□ 5
b Accomplished less than you would like	□ 1	□ 2	□ 3	□ 4	□ 5
c Were limited in the kind of work or other activities	□ 1	□ 2	□ 3	□ 4	□ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	□ 1	□ 2	□ 3	□ 4	□ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time ▼	Most of the time ▼	Some of the time ▼	A little of the time ▼	None of the time ▼
a Cut down on the amount of time you spent on work or other activities	□ 1	□ 2	□ 3	□ 4	□ 5
b Accomplished less than you would like	□ 1	□ 2	□ 3	□ 4	□ 5
c Did work or other activities less carefully than usual	□ 1	□ 2	□ 3	□ 4	□ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
☐₁	☐₂	☐₃	☐₄	☐₅

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
▼	▼	▼	▼	▼	▼
☐₁	☐₂	☐₃	☐₄	☐₅	☐₆

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
☐₁	☐₂	☐₃	☐₄	☐₅

9. These questions are about how you feel and how things have been with you
   <u>during the past 4 weeks</u>. For each question, please give the one answer that
   comes closest to the way you have been feeling. How much of the time
   during the <u>past 4 weeks</u>…

	All of the time ▼	Most of the time ▼	Some of the time ▼	A little of the time ▼	None of the time ▼
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or
    emotional problems</u> interfered with your social activities (like visiting with
    friends, relatives, etc.)?

All of the time ▼	Most of the time ▼	Some of the time ▼	A little of the time ▼	None of the time ▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

A4-15

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Hospital Anxiety and Depression Scale (HADS)

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings she or he will be able to help you more. This questionnaire is designed to help your clinician to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought-out response.

I feel tense or 'wound up':   **A**

Most of the time	❏	3
A lot of the time	❏	2
From time to time, occasionally	❏	1
Not at all	❏	0

I still enjoy the things I used to enjoy: **D**

Definitely as much	❏	0
Not quite so much	❏	1
Only a little	❏	2
Hardly at all	❏	3

I get a sort of frightened feeling as if something awful is about to happen: **A**

Very definitely and quite badly	❏	3
Yes, but not too badly	❏	2
A little, but it doesn't worry me	❏	1
Not at all	❏	0

I can laugh and see the funny side of things   **D**

As much as I always could	❏	0
Not quite so much now	❏	1
Definitely not so much now	❏	2
Not at all	❏	3

Worrying thoughts go through my mind   **A**

A great deal of the time	❏	3
A lot of the time	❏	2
From time to time but not too often	❏	1
Only occasionally	❏	0

I feel cheerful   **D**

Not at all	❏	3
Not often	❏	2
Sometimes	❏	1
Most of the time	❏	0

I can sit at ease and feel relaxed   **A**

Definitely	❏	0
Usually	❏	1
Not often	❏	2
Not at all	❏	2

I feel as if I am slowed down   **D**

Nearly all the time	❏	3
Very often	❏	2
Sometimes	❏	1
Not at all	❏	0

I get a sort of frightened feeling like 'butterflies' in the stomach   **A**

Not at all	❏	0
Occasionally	❏	1
Quite often	❏	2
Very often	❏	3

I have lost interest in my appearance   **D**

Definitely	❏	3
I don't take as much care as I should	❏	2
I many not take quite as much care	❏	1
I take just as much care as ever	❏	0

I feel restless as if I have to be on the move   **A**

Very much indeed	❏	3
Quite a lot	❏	2
Not very much	❏	1
Not at all	❏	0

I look forward with enjoyment to things   **D**

As much as I ever did	❏	0
Rather less than I used to	❏	1
Definitely less than I used to	❏	2
Hardly at all	❏	3

I get sudden feelings of panic   **A**

Very often indeed	❏	3
Quite often	❏	2
Not very often	❏	1
Not at all	❏	0

I can enjoy a good book or radio or TV programme   **D**

Often	❏	0
Sometimes	❏	1
Not often	❏	2
Very seldom	❏	3

Now check that you have answered all the questions

For office use only:
Questions relating to anxiety are indicted by an 'A' while those relating to
depression are shown as 'D'

A: [   ]   Borderline 8-10

D: [   ]   Borderline 8-10

Zigmond AS, Snaith, RP. The Hospital Anxiety and Depression Scale. Acta
Psychiatr Scand 1983; 67: 361-370.

APPENDIX 5

VERBAL INSTRUCTIONS

FOR PERFORMING

QUANTITATIVE SENSORY TESTING

Rolke R, Baron R, Maier C, Tölle TR, Treede R-D, Beyer A, Binder A, Birbaumer N, Birklein F, Bötefür IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihöfner 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: 231-243.

Test 1. Thermal testing procedures (CDT, WDT, TSL, PHS, CPT, HPT).
"A temperature test of your skin will be performed. First we are testing your ability to detect a change of temperature to ´cool´ or ´warm´. A special device that cools or warms your skin will be placed over your... (specify practice area, control and test areas). *Secondly another temperature test of your skin will be performed to find the temperature that feels ´painfully cold or hot´."*

Instructions for testing of cold detection threshold (CDT).

"Please press the stop-button as soon as you feel the slightest change of temperature to ´cold´. Then the thermode will warm up to starting temperature. This procedure will start in a few seconds and will be repeated a total of 3 times."

Instructions for testing of warm detection threshold (WDT).

"Please press the stop-button as soon as you feel the slightest change of temperature to ´warm´. Then the thermode will cool down to starting temperature. This procedure will start in a few seconds and will be repeated a total of 3 times."

Instructions for testing of thermal sensory limen (TSL).

"Please press the stop-button as soon as you feel the slightest change of temperature to ´warm´ or ´cold´, and say as you do so whether the sensation you feel is warm or cold. Then the test continues immediately without prior warming up or cooling down to normal skin temperature. This procedure will be repeated a total of 6 times in a row and start in a few seconds."

Instructions for testing of paradoxical heat sensations (PHS) during the TSL procedure.
Instruction to the investigator: Some subjects will report a sensation of "warm" or "hot" or "painfully hot" upon cold stimulation during the TSL procedure. These reports have to be marked as "paradoxical heat sensation".

Instructions for testing of cold pain threshold (CPT).

"The temperature of the skin will decrease to ´cold´. Eventually a painful component will be added to the sensation of ´cold´, and it will change in quality from cold to, for example, ´aching´, ´stinging´, or ´burning´. Please press the stop button immediately at the first painful sensation. After pressing the stop-button the thermode will warm up to starting temperature. This procedure will start in a few seconds and will be repeated a total of 3 times."

Instructions for testing of heat pain threshold (HPT).

"The temperature of the skin will increase to ´warm´ and a few moments later to ´hot´. Eventually a painful component will be added to the sensation of ´hot´, and it will change in quality from ´hot´ to, for example, ´burning´ or ´stinging hot´. Please press the stop-button immediately at the first ´burning´ or ´stinging hot´ sensation. Then the thermode will cool down to starting temperature. This procedure will start in a few seconds and will be repeated a total of 3 times."

Test 2. Testing of the mechanical detection threshold (MDT).

"This is a test of your ability to detect light touch. I will press these hairs to your skin (specify practice area, and control and test areas). *Please say ´Yes´, if you feel the slightest light touch."*

Test 3. Testing of the mechanical pain threshold (MPT).

"This is a test of your ability to detect a sensation of ´pricking´ or ´stinging´. Blunt needles that increase in sharpness will be pressed gently against your skin (specify practice area, and control and test areas). *At first you may be able to feel them, but not feel that they are ´pricking´ or ´stinging´ in any way. However, eventually a component of slight ´pricking´ or ´stinging´ will be added to this sensation. Please say "sharp", immediately as you feel the slightest ´pricking´ or ´stinging´ sensation! If you feel the needle touching your skin without any ´pricking´ or ´stinging´, please say "blunt".*

Test 4. Testing of stimulus-/response-functions (MPS and ALL).

"This is a test of your ability to feel different intensities of pain. As in the previous test, blunt needles that increase in sharpness will be pressed gently against your skin. In between you will be touched by gently moving stimuli. Some of these stimuli will be accompanied by a sensation that has a ´pricking´, ´burning´ or ´scraping´ quality, some may not be ´pricking´, ´burning´ or ´scraping´ at all, and some you may not even be able to detect. Please give a number between ´0´ and ´100´ for the ´prickingness´, ´sharpness´ or ´strongness of the burning or scraping sensation´ of each stimulus.
´0´ indicating no pain or any kind of ´slightly pricking, stinging, burning or scraping sensation´. ´100´ indicating most intense pain, pricking, stinging, burning or scraping imaginable."

Test 5. Performing the ´wind-up´ procedure (WUR).

"This is a test of repeated pinpricks, using the same kind of blunt needle that was used in the last two tests. I will now apply a single pinprick. Please give a number between ´0´ and ´100´ for the ´prickingness´ or ´sharpness´ of that stimulus.
´0´ again indicating no pain or any kind of ´slightly pricking or stinging sensation´.
´100´ indicating most intense pain, pricking or stinging imaginable."

Continue, when the subject has rated the single pinprick stimulus:
"I will now apply a series of 10 pinpricks in a row. Please give a number between ´0´ and ´100´ for the prickingness or sharpness over that whole series of 10 pinpricks.
´0´ indicating no pain or any kind of ´slightly pricking or stinging sensation´.
´100´ indicating most intense pain imaginable."

Test 6. Testing of the vibration detection threshold (VDT).

"This is a test of your ability to detect vibration. Now I will put this tuning fork, once I have made it vibrate, on your… (specify practice area, control and test areas, and

place the tuning fork over a bony part of the referring area). *Please tell me if you feel any vibration, and say ´Now´ immediately that this vibration disappears. This procedure will be repeated a total of 3 times."*

Test 7. Testing of the pressure pain threshold (PPT).
"This is a test of your sensitivity to deep pain. Now I will press this pressure meter against your... (specify practice area, and control and test areas)*, and will gradually increase the pressure. Please say ´Now´ as soon as the pressure starts to be painful. This procedure will be repeated a total of 3 times."*

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Kind regards,

Kiley N. Thornton

Program Coordinator

_____

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ORIGINAL_AUTHOR: No
TRANSLATE_MODIFY: No
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INTENDEDAUDIENCE: Health professionals interested in quantitative sensory testing in patients with neck/arm pain.PhD thesis will be accessible electronically through the library at Curtin University, Perth, Australia
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APPENDIX 6

RECORDING SHEETS FOR

QUANTITATIVE SENSORY TESTING

QST TESTING

ID number:_____Date:_____Room temperature:_____

Order of testing:_____

Control area:_____Test area:_____

VAS before QST:_____

THERMAL TESTING

Control Area						Symptomatic Area				
CDT	**WDT**	**TSL**	**CPT**	**HPT**		**CDT**	**WDT**	**TSL**	**CPT**	**HPT**
°C	°C	°C	°C	°C		°C	°C	°C	°C	°C
°C	°C	°C	°C	°C		°C	°C	°C	°C	°C
°C	°C	°C	°C	°C		°C	°C	°C	°C	°C

PHS /3 (Control Area)

PHS /3 (Symptomatic Area)

MDT Mechanical detection threshold (von Frey filaments) (pinprick)
(start with 16mN)

MPT Mechanical pain threshold
(start with 8mN)

Control Area — felt / Not felt

felt	Not felt
	mN
mN	
	mN
mN	
	mN
mN	
	mN
mN	

Symptomatic Area — felt / Not felt

felt	Not felt
	mN
mN	
	mN
mN	
	mN
mN	
	mN
mN	

Control Area — blunt / sharp

blunt	sharp
	mN
mN	
	mN
mN	
	mN
mN	
	mN
mN	

Symptomatic Area — blunt / sharp

blunt	sharp
	mN
mN	
	mN
mN	
	mN
mN	
	mN
mN	

SR FUNCTION: MPS: pinprick; ALL: brush (BR), Q-tip (QT), cotton wool (CW)

Control Area

	VAS/100			VAS/100			VAS/100			VAS/100			VAS/100
128			CW			32			256			BR	
CW			256			128			8			32	
32			128			BR			CW			16	
256			8			CW			QT			128	
BR			32			16			128			512	
8			QT			256			64			CW	
16			BR			512			32			64	
QT			64			8			512			256	
512			16			64			BR			QT	
64			512			QT			16			8	

Symptomatic Area

	VAS/100			VAS/100			VAS/100			VAS/100			VAS/100
8			16			QT			512			64	
QT			BR			64			16			512	
256			512			8			64			QT	
64			32			512			BR			16	
CW			64			256			QT			8	
512			128			16			32			BR	
128			QT			CW			8			256	
16			CW			BR			128			32	
32			8			128			256			CW	
BR			256			32			CW			128	

WUR; wind up (series of 10 stimuli/ single stimulus) (256 mN for foot and hand)

VDT; Vibration detection threshold

PPT; pressure pain threshold kPa

Control Area		Sympt Area		Control	Sympt	Control	Sympt
VAS		**VAS**		/8	/8		
Single	Series	Single	Series	/8	/8		
				/8	/8		

ID number:_____Date:_____

A6-4

NPT_{MEDIAN}

NPT_{MEDIAN}
Degree of shoulder abduction:

Symptomatic side			Control side	
P1	**P2**		**P1**	**P2**

Symptoms produced: