Quantitative sensory testing (QST)

Konopka, Karl-Heinz

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Does assessing sense make sense?

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STELLINGEN

behorenden bij het proefschrift getiteld

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1. In clinical practice, most often the contralateral, non-affected side of a patient is used as reference for the identification of sensory signs at the affected side. In unilateral neuropathic pain bilateral somatosensory changes i.e. changes at the affected as well as the contralateral side occur frequently. To avoid potential misjudgement of the quality of sensory abnormalities we suggested that QST reference values obtained from healthy controls should be used.

2. Despite similar numbers of sensory abnormalities for the different grades of neuropathic pain, aspects of the pattern of sensory signs were different between 'definite' and 'probable' neuropathic pain and 'unlikely' neuropathic pain. The identification of differences in patterns of sensory abnormality in neuropathic pain patients could lead to a mechanistic understanding of somatosensory abnormalities in neuropathic pain.

3. A single QST parameter, i.e. mechanical pain sensitivity (MPS), can be used to identify distinct subgroups of neuropathic pain patients.
   a. QST phenotypic characterization e.g. MPS response pattern, as a tool for patient selection for enrolment into clinical trials could be used to decrease variance and increase the power to detect meaningful drug effects.
   b. Pharmacological intervention studies of patients with different response pattern to MPS could also help to determine a mechanism-based therapy for neuropathic pain.

4. Sensitisation may play a role in the explanation of pain during and after sports activity in patients with patella tendinopathy. Results of this QST study indicate that treatment and medical management of tendinopathies could be adapted accordingly.

5. Improved knowledge of the subjective nature of pain and related sensory processes e.g. somatosensory functioning could help to optimize the choice of pain patient study population and appropriate measurements for proof-of concept trails with putative pain therapies.

6. A subset of the standardized QST battery could be introduced to establish normative data of sensory function for clinical setting either with or without pharmacological intervention. The utility of different outcome measures in clinical trials could be investigated with the aim to maximise validity and reliability.

7. Using a standardized approach to obtain reference values from healthy controls for pharmaceutical research allows the direct comparison of efficacy of compounds between studies. Such approach might allow a direct identification of superiority of novel compounds over other drugs at an early stage of development and potentially reduces costs.

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To my parents

Paranimfen

Marten Harbers
Aribert Bardehle

Studies presented in this thesis were performed at:

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List of abbreviations

CDT	Cold Detection Threshold
CI	Confidence interval
CPT	Cold Pain Threshold
CRPS	Complex Regional Pain Syndrome
CTS	Carpal Tunnel Syndrome
DFNS	German Research Network on Neuropathic Pain
DMA	Dynamic Mechanical Allodynia
DN-4	Douleur Neuropathique 4
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
HCW	Heat Capsaicin Warmth
HPT	Heat Pain Threshold
Hz	Hertz
IASP	International Association for the Study of Pain
IL	Interleukin
MDT	Mechanical Detection Threshold
mN	Milli Newton
MPS	Mechanical Pain Sensitivity
MPT	Mechanical Pain Threshold
NGF	Nerve Growth Factor
NRS	Numerical Rating Scale
NS	Nociceptive Specific
NSAIDS	Non-steroidal Anti-inflammatory Drugs
PAG	Periaqueductal Grey
PB	Parabrachial
PHS	Paradoxical Heat Sensation
POMS	Profile of Mood States
PPT	Pressure Pain Threshold
PT	Patellar Tendinopathy
QST	Quantitative Sensory Testing
RVM	Rostral Ventromedial Medulla
SCL-90	Symptom Check List-90
TNF	Tumour Necrosis Factor
TSL	Thermal Sensory Limen
VAS	Visual Analogue Scale
VDT	Vibration Disappearance Threshold
VISA-P	Victorian Institute of Sports Assessment – Patellar Questionnaire
WDR	Wide Dynamic Range
WDT	Warm Detection Threshold
WUR	Wind Up Ratio

Chapter 1

General introduction

1. General introduction

Aristotle (384 to 322 BC) (Fig.1-1), the great Greek philosopher, was the first to describe "sense". He described five senses: sight, hearing, taste, smell, and touch. For Aristotle, the brain had no function in sensory processing. The sensorium commune, or center of sensory perception, was located in the heart, which he considered the center of all the fundamental life functions and the location of the soul. He contemplated the function of the brain to be limited to the production of cool secretions that cooled the hot air and blood arising from the heart. For him, an excess of vital heat in combination with an increased sensitivity to sensations, in particular touch, was responsible for the "emotion" pain (Bonica 1991).

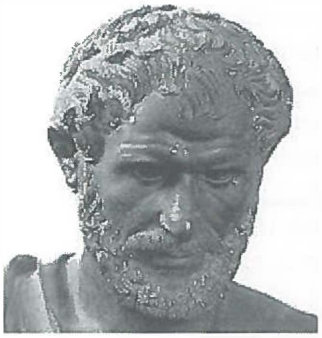

Figure 1-1: Picture of Aristotle
From: biography4u.com

Today we still believe there are five senses including touch. Arrays of receptors such as Pacinian and Meissner corpuscles, Merkel's disks and Ruffini endings sense different aspects of touch throughout our bodies. They are tuned to different aspects of the somatosensory world – touch, temperature and body position - with yet others for the sensations of pain. Although often classed with touch, pain is actually a phenomenon serving different functions and involves a different anatomical organisation.We recognise peripheral nerves, the spinal cord and the brain as major structures involved in the perception and interpretation of painful sensory information. The interplay of sensory information within these structures is not only relevant for the perception of pain per se but it also enables pain to serve a biologically important protective function. In this context, the sensation of pain is a normal response to injury or disease and induces withdraw from potentially damaging situations and protects a damaged body part while it heals.

In the last few decades basic research brought detailed understanding of concepts and theories regarding pain mechanisms. In 1965, Pat Wall and Ron Melzack published their paper in Science, entitled a 'New Theory of Pain' (Melzack & Wall 1965). The gate control theory stated that the transmission of pain from the peripheral nerve through the spinal cord was subject to modulation by both intrinsic neurons and controls from the brain. This theory explains how the central nervous system deals with sensory inputs but does not emphasise peripheral processes. In the peripheral nervous system there are three main types of sensory fibres involved in the sensory experience, Aβ-fibres, Aδ-fibres, and C-fibres (Fig. 1-2). Aβ-fibres are large in diameter and highly myelinated, allowing a fast conduction of action potentials. These fibres have low activation thresholds and normally respond to light touch. Aδ-fibres are smaller in diameter and thinly myelinated, and therefore slower-conducting than Aβ-fibres. Aδ-fibres have higher activation thresholds and respond to both thermal and mechanical

stimuli. C-fibres are unmyelinated and the smallest and the slowest conducting type of primary afferents. They have the highest thresholds for activation and therefore detect selectively nociceptive or 'painful' stimuli. Collectively, both Aδ- and C-fibres can be termed as nociceptors or 'pain fibres', responding to noxious stimuli which may be mechanical, thermal, or chemical (D'Mello & Dickenson 2008). However, this might be a simplistic presumption since other authors now consider some Aβ-afferents also as nociceptors (Djouhri & Lawson 2004). These fibres are affected in clinical pains which may arise from different sources, for instance damage to tissue due to inflammation or damage to nerves in case of so-called neuropathic pain (Baron 2000; 2006; Basbaum et al 2009; Melzack et al 2001). Both may cause subsequent profound changes in the spinal cord and the brain.

It is believed that all persistent forms of pain induce plasticity including altered mechanisms in peripheral and central signalling, suggesting that the mechanisms involved in pain are likely to be multiple and located at a number of sites (Dickenson 1995; Dickenson et al 2002; Schaible 2007; Treede et al 1992). In 1970, David Hubel and Torsten Wiesel published intriguing results of plastic changes in the brain in their work with kittens (Hubel & Wiesel 1970). In their experiments, they shut one eye by sewing the eyelids together and electrophysiologically recorded cortical brain maps. They saw that the portion of the kitten's brain associated with the shut eye was not inactive, as expected. Instead, it processed visual information from the open eye. This property of the nervous system to adapt morphologically and functionally to external stimuli is known as neuroplasticity.

Altered mechanisms in the peripheral and central signalling in chronic pain can lead to hypersensitivity to peripheral stimuli. Two types of hypersensitivity can be distinguished. First, allodynia is defined as pain in response to a non-nociceptive stimulus. In cases of mechanical allodynia, even gentle mechanical stimuli such as a slight touch can evoke severe pain. Second, hyperalgesia is defined as increased pain sensitivity to a nociceptive stimulus. Here, patients experience a painful stimulus such as a prick with greater intensity. Both, peripheral and central sensitisations are known to be involved in the generation of hypersensitivity. Peripheral sensitisation is a reduction in threshold and an increase in responsiveness of the peripheral ends of nociceptors. Whereas, central sensitisation is an increase in the excitability of neurons within the central nervous system, so that normal inputs produce abnormal responses. The increased excitability is typically triggered by a burst of activity in nociceptors, which alter the strength of synaptic connections between the nociceptor and the neurons of the spinal cord (so-called activity-dependent synaptic plasticity) (Hunt & Mantyh 2001; Woolf 2010; Woolf & Mannion 1999). As a result, an input that would normally evoke an innocuous sensation may now produce pain (Scholz & Woolf 2002; Woolf & Salter 2000). Altered peripheral and central signalling could be regarded as the structural correlate leading to

ongoing pain, hyperalgesia and / or allodynia which are frequently reported by patients with neuropathic pain.

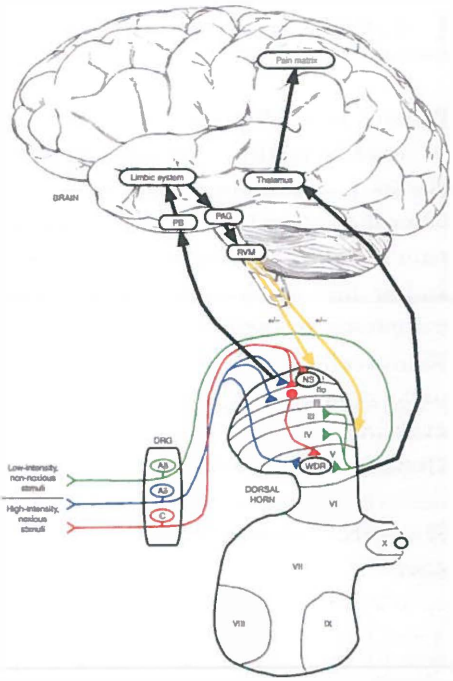

Figure 1-2: Pain pathways from periphery to brain

Primary afferent fibres (Aβ-, Aδ-, and C-fibres) transmit impulses fromthe periphery, through the dorsal root ganglion (DRG) and into the dorsal horn of the spinal cord. Nociceptive specific (NS) cells are mainly found in the superficial dorsal horn (laminae I–II), whereas most wide dynamic ranges (WDRs) are located deeper (lamina V). Projection neurones from lamina I innervate areas such as the parabrachial area (PB) and periaqueductal grey (PAG) and such pathways are affected by limbic areas. From here descending pathways (yellow arrows) from brainstem nuclei such as the rostral ventromedial medulla (RVM) are activated and modulate spinal processing. Lamina V neurones mainly project to the thalamus (spinothalamic tract), and from here the various cortical regions forming the 'pain matrix' (primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices) are activated.

From: D'Mello R., Dickenson A. H., Br. J. Anaesth. 2008;101:8-16 (with permission).

1.1. Neuropathic pain

The International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Most pain resolves quickly but sometimes pain becomes chronic despite removal of the stimulus and apparent healing of the body. Chronic pain is defined as pain lasting more than three months (Woolf & Mannion 1999). A specific subclass of chronic pain is neuropathic pain. The IASP defined neuropathic pain as a direct consequence of a lesion or disease affecting the somatosensory system (Treede et al 2008). The prevalence of neuropathic pain is estimated to be as much as 7–8% of the general population in Europe (Bouhassira et al 2008; Torrance et al 2006). Clinical entities of neuropathic pain include diabetic polyneuropathies, postherpetic neuralgia, trigeminal neuralgia, central post stroke pain and spinal cord injury pain. But also traumatic / postsurgical neuropathies and painful radiculopathies represent common conditions (Torrance et al 2006).

1. General introduction

Patients report that their neuropathic pain symptoms often have a burning, lancinating, or shooting quality with unusual tingling, crawling, or electrical sensations (Bennett et al 2007), which can be persistent or paroxysmal pain that is independent of a stimulus (Woolf & Mannion 1999). Patients with neuropathic pain may also experience evoked pain (i.e., stimulus-induced pain and hypersensitivity), mostly reported as mechanical and/or thermal hypersensitivity. Table 1-1 shows a summary of terms to describe symptoms and sensory signs commonly seen in neuropathic pain patients.
Neuropathic pain can be very disabling, severe and intractable for patients. The understanding of the underlying neurobiological processes in neuropathic pain is still evolving (Haanpaa et al 2009). The Joint Commission on Accreditation of Healthcare Organizations, USA, acknowledged the lack of understanding in the field of pain and declared the ten-years beginning 2001 as the "Decade of Pain Control and Research". Since the beginning of the new millennium pain is also regarded as the fifth vital sign.

Table 1-1: Common symptoms and signs in neuropathic pain

TERMS	DEFINITION
Symptoms	
Paresthesias	Non-painful positive sensations ("ant-crawling", "tingling")
Burning pain	Frequent quality of spontaneous pain sensations
Shooting pain	Spontaneous or evoked intense pain sensations of several seconds duration
Signs	
Hypesthesia	Impaired sensitivity to a stimulus
Tactile hypesthesia	Impaired sensitivity to tactile stimuli
Cold hypesthesia	Impaired sensitivity to cold
Hypoalgesia	Impaired sensitivity to a normally painful stimulus
Hyperalgesia	Increased pain sensitivity (may include a decrease in threshold and an increase in suprathreshold response)
Punctate hyperalgesia	Hyperalgesia to punctuate stimuli such as pinprick
Static hyperalgesia	Hyperalgesia to blunt pressure
Heat hyperalgesia	Hyperalgesia to heat stimuli
Cold hyperalgesia	Hyperalgesia to cold stimuli
Allodynia	Pain due to a non-nociceptive tactile stimulus

Adapted from Haanpää, M.L. et al., 2009; Am J Med , 2009; 122:S13-21

1.1.1. Diagnosis of neuropathic pain

Neuropathic pain is characterised by spontaneous and evoked pain (Fig. 1-3), by other positive symptoms such as paresthesias and by negative signs reflecting the neural damage (Table 1-1). It is not possible to determine the aetiology of neuropathic pain from the clinical characteristics of the pain (Attal et al 2008). Therefore, the diagnosis neuropathic pain should be made on grounds of coherent patient history and medical examination. Investigations of spontaneous pain features include "Neuropathic Symptoms Tools" such as pain scales, inventories and questionnaires. Physical examinations such as bedside tests are aimed to qualify sensory abnormalities. Additional appropriate laboratory studies including blood and serologic tests, magnetic resonance imaging, and electrophysiological studies should be conducted. In some instances, nerve or skin biopsy is necessary to directly visualise nerve fibres. Detailed guidelines on neuropathic pain assessment have been described recently (Cruccu et al 2010; Haanpaa et al 2010).

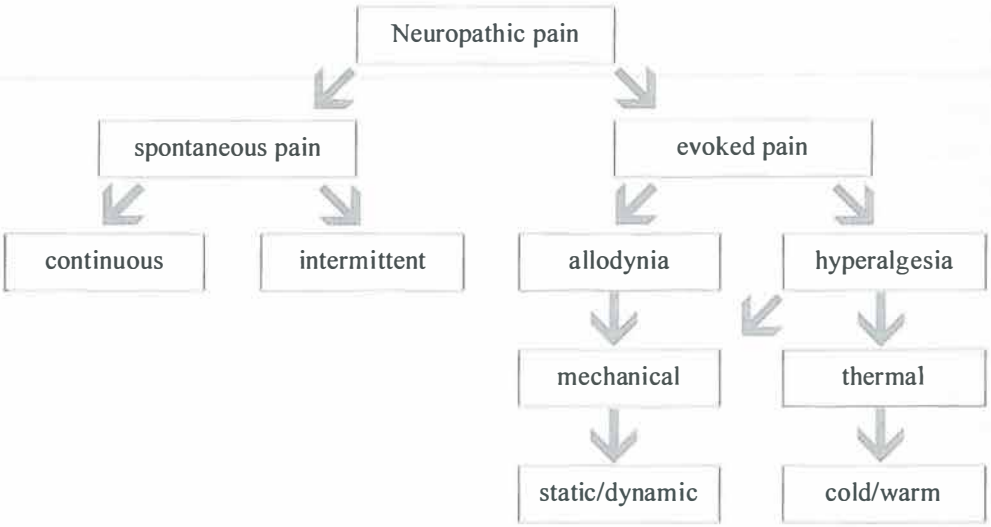

Figure 1-3: Components of neuropathic pain; adapted from Woolf C.J., Mannion R.J.,Lancet 1999; 353:1959-1964

Neuropathic pain is not only very challenging to diagnose but also to manage due to the heterogeneity of its aetiologies, symptoms and underlying mechanisms (Beniczky et al 2005).

1.1.2. Treatment of neuropathic pain

Neuropathic pain is often difficult to treat, as many medications are ineffective and/or, if effective, lead to intolerable adverse effects. Drugs that are used to manage neuropathic pain include antidepressants, anti-convulsant drugs, opioids and topical treatments such as capsaicin and lidocaine. Simple analgesics such as non-steroidal anti-inflammatory

drugs (NSAIDS) and paracetamol are considered not to be efficacious for this type of pain (Dickenson 1995). Many patients require treatment with more than one drug or classes of drugs, but the correct choice of drugs, and the optimal sequence for their use, is still not defined. Therefore, management of pain should be tailored to the individual patient on the basis of type of pain, the causative disease, and psychosocial aspects. A treatment cascade was implemented recently, incorporating an evidence-based symptomatic pharmacotherapy of neuropathic pain (Attal et al 2010; Dworkin et al 2007b).
During the last decades, basic pain research brought detailed understanding of concepts and theories regarding pain mechanisms such as the gate control theory (Melzack & Wall 1965) the concept of neuroplasticity (Melzack et al 2001; Woolf & Salter 2000), and an understanding of the cellular and molecular mechanisms of peripheral and central sensitisation (Basbaum et al 2009; Hunt & Mantyh 2001; Ji et al 2003). These developments in the understanding of pain mechanisms have been translated into clinical practice, resulting in a multimodal approach to pain relief. However, in neuropathic pain patients a decrease of pain of more than 50% is only achieved in less than one-third of the patients studied (Argoff et al 2006; Farrar et al 2001; McQuay et al 1996; Sindrup & Jensen 1999; Ziegler 2008). The lack of efficacy could be based on the limiting side-effect profile or due to addictive properties of the drug, which might compromises the therapeutic dose window. On other hand, such a lack in treatment efficacy might be based on the fact that neuropathic pain is still being classified based on its underlying aetiology (Hansson 2003; Jensen et al 2001; Woolf & Mannion 1999). There are, however, promising developments to address these short-comings.

Recently, a more neurological approach to categorise neuropathic pain was suggested. In order to determine with a greater level of certainty whether a pain condition is neuropathic, a grading system of definite, probable, possible and unlikely neuropathic pain was proposed (Treede et al 2008). Briefly, the grade 'unlikely' excludes patients lacking a history of a lesion or disease for a plausible neuroanatomical distribution of their pains. The grade 'possible' is regarded as a working hypothesis, which does not exclude, neither diagnoses neuropathic pain. Patients who fall into the category 'possible' neuropathic pain can be transferred into the grades 'probable' and 'definite' if neurologic examination and / or a test e.g. MRI, biopsy or laboratory parameter confirm the diagnosis of the suspected lesion or disease, respectively. An advantage of this grading system is the precise identification of a lesion or disease and the ability to directly link these to somatosensory changes.

A few years ago, a new hypothetical concept was proposed, in which pain is classified on the basis of underlying mechanisms (Dworkin et al 2003; Sindrup & Jensen 1999; Woolf et al 1998). Supportive to this concept are clinical experimental studies (Attal et al 2004; Baron et al 2009) indicating that a specific symptom might be generated by

several entirely different underlying pathophysiological mechanisms. This implies that a specific symptom profile rather than a single symptom might be required to predict the underlying mechanism (Baron 2006). It is obvious that new concepts such as a mechanism-based classification of neuropathic pain aiming for a better understanding and improved treatment for neuropathic pain should be further explored. Precise somatosensory phenotyping of patients with neuropathic pain might enable the direct translation of these ideas into the clinic. In this context, a comprehensive understanding of the somatosensory representation of neuropathic pain is evolving and Quantitative Sensory Testing plays a major role on this stage.

1.2. Quantitative Sensory Testing (QST)

In 2006, Rolke and colleagues published sequential papers evaluating a quantitative sensory testing battery aimed to precisely characterize somatosensation in patients with neuropathic pain and healthy volunteers (for reference data) (Rolke et al 2006a; Rolke et al 2006b). Limited sensory testing such as bedside testing has been used by clinicians to identify and qualify neuropathic pain. In contrast, with the development of standardized Quantitative Sensory Testing (QST) protocols such as was provided by the German Research Network on Neuropathic Pain (DFNS), a methodology is available to detect and quantify sensory loss and sensory gain in a standardized manner. This DFNS protocol uses 13 different mechanical and thermal stimuli (e.g. graded von Frey filaments, pin-prick devices, a pressure algometer, and quantitative thermo-testing). It takes about 30 minutes to test one location of the body in healthy volunteers, versus about 45 minutes in patients.

This QST battery tests different sub-modalities of nerve fibres involved in the transduction of sensory information from the periphery to the spinal cord such as Aβ-fibre, Aδ-fibre and C-fibre (Table 1-2). When present, allodynia or hyperalgesia can be quantified by measuring intensity, threshold for elicitation and duration (Rolke et al 2006a; Rolke et al 2006b). It has been shown that QST is sensitive for quantifying sensory abnormalities on an individual patient level (Rolke et al 2006a). Subsequently, it may be presumed that QST applied in large patient samples might allow to discriminate distinct responders to the different stimuli on a group level.

Table 1-2: Simplified overview of nerve fibres sub-modalities tested by QST

QST parameter	CPT	HPT	WDT	WUR	CPT	TSL	PHS	MPT	MPS	MDT	DMA	VDT	PPT
C-fibre	X	X	X	X									X
Aδ-fibre					X	X	X	X	X				X
Aβ-fibre										X	X	X	

Potential overlapping modalities for each nerve fibre type are not shown. QST parameters are: Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Warm Detection Threshold (WDT), Wind Up Ratio (WUR), Cold Detection Threshold (CDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensation (PHS), Mechanical Pain Threshold (MPT), Mechanical Pain Sensitivity (MPS), Mechanical Detection Threshold (MDT), Dynamic Mechanical Allodynia (DMA), Vibration Disappearance Threshold (VDT) and Pressure Pain Threshold (PPT). All nerve fibre functionality tests are applied to the skin with exception of PPT (deep tissue C-fibre/Aδ-fibre test).

1.2.1. QST and homogenous groups of somatosensory abnormalities

QST might offer a tool to identify homogenous groups of somatosensory abnormalities in patients with neuropathic pain for the evaluation of novel pain compounds. The approach currently used in clinical trials is the assessment of general pain relief values for specific aetiologies, which might partially explain the failure to obtain complete pain relief in neuropathic pain conditions (Baron 2006). This is in line with the Food and Drug Administration (FDA) that requests the inclusion of patient populations for clinical trial based on disease endpoints for the registration of pain medication. More pragmatic in the current environment is to use a disease endpoint recognised by the FDA but to reduce heterogeneity in the patient group in order to reduce variability in the trial and increase the power. A classification based on sensory abnormalities rather than based merely on aetiology could contribute to minimising pathophysiological heterogeneity within study groups (Attal et al 2008). Such an approach would recognise not only pain as an outcome measure but also addresses troublesome features such as hyperalgesia and allodynia frequently reported by patients with neuropathic pain. There is a need for a different method of evaluating pain medications to increase positive treatment responses e.g. increase assay sensitivity. QST-based identification of homogenous patient populations could help to clarify the relationships between the aetiology and somatosensory abnormalities in neuropathic pain patients. This is a particularly interesting approach when such groups of somatosensory-wise homogenous pain patients are investigated further with e.g. neuroimaging techniques to reveal potential group-specific changes in the brain.

Human brain imaging studies show that structural changes and brain function changes in different neural regions including the thalamus, nucleus accumbens, basal ganglia,

dorsolateral prefrontal cortex, and cerebellum occur in chronic pain (Apkarian et al 2011; DaSilva et al 2008; Geha et al 2008; Gustin et al 2011; Schweinhardt & Bushnell 2010; Tracey 2007; 2008; Tracey & Bushnell 2009; Tracey et al 2002). Precise phenotypic characterisation and imaging may be used to set objective criteria with which to measure disease and evaluate its treatment. QST phenotypic characterisation aiming to select patients for enrolment into clinical trials might decrease variance and increase the power to detect meaningful drug effects.

Objectives of this thesis are to investigate:

1. Implications of QST for clinical neuropathic pain practice:
   - **a.** Are there differences in the diagnostic outcome of sensory signs in patients with neuropathic pain assessed by QST and bedside tests? (chapter 2)
   - **b.** Does a greater level of certainty whether a pain condition is neuropathic reflect an increase in numbers of sensory abnormalities or/and specific patterns of sensory signs? (chapter 3)

2. Implications of QST for clinical neuropathic pain research:
   - **a.** Is QST valid to be used as a tool to identify somatosensory homogenous groups of patients with neuropathic pain? (chapter 4)

3. Implications of QST in non-neuropathic pain diseases:
   - **a.** Is QST sensitive to identify pain-contributing somatosensory changes in patients with patellar tendinopathies? (chapter 5)

To address these objectives, a large QST database including healthy volunteers and patients with neuropathic pain was established. QST data from neuropathic pain patients were compared to those obtained from healthy controls with the aim to gain insight into the presence of abnormal somatosensory function in neuropathic pain patients.

Chapter 2

Bilateral sensory abnormalities in patients with unilateral neuropathic pain; a Quantitative Sensory Testing (QST) study

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submitted

2. Bilateral abnormalities in neuropathic pain

Abstract

In patients who experience unilateral chronic pain, abnormal sensory perception at the non-painful side has been reported. Contralateral sensory changes in these patients have been given little attention, possibly because they are regarded as clinically irrelevant. Still, bilateral sensory changes in these patients could become clinically relevant if they challenge the correct identification of their sensory dysfunction in terms of hyperalgesia and allodynia. Therefore, we have used the standardized quantitative sensory testing (QST) protocol of the German Research Network on Neuropathic Pain (DFNS) to investigate somatosensory function at the painful side and the corresponding non-painful side in unilateral neuropathic pain patients using gender- and age-matched healthy volunteers as a reference cohort.

Sensory abnormalities were observed across all QST parameters at the painful side, but also, to a lesser extent, at the contralateral, non-painful side. Similar relative distributions regarding sensory loss/gain for non-nociceptive and nociceptive stimuli were found for both sides. Once a sensory abnormality for a QST parameter at the affected side was observed, the prevalence of an abnormality for the same parameter at the non-affected side was as high as 58% (for Pressure Pain Threshold).

Our results show that bilateral sensory dysfunction in patients with unilateral neuropathic pain is more rule than exception. Therefore, this phenomenon should be taken into account for appropriate diagnostic evaluation in clinical practice. This is particularly true for mechanical stimuli where the 95% Confidence Interval for the prevalence of sensory abnormalities at the non-painful side ranges between 35% and 52%.

2. Bilateral abnormalities in neuropathic pain

1. Introduction

In clinical practice, the assessment of chronic pain includes documentation of pain location, intensity, quality and onset/duration aimed to elucidate the underlying pathophysiological mechanism. Sensory testing is an important part of this assessment which is aimed at identifying phenomena such as hyperalgesia (increased response to painful stimuli) and allodynia (painful response to normally non-painful stimuli) for thermal and mechanical stimuli (Haanpaa et al 2009). For this clinical evaluation, patients are generally used as their own control when comparing profiles of sensory dysfunction at the painful side with the contralateral non-painful area (Haanpaa et al 2009; Walk et al 2009). The correct identification of the specifics of sensory dysfunction in each chronic pain patient is obviously of major importance for addressing the underlying mechanism such as peripheral or spinal hyperexcitability and has consequences for pharmacological treatment.

There are only a few studies reporting bilateral sensory abnormalities in chronic pain conditions. Huge and co-workers, 2008 investigated thermal sensory function at the affected and non-affected side of acute and chronic complex regional pain syndrome (CRPS) patients and found bilateral sensory changes for both patient groups (Huge et al 2008). Another study investigating bilateral warmth/cold detection and heat/cold pain thresholds over the hand/wrist in patients with unilateral carpal tunnel syndrome (CTS) revealed bilateral thermal hyperalgesia in patients with strictly unilateral CTS compared to controls (de la Llave-Rincon et al 2009). In a similar patient population, Fernández-de-las-Peñas and colleagues (2009) reported bilateral pressure pain hyperalgesia in patients with unilateral CTS.

In spite of the studies referred to above, the occurrence of contralateral sensory changes in situations where the pain is experienced only unilaterally is still not generally acknowledged. Possibly this is because it is regarded clinically irrelevant. However, bilateral sensory changes could become clinically relevant in patients with unilateral pain if they challenge the correct qualification of sensory dysfunction. For example, if a mechanical stimulus which is known to be slightly painful presented at the non-affected and affected side is rated by the patient as equally painful at both sides, one could conclude normal sensory functioning. However, if both the non-affected and affected side of this patient are hyperalgesic for this particular stimulus, the conclusion of a mechanical hyperalgesia could be overseen. The German Research Network on Neuropathic Pain (DNFS) established a standardized Quantitative Sensory Testing (QST) protocol which allows a comprehensive somatosensory characterisation of chronic neuropathic pain patients, using reference values from healthy volunteers (Rolke et al 2006a). Since this approach does not rely on reference values obtained from the patient's own contralateral side, it offers a unique opportunity to study bilateral somatosensory function in patients with chronic unilateral pain in a detailed, standardized manner.

2. Bilateral abnormalities in neuropathic pain

Based on previous reports we hypothesize that bilateral somatosensory abnormalities are frequently present in unilateral chronic pain patients and that bilateral sensory changes may exist for the same QST parameter. To test this we selected a large cohort of patients with unilateral neuropathic pain. We examined the painful side and its corresponding contralateral area using the standardized DNFS QST protocol comparing values with those obtained from age- and gender-matched healthy volunteers.

2. Methods

The study adhered to the declaration of Helsinki was approved by the medical ethical committee "Stichting Beoordeling Ethiek Bio-Medisch Onderzoek, P.O. Box 1004, 9400 BA Assen, The Netherlands", including patients and healthy controls from the local region. All participants signed an informed consent form.

2.1. Description of healthy controls

In total, 209 age- and gender-matched healthy volunteers (age range 20-73 years), 138 females (age 45.3 ± 13.4 years) and 71 males (age 48.7 ± 14.0 years) underwent the QST assessments on their dorsal hand and foot. These body locations have been indicated by Rolke et al., 2006 as reference sites for QST (Rolke et al 2006a). A previous study concluded that there were no significant differences in QST parameters between the right and left sides of the body in healthy volunteers (Rolke et al 2006a), thus we obtained QST reference values from one side of the body. In total, 418 QST references from the upper and the lower extremity were obtained. Healthy subjects were identified according to medical history. Subjects were specifically questioned about previous injuries or diseases. The healthy subjects did not use pain medication regularly and were free of medication at the time of the assessments.

2.2. Description of the patient cohort

Patients were recruited from the outpatient Department of the Pain Management Unit of the University Medical Center Groningen, The Netherlands. All patients were diagnosed as suffering from neuropathic pain by the physicians of the pain management unit. Neuropathic pain diagnosis was made on grounds of coherent patient history, medical history, physical examination, including neurologic function tests. Each clinical diagnosis was additionally confirmed by an experienced pain specialist of the Pain Management Unit based on patient's files. In total, 81 neuropathic pain patients (43 females age 52.6 ± 12.7 years and 38 males age 49.8 ± 13.0 years) underwent the QST assessment, each at the area where the most profound pain was experienced and at their contralateral counterpart (leg: n=42, arm: n=19, thorax: n=7, groin: n=4, shoulder: n=3, back: n=2, neck: n=1, abdomen: n=1, flank: n=1).

Prior to undergoing the QST assessments, patients were asked to rate their ongoing

pain level using a Numerical Rating Scale (NRS) of '0' indicating "no pain", and '100' indicating "most intense pain imaginable". Patients did not discontinue their regular pain treatment if applicable.

2.3 Quantitative sensory testing (QST)

The QST battery consisted of seven tests, measuring thirteen parameters and was applied according to the standardized protocol of Rolke et al., 2006 (Rolke et al 2006a). QST was performed by two research nurses, who underwent a comprehensive training at the DNFS in Germany. All tests were performed at the same research facility of PRA Int., Groningen, The Netherlands. The average room temperature was 22.8°C; SD ± 1.8°C.

Thermal QST tests were performed using the Medoc Pathway System (Medoc, Israel) and consisted of six parameters: threshold assessments for warm and cold detection (WDT, CDT) and heat pain and cold pain (HPT, CPT). In addition, subjects were asked about paradoxical heat sensations (PHS) during the thermal sensory limen (TSL) procedure of alternating warm and cold stimuli.

Mechanical QST tests consisted of seven different parameters. The mechanical detection threshold (MDT) was determined with a standardized set of modified von Frey filaments (Optihair2-Set, Marstock Nervtest, Germany). The mechanical pain threshold (MPT) was measured using a set of seven pinprick devices (flat contact area of 0.2 mm in diameter) with fixed stimulus intensities that exerted forces of 8, 16, 32, 64, 128, 256, and 512 mN. Mechanical pain sensitivity (MPS) was assessed using the same set of seven weighted pinprick stimuli to obtain a stimulus–response function for pinprick-evoked pain. Dynamic mechanical allodynia (DMA) was assessed as part of the test above, using a set of three light tactile stimulators as dynamic innocuous stimuli: cotton wisp, cotton wool tip fixed to an elastic strip and a standardized brush (SENSElab No.5, Somedic, Sweden).

Vibration detection threshold (VDT) was performed with a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale) that was placed over a bony prominence. The wind up ratio (WUR) test was assessed with a pinprick intensity of 256 mN. The pressure pain threshold (PPT) was determined over muscle with a pressure gauge device (FDN200, Wagner Instruments, CT, USA).

2.4. Data analysis and statistics

2.4.1. Z-transformation of QST data

QST data of patients with neuropathic pain were compared with reference data from gender and age matched healthy subjects. Both, patients and healthy subjects were

divided into two age groups each (20-45 years of age and 46-75 years of age). QST values of chronic pain locations and their mirror image area at the upper extremities were compared to QST reference values obtained from the dorsal hand of healthy controls (n=63 for females and n=29 for males for age group 20-45 years; n=75 for females and n=42 for males for age group 46-75 years), whereas values from chronic pain locations at lower extremities and their mirror image area were compared to reference values obtained from the dorsal foot of healthy controls (n=63 for females and n=29 for males for age group 20-25 years; n=75 for females and n=42 for males for age group 46-75 years). QST values from each patient were transformed to z-scores as described by Rolke et al., 2006 (Rolke et al 2006a). A score above 1.96 or below -1.96 falls outside the 95% confidence interval of the mean reference value and was considered as a sensory abnormality. Abnormalities were subsequently categorized as either a sensory gain or a sensory loss.

Because "dynamic mechanical allodynia" (DMA) never occurs in healthy volunteers, the QST parameter could not be used for z-score analysis. Alternatively, patients ratings greater than NRS 10 (scale 0-100) were regarded as clinically relevant and were identified as abnormal.

For the QST parameter "wind up ratio" (WUR), twenty-three patients (thirteen assessments at the affected side and ten assessments at the contralateral side) rated the single pinprick stimulus as "0" making ratio calculations (painfulness of one pinprick stimulation vs. painfulness of a train of ten pinprick stimulations) for Wind-up impossible. For these patients WUR was not used for subsequent analyses.

2.4.2. Proportion of patients with sensory abnormalities at the affected side

For each QST parameter, the proportion of patients with sensory abnormalities at the painful, affected side was calculated. To estimate the prevalence of sensory abnormalities in the general patient population we calculated the 95% confidence intervals of the calculated proportions using the 'Wilson Estimate' of proportion (Moore & McCabe 2003). These 95% confidence intervals give an indication of the expected range of the occurrence of abnormalities in the general pain patient population with neuropathic pain and tests whether the proportion differs significantly from zero ($p<0.05$).

2.4.3. Proportion of patients with sensory abnormalities at the contralateral side

For each QST parameter, the proportion of patients with sensory abnormalities at the non-painful, contralateral side was calculated applying the same procedure (see 2.4.2.).

2.4.4. Proportion of patients with sensory abnormalities for the same QST parameter at the affected and contralateral side

For each patient, the presence or absence of a sensory abnormality at the contralateral side for a particular QST parameter was determined when the patient had already shown a sensory abnormality for this QST parameter at the affected side. This allowed the direct identification of a relationship between bilateral sensory abnormalities for the same QST parameter. To increase statistical power we recalculated the above proportions but now pooled the thermal QST parameters (CPT, HPT, WDT, CDT, TSL and PHS) into one overall thermal QST domain and pooled the mechanical QST parameters (WUR, MPT, MPS, MDT, VDT, PPT and ALL) into one overall mechanical domain.
Again we estimated the prevalence of sensory abnormalities in the general patient population with the 'Wilson Estimate'. All proportions are reported as percentages.

2.4.5. Correlation between background pain and sensory abnormalities

To identify correlations between ongoing background pain and values for each QST parameter Pearson correlations were calculated.

2.4.6. Correlation between numbers of sensory abnormalities at the affected and contralateral side

The overall numbers of sensory abnormalities for the affected and contralateral side across the thirteen QST parameters were compared to identify possible relationships using Pearson correlations.

3. Results

3.1. QST observations in healthy controls

From the healthy volunteer cohort (n=209) investigated in this study, a total of 418 locations were assessed and 5434 measurements were analysed by means of z-score profiling.

3.1.1. Sensory function in healthy controls

Although the majority of the QST results obtained in healthy subjects confirmed normal sensory function for this cohort, incidental sensory abnormalities (4.3%) were observed for all QST parameters with the exception of DMA.
Out of the total of 418 different body areas that were tested across all healthy controls 62.0% (259 locations) showed normal sensory function and 38.0% (159 locations) showed a sensory abnormality for at least one QST parameter. Sensory abnormalities were regarded as sensory gain in 20.8%, sensory loss in 12.7% and a mixture of sensory gain and sensory loss in 4.5% of the cases (Fig.2-1).

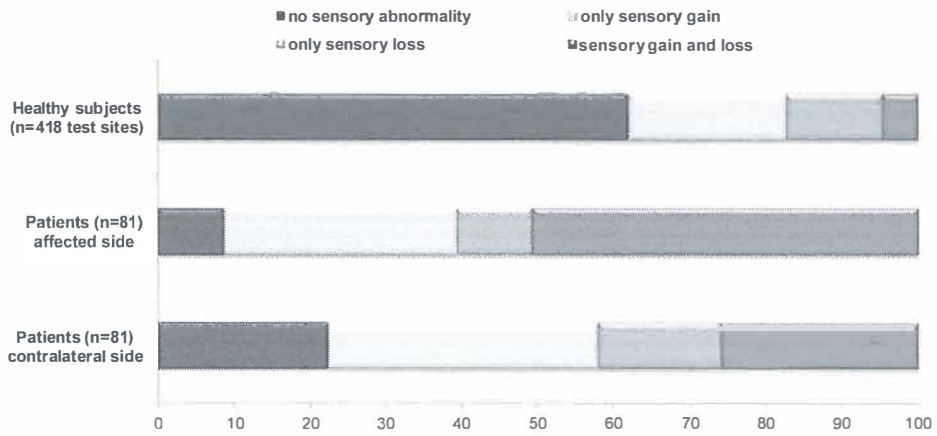

Figure 2-1: Sensory findings (gain and/or loss of sensory function) in % for healthy controls (n=208 with 418 test sides) and for patients at the affected and contralateral side (n=81). "No sensory abnormalities": none of the Quantitative Sensory Testing (QST) parameters were outside the 95% CI. "Only sensory gain": at least one QST parameter indicating thermal or mechanical hyperesthesia or hyperalgesia without the presence of hypoesthesia or hypoalgesia. "Only sensory loss": at least one QST parameter indicating thermal or mechanical hypoesthesia or hypoalgesia without the presence of hyperesthesia or hyperalgesia. "Sensory gain and loss": at least one positive sign combined with one negative sign.

3.2. Demographics of patients

Demographic data of the patients are shown in Table 2-1. All patients reported ongoing spontaneous pain only at their affected side ranging from 3 to 90 (Mean 64.1± 21.4 SD) on a 0-100 NRS just before the QST assessment took place. The aetiology of patient's pain in our sample was quite diverse, but did not include central pain patients. The largest subgroups developed pain after a surgical intervention (n=27) including one patient with Complex Regional Pain Syndrome-II (CRPS) followed by an accident with trauma including fractures (n=26). Other patients reported pain after failed back surgery (n=8), Herniated nucleus pulposus (n=7), amputation (n=4), radiotherapy (n=3), peripheral nerve entrapment (n=2). Three patients were diagnosed with postherpetic neuralgia and one patient was with Meralgia paresthetica (see Table 2-1).

2. Bilateral abnormalities in neuropathic pain

Table 2-1. Demographics of patients.

Patient	Gender	Age	Pain NRS (0-100)	Cause of Pain	Involved nerve	Clinical diagnosis	Number of QST abnormalities at affected side	Number of QST abnormalities at contralateral side
1	F	25	70	Accident with trauma	N. digitalis	peripheral nerve injury	3	2
2	F	39	80	Postsurgical pain	N. radialis	peripheral nerve injury	1	1
3	F	41	40	Postsurgical pain	TH 11	peripheral nerve injury	3	0
4	F	41	70	Metacarpal fracture	N. ulnaris	peripheral nerve injury	3	0
5	F	46	75	Accident with trauma	C 6	peripheral nerve injury	1	1
6	F	46	85	Postsurgical pain	N. digitalis palmaris	peripheral nerve injury	2	2
7	F	46	40	Amputation	N. cutaneous brachii	peripheral nerve injury	3	1
8	F	48	60	Accident with trauma	N. ulnaris	peripheral nerve injury	0	0
9	F	51	80	Peripheral nerve entrapment	C 6/7	peripheral nerve injury	4	2
10	F	51	70	Postsurgical pain	TH 11/12	peripheral nerve injury	2	2
11	F	53	80	Radiotherapy	TH 3-TH 6	peripheral nerve injury	4	3
12	F	64	60	Accident with trauma	TH 9/10	peripheral nerve injury	3	1
13	F	66	75	Accident with trauma	Cranial nerve XI	peripheral nerve injury	3	2
14	F	67	85	Herniated nucleus pulposus	TH 6/7	peripheral nerve injury	3	0
15	F	71	3	Herpes zoster	TH 12	postherpetic neuralgia	6	1
16	F	73	25	Herpes zoster	TH 11	postherpetic neuralgia	3	0
17	F	27	70	Femur fracture	N. sapheneus internus	peripheral nerve injury	8	2
18	F	36	80	Cruris fracture	N. tibialis	peripheral nerve injury	6	3
19	F	37	80	Postsurgical pain	TH 9/10	peripheral nerve injury	2	3
20	F	40	70	Amputation	N. tibialis	peripheral nerve injury	4	1
21	F	41	70	Postsurgical pain	N. peroneus and N. tibialis	peripheral nerve injury	4	0
22	F	42	70	Herniated nucleus pulposus	N. peroneus profundus	peripheral nerve injury	4	1
23	F	43	75	Accident with trauma	N. tibialis	peripheral nerve injury	4	2
24	F	43	75	Meralgia paresthetica	N. femoralis	peripheral nerve injury	2	3
25	F	46	75	Accident with trauma	N. peroneal	peripheral nerve injury	3	2
26	F	47	80	Accident with trauma	L 4	peripheral nerve injury	2	3
27	F	49	50	Accident with trauma	N. tibialis	peripheral nerve injury	4	5
28	F	49	30	Failed back surgery	L 5-S 1	peripheral nerve injury	5	3
29	F	50	10	Radiotherapy	Plexus brachialis	peripheral nerve injury	3	3
30	F	52	100	Failed back surgery	L 5/6	peripheral nerve injury	3	2
31	F	55	90	Herniated nucleus pulposus	L 5-S 1	peripheral nerve injury	3	2
32	F	56	90	Postsurgical pain	N. Suralis	peripheral nerve injury	2	1
33	F	58	90	Postsurgical pain	N. femoralis	peripheral nerve injury	2	1
34	F	59	60	Postsurgical pain	N. plantaris	peripheral nerve injury	5	1
35	F	61	80	Postsurgical pain	L 4/5	peripheral nerve injury	2	3
36	F	62	80	Failed back surgery	L 5-S 1	peripheral nerve injury	6	0
37	F	65	70	Herniated nucleus pulposus	L 5-S 1	peripheral nerve injury	5	6
38	F	65	50	Amputation	Peroneal nerves	peripheral nerve injury	7	1
39	F	66	70	Postsurgical pain	N. peroneus	peripheral nerve injury	2	1
40	F	66	90	Postsurgical pain	N. tibialis	peripheral nerve injury	5	3
41	F	71	65	Failed back surgery	L 5-S 1	peripheral nerve injury	3	2
42	F	72	80	Failed back surgery	L 4/5	peripheral nerve injury	2	2
43	F	75	80	Herniated nucleus pulposus	L 4/5	peripheral nerve injury	4	2
44	M	23	70	Postsurgical pain	TH 8/9	peripheral nerve injury	2	2
45	M	26	85	Accident with trauma	C 8	peripheral nerve injury	5	0
46	M	32	40	Postsurgical pain	TH 11	peripheral nerve injury	4	1
47	M	38	90	Accident with trauma	N. brachialis	peripheral nerve injury	1	6
48	M	47	80	Accident with trauma	L 4/5	peripheral nerve injury	8	5
49	M	42	70	Failed back surgery	L 5/6	peripheral nerve injury	7	2
50	M	43	90	Postsurgical pain	TH 10 /12	peripheral nerve injury	6	3
51	M	49	40	Accident with trauma	N. ulnaris	peripheral nerve injury	2	1
52	M	50	70	Radiotherapy	TH 2	peripheral nerve injury	1	4
53	M	50	75	Rib fracture	TH 11	peripheral nerve injury	6	2
54	M	52	55	Postsurgical pain	N. ulnaris	CRPSII	2	2
55	M	53	45	Accident with trauma	N. ulnaris	peripheral nerve injury	2	2
56	M	55	50	Accident with trauma	N. radialis	peripheral nerve injury	2	1
57	M	56	55	Postsurgical pain	N. axillaris	peripheral nerve injury	1	1
58	M	58	40	Herniated nucleus pulposus	C 5-C 7	peripheral nerve injury	0	0
59	M	58	80	Postsurgical pain	N. radialis	peripheral nerve injury	1	1
60	M	59	60	Accident with trauma	N. radialis	peripheral nerve injury	2	1
61	M	60	80	Postsurgical pain	C 4	peripheral nerve injury	0	1
62	M	63	65	Accident with trauma	N. digiti	peripheral nerve injury	0	0

to be continued on page 34

continued from page 33

Table 2-1. Demographics of patients.

Patient	Gender	Age	Pain NRS (0-100)	Cause of Pain	Involved nerve	Clinical diagnosis	Number of QST abnormalities at affected side	Number of QST abnormalities at contralateral side
63	M	73	10	Herpes zoster	TH 8	postherpetic neuralgia	0	0
64	M	24	50	Postsurgical pain	N. Ilioinguinalis	peripheral nerve injury	8	2
65	M	28	75	Postsurgical pain	N. tibialis	peripheral nerve injury	5	1
66	M	40	60	Amputation	N. plantaris	peripheral nerve injury	2	1
67	M	41	3	Failed back surgery	S 1	peripheral nerve injury	4	1
68	M	43	60	Accident with trauma	L 4	peripheral nerve injury	4	1
69	M	44	40	Accident with trauma	N. femoralis	peripheral nerve injury	1	0
70	M	44	35	Postsurgical pain	N. Ilioinguinalis	peripheral nerve injury	2	0
71	M	46	65	Failed back surgery	L 4/5	peripheral nerve injury	0	0
72	M	47	75	Postsurgical pain	N. tibialis	peripheral nerve injury	4	1
73	M	51	70	Postsurgical pain	N. femoralis	peripheral nerve injury	3	0
74	M	53	70	Accident with trauma	L 5	peripheral nerve injury	0	0
75	M	54	50	Postsurgical pain	N. grenito-femoralis	peripheral nerve injury	2	0
76	M	57	75	Tibia fracture	N. tibialis	peripheral nerve injury	5	4
77	M	62	70	Accident with trauma	N. peroneus	peripheral nerve injury	2	0
78	M	63	80	Postsurgical pain	N. saphenus	peripheral nerve injury	1	1
79	M	65	65	Herniated nucleus pulposus	L 5	peripheral nerve injury	5	4
80	M	73	10	Peripheral nerve entrapment	L 5-S 1	peripheral nerve injury	3	2
81	M	75	60	Postsurgical pain	N. tibialis	peripheral nerve injury	1	2

Demographic patient overview; Patient ID, gender and age are indicated. Patient's rating of ongoing pain prior to Quantitative Sensory Testing (QST) using a Numeric Rating scale (NRS) indicating "0" as "no pain" and "100" as the "most intense pain imaginable". Involved nerve indicates nerves (N.) or innervations area of nerves affected in relation to the cause of pain. Number of QST abnormalities refers to the number of QST parameter exceeding CI 95% of z-scores at the affected and contralateral side.

3.3. QST observations in patients

For the 81 patients investigated in this study, 2106 QST data measurements were obtained from both the affected and contralateral side. The total of 2083 measurements were analysed by means of z-score profiling.

3.3.1. Sensory function in patients

In patients with neuropathic pain, sensory abnormalities were observed in all QST parameters at both affected and contralateral side (Fig. 2-2). In our patient cohort, 91% had at least one QST abnormality at the affected side. Of the patients without sensory abnormalities at the affected side (9%), 14% still showed at least one sensory abnormality at the contralateral side. At the affected side, 50% of the patients had a mixture of sensory gain and loss, 31% had only sensory gain (hyperalgesia), and 10% had only sensory loss (hypesthesia) (Fig. 2-1).

At the contralateral side, 78% of the patients had at least one QST abnormality. In 26% of the patients a mixture of sensory gain and loss was present. Almost 36% of the patients showed only sensory gain and 16% had only sensory loss at the contralateral side (Fig. 2-1).

2. Bilateral abnormalities in neuropathic pain

95% Confidence Intervals confirmed that the prevalence of normal sensory function differs significantly between healthy controls and patients at the painful and non-painful side (all $p<0.05$). A significant difference was also present between the painful side and non-painful side of the patients ($p<0.05$).

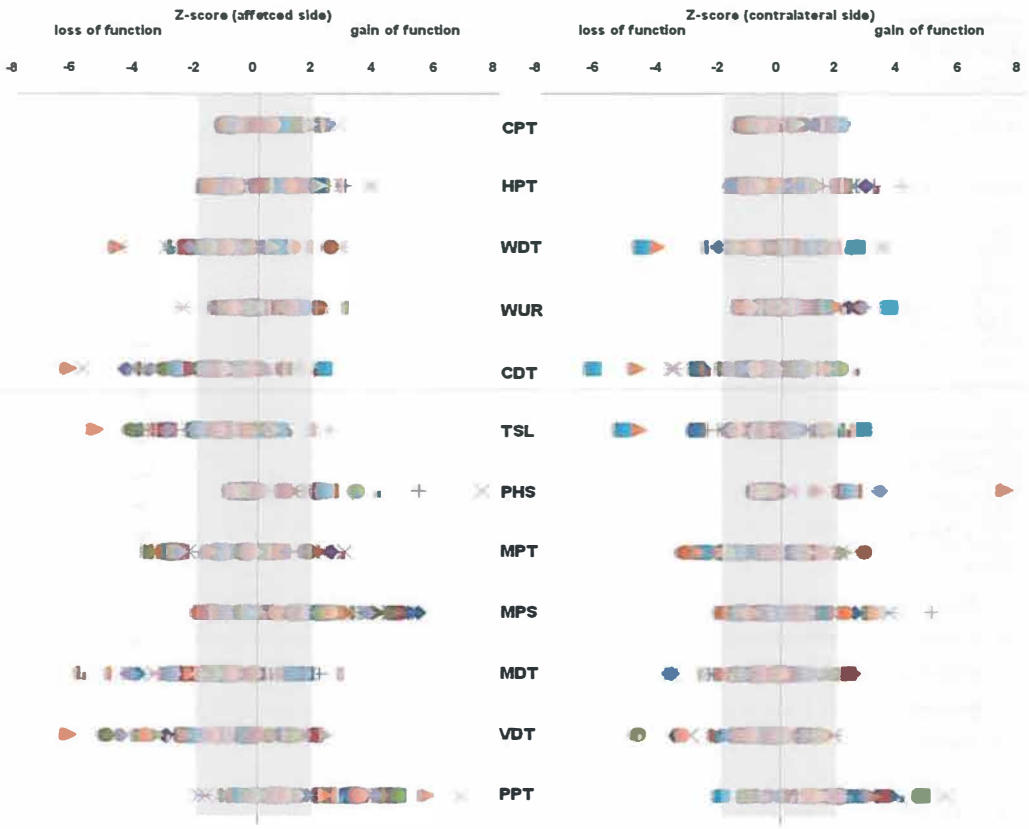

Fig. 2-2: Z-score profile for each Quantitative Sensory Testing (QST) parameter at the affected side (left) and contralateral side (right) in 81 neuropathic pain patients. Gray shade indicates normative data with 95% CI obtained from healthy references. A Z-score exceeding the upper or lower bound of CI 95% is regarded as a significant gain or loss of function, respectively. QST parameters: Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Warm Detection Threshold (WDT), Wind Up Ratio (WUR), Cold Detection Threshold (CDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensation (PHS), Mechanical Pain Threshold (MPT), Mechanical Pain Sensitivity (MPS), Mechanical Detection Threshold (MDT), Vibration Disappearance Threshold (VDT), Pressure Pain Threshold (PPT).

3.3.2. Sensory changes at patients affected side

Sensory abnormalities at the affected side ranged from 7.4% (n=5) for WUR to 48.1% (n=39) for PPT. 95% Confidence Intervals confirmed that the prevalence differed significantly from zero ($p<0.05$) for all QST parameters with highest incidence for MPT (95CI: 27%-48%) and PPT (95CI: 38%-59%) (Table 2-2A).

For the nociceptive parameters (CPT, HPT, PPT, MPS, WUR) there were predominantly changes reflecting hyperalgesia, whereas for the non-nociceptive ones (CDT, WDT, TSL, MDT, VDT) they reflected hypesthesia (Fig. 2-3).

Table 2-2A and 2-2B: Overview of sensory abnormalities in QST

2A

QST parameter affected side	CPT	HPT	WDT	WUR	CDT	TSL	PHS	MPT	MPS	MDT	VDT	PPT	DMA
n of sensory abnormality	7	11	17	5	20	21	20	30	20	25	19	39	16
n of sensory gain	7	11	3	4	1	1	20	6	20	2	1	39	16
n of sensory loss	0	0	14	1	19	20	0	24	0	23	18	0	0
% of sensory abnormality	8,6	13,6	21,0	7,4	24,7	25,9	24,7	37,0	24,7	30,9	23,5	48,1	19,8
Wilson estimates lower CI 95%	4,0	7,6	13,5	2,9	16,6	17,6	16,6	27,3	16,6	21,9	15,5	37,6	12,5
Wilson estimates upper CI 95%	17,1	22,9	31,2	16,6	35,2	36,5	35,2	47,9	35,2	41,7	33,9	58,9	29,9
p<0.05	*	*	*	*	*	*	*	*	*	*	*	*	*

2B

QST parameter contralateral side	CPT	HPT	WDT	WUR	CDT	TSL	PHS	MPT	MPS	MDT	VDT	PPT	DMA
n of sensory abnormality	1	9	9	7	12	12	9	15	11	10	9	24	3
n of sensory gain	1	9	5	7	2	5	9	2	9	2	0	24	3
n of sensory loss	0	0	4	0	10	7	0	13	2	8	9	0	0
% of sensory abnormality	1,2	11,1	11,1	9,9	14,8	14,8	11,1	18,5	13,6	12,3	11,1	29,6	3,7
Wilson estimates lower CI 95%	-0,4	5,8	5,8	4,6	8,6	8,6	5,8	11,5	7,6	6,7	5,8	20,8	0,9
Wilson estimates upper CI 95%	7,5	20,1	20,1	19,4	24,4	24,4	20,1	28,5	22,9	21,5	20,1	40,4	10,9
p<0.05	n.s.	*	*	*	*	*	*	*	*	*	*	*	*

Patient numbers with sensory abnormalities at the affected (Table 2-2A, top) and contralateral side (Table 2-2B, bottom). Shown are direction (n of sensory gain / n of sensory loss) and overall abnormalities in percent (% of sensory abnormality) for each Quantitative Sensory Testing (QST) parameters in 81 chronic pain patients. QST parameter: Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Warm Detection Threshold (WDT), Wind Up Ratio (WUR), Cold Detection Threshold (CDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensation (PHS), Mechanical Pain Threshold (MPT), Mechanical Pain Sensitivity (MPS), Mechanical Detection Threshold (MDT), Vibration Disappearance Threshold (VDT), Pressure Pain Threshold (PPT) and Dynamic Mechanical Allodynia (DMA). Wilson estimates with upper and lower bound of the 95% CI for each QST parameter (* $p<0.05$); n.s. indicates not significant.

For the nociceptive parameters CPT and HPT, thermal pain threshold were decreased indicating a thermal hyperalgesia. An increased pain due to blunt pressure (PPT) and an increased sensitivity to mechanical pain (MPS) were observed indicating only hyperalgesia for these parameters. For MPT a greater incidence for mechanical hypo- than hypersensitivity was detected. WUR was more frequently increased than decreased indicating a greater incidence for hyper- than hyposensitivity.

Thermal hypesthesias were observed also in most of the patients for CDT, WDT and TSL. For MDT there was predominantly a sensory loss observed indicating a mechanical hypesthesia. It was possible to detect hyperesthesia for VDT for one patient, but for the large majority VDT responses indicated hypesthesia.

In 25% (n=20) of the patients a sensory gain for PHS was detected at the affected side. DMA was present in 26% of the patients, in 6% of very mild intensity, however, 20% of patients showed a clinical relevant increased response for DMA indicating a dynamic allodynia.

3.3.3. Sensory changes at the patient's contralateral side

Sensory abnormalities at the contralateral side ranged from 1.2% (n=1) for CPT to 29.6% (n=24) for PPT. With the exception of CPT, 95% Confidence Intervals confirmed that the prevalence differed significantly from zero ($p<0.05$) for all QST parameters with highest incidence for MPT (95CI: 12%-29%) and PPT (95CI: 21%-40%) (Table 2-2B).

Overall there were less sensory abnormalities at the contralateral side than at the affected side.

For nociceptive parameters there was predominantly sensory gain observed, suggesting the presence of hyperalgesia, whereas for non-nociceptive parameters predominantly a sensory loss was identified suggesting hypesthesia (Fig. 2-3).

Only sensory gain for CPT, HPT, PPT and WUR were observed suggesting hyperalgesia. For MPT sensory loss was more frequently observed than sensory gain indicating a greater incidence for mechanical hyposensitivity than hypersensitivity. In contrast, for MPS was sensory gain was more frequently observed than sensory loss indicating a greater incidence for mechanical hypersensitivity than hyposensitivity.

Thermal hypesthesias were observed for most of the cases for CDT and for TSL, only 6.2% of patients showed hyperesthesia for TSL and 2.5% for CDT. WDT abnormalities were observed in 11.0% of the cases and this was due to both sensory loss and gain. For MDT at the contralateral side sensory loss was observed twice as often as sensory gain, indicating a greater incidence for mechanical hypesthesia. There was only hypesthesia for VDT at the contralateral side.

In 11.1% of the patients a sensory gain for PHS at the contralateral side was detected. DMA was present in 19.8% of patients, but mostly of very mild intensity. However, 3.7% of patients showed a clinically relevant sensory gain for DMA indicating a dynamic allodynia.

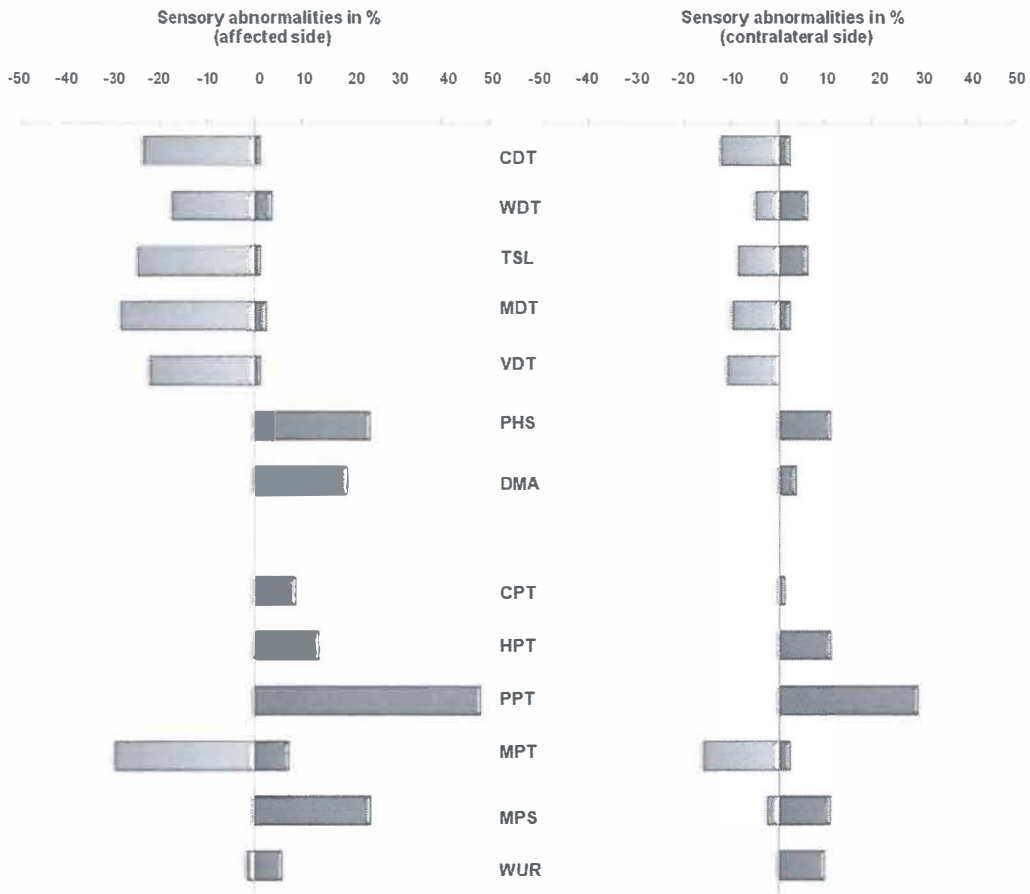

Fig 2-3: Quantitative Sensory Testing (QST) z-score abnormalities in % at the affected (left) and contralateral side (right) in 81 neuropathic pain patients. QST parameter are ordered as sensory parameters: Cold Detection Threshold (CDT), Warm Detection Threshold (WDT), Thermal Sensory Limen (TSL), Mechanical Detection Threshold (MDT), Vibration Disappearance Threshold (VDT), Paradoxical Heat Sensation (PHS), Dynamic Mechanical Allodynia (DMA) and nociceptive parameters: Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Pressure Pain Threshold (PPT), Mechanical Pain Threshold (MPT), Mechanical Pain Sensitivity (MPS) and Wind Up Ratio (WUR). Z-scores with positive sensory signs (gain of sensory function) plotted rightwards and negative sensory signs (loss of sensory function) plotted leftwards. Absence of DMA is normal and therefore no negative sign possible.

Table 2-3: Overview of sensory abnormalities at the contralateral side given an abnormality at the affected side

QST parameter	CPT	HPT	WDT	WUR	CDT	TSL	PHS	MPT	MPS	MDT	VDT	PPT	DMA
n of sensory gain similar to affected side	1	4	2	2	0	1	6	0	8	0	0	23	2
n of sensory loss similar to affected side	0	0	3	0	6	3	0	8	0	6	8	0	0
% of sensory abnormality similar to affected side	27,3	40,0	33,3	50,0	34,8	25,0	33,3	29,4	41,7	29,6	45,5	58,1	20,0
Wilson estimates lower CI 95%	1,0	15,2	13,2	15,4	15,3	8,0	14,5	14,1	21,9	12,4	24,6	43,4	2,5
Wilson estimates upper CI 95%	53,6	64,8	53,5	84,6	54,2	42,0	52,2	44,7	61,4	46,9	66,3	72,9	37,5
p<0.05	*	*	*	*	*	*	*	*	*	*	*	*	*

Percent (% of sensory abnormality) indicates overall occurrence of sensory abnormalities for each Quantitative Sensory Testing (QST) parameter at the contralateral side once there was already an abnormality for the same parameter detected at the affected side in 81 chronic pain patients. QST parameters: Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Warm Detection Threshold (WDT), Wind Up Ratio (WUR), Cold Detection Threshold (CDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensation (PHS), Mechanical Pain Threshold (MPT), Mechanical Pain Sensitivity (MPS), Mechanical Detection Threshold (MDT), Vibration Disappearance Threshold (VDT), Pressure Pain Threshold (PPT) and Dynamic Mechanical Allodynia (DMA). Wilson estimates with upper and lower bound of the 95% CI for each QST parameter (* $p<0.05$).

3.3.3.1. Example of magnitude of somatosensory abnormalities

Here we describe one patient in greater detail for better understanding of the magnitude of somatosensory abnormalities based on raw values of the QST battery.

A25 year old woman (ID1) suffered from a cut injury at her left hand with a lesion of the digitalis nerve. Subsequently, she developed severe pain at left palm including digits IV and V. Bedside tests using von Frey filaments and a brush confirmed impaired sensibility including allodynia of left hand. These sensory signs were within neuroanatomical plausible distribution of the digitalis nerve. The clinical diagnosis "peripheral nerve injury" was made. The QST assessment took place in the area of greatest pain complaints and on the same contralateral site. Normative data obtained from dorsal hand were from 63 age- and gender matched subject's ± SD indicated in brackets. For the affected side the patient rated the different pinprick forces with a NRS score of 53.1 indicating an increased sensitivity for mechanical pain (MPS) (0.62 ± 1.00). The NRS ratio for Wind up (WUR) test was increased to 6.5 suggesting central sensitisation (NRS 2.53 ± 2.33). Her ratings for DMA pain of NRS 54.7 indicated allodynia. Clinically, this QST profile indicates a predominant gain of sensory function due to small and large fibre sensitisation. At the contralateral side the patient displayed a decreased threshold for MDT of 0.5mN (2.22 ± 2.27 mN) and a decreased threshold for CDT of 24.9 ° C (30.7 ± 0.77 ° C). DMA pain of NRS 3.5 indicates minor allodynia. Clinically, for the contralateral side a predominant gain of sensory function was found indicating small and large fibre sensitisation.

3.3.4. Sensory changes at the contralateral side in relation to sensory changes at the affected side

To further investigate the extent of contralateral abnormalities we determined the

presence or absence of abnormalities in each of the QST parameters at the contralateral side given that an abnormality for the same parameter was present at the affected side (Table 2-3). This occurred in 20% (for DMA) to 58% (for PPT) of the cases (Fig. 2-4). Confidence Intervals (95%) confirmed the prevalence to be significantly ($p<0.05$) different from zero for all QST parameters (see Table 2-3). The highest proportions were seen for the VDT (95CI: 25%-66%) and PPT (95CI: 43%-73%). Although all proportions were significant, some confidence intervals were very large due to small numbers of observations. This was especially true for WUR and for most of the thermal QST parameters.

To increase statistical power with the purpose to allow a more accurate estimation of the prevalence of sensory abnormalities in the general chronic pain patient population, thermal and mechanical QST parameters were combined into one thermal and one mechanical domain. For the affected side this grouping resulted in 20.0% (95CI: 16%-23%) thermal abnormalities and 27.9% (95CI: 24%-31%) mechanical abnormalities. For the contralateral side 11.0% (95CI: 8%-14%) thermal abnormalities and 14.4% (95CI: 11%-17%) mechanical abnormalities were found. To investigate the occurrence of bilateral manifestations of sensory abnormalities we calculated the prevalence of thermal and mechanical abnormalities at the contralateral side given that there was an abnormality at the affected side for the same QST domain in the same patient. This resulted in 95% CI's for bilateral abnormality ranging from 14%-28% and 35%-52% for thermal and mechanical QST domains, respectively.

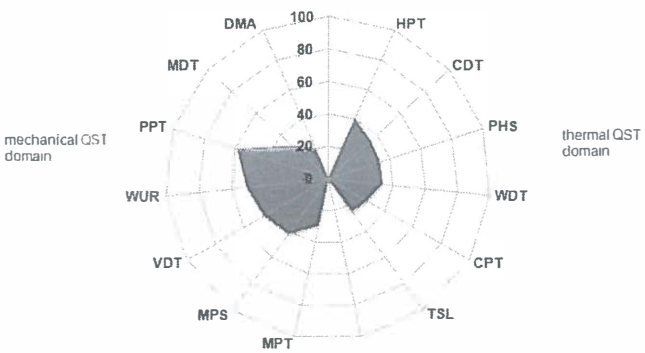

Fig. 2-4: Incidence of QST abnormalities at the contralateral side in 81 neuropathic pain patients
Sensory abnormality in percent (%) of either gain or loss of function for each Quantitative Sensory Testing (QST) parameter at the contralateral side once there was already an abnormality detected for the same parameter at the affected side. QST parameter in this radar diagram are ordered as mechanical stimuli consisting of Mechanical Pain Threshold (MPT), Dynamic Mechanical Allodynia (DMA), Pressure Pain Threshold (PPT), Vibration Disappearance Threshold (VDT), Mechanical Detection Threshold (MDT), Mechanical Pain Sensitivity (MPS) and Wind Up Ratio (WUR) (left side) and thermal stimuli consisting of Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Warm Detection Threshold (WDT), Cold Detection Threshold (CDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensation (PHS) (right side).

3.3.5. Correlation between background pain and QST parameters

All patients reported ongoing spontaneous pain (NRS mean 64.1, SD ± 21.4) at their affected side before the QST assessment took place (see Table 2-1). There were no significant correlations found using Pearson correlations between background pain and QST parameters. A significant correlation was found between the frequencies of sensory abnormalities at the contralateral side with background pain ($r=0.231$; $p<0.05$). Furthermore, this effect was supported by the correlation between the increase of sensory gain at the contralateral side and background pain ($r=0.270$; $p=0.015$).

3.3.6. Correlation between numbers of sensory abnormalities at the affected and contralateral side

The number of sensory abnormalities for patients varied between 0 and 8 for the affected and 0 and 6 for the contralateral side for the thirteen QST parameters assessed (see Table 2-1). The overall occurrence of contralateral abnormalities were significantly correlated with abnormalities at the affected side ($r=0.310$; $p<0.01$). Furthermore, a modest correlation was observed between the presence of sensory loss at the affected and contralateral side ($r=0.400$; $p<0.01$), whereas for the presence of sensory gain at the affected and contralateral side a stronger correlation was found ($r=0.483$; $p<0.01$).

4. Discussion

This QST study shows that patients with unilateral neuropathic pain have a diversity of sensory abnormalities at the painful side, and to a lesser extent, at the contralateral non-painful side. Using the standardized QST protocol with 13 different parameters to obtain a complete sensory profile, it was demonstrated that bilateral sensory abnormalities are apparent in a considerable number of the patients that experience chronic unilateral pain.

There was a significant correlation between the number of abnormalities at the painful side and the contralateral side. Even more so, if a particular abnormality was detected at the painful side this abnormality was then the most likely abnormality to occur contralaterally. This was particularly striking for the group of mechanical stimuli where the estimated prevalence of sensory abnormalities at the non-painful side was 35%-52% (95% CI) in case a mechanical abnormality was detected at the painful side. These results have implications for the evaluation of patients in clinical practice, since often the non-affected side is used as the reference side. Our results show that using the contralateral side as the reference to identify sensory abnormalities at the affected side might lead to misinterpretation of the clinical manifestation.

4.1. Somatosensory function in healthy controls

Z-score transformation of QST data revealed one or more somatosensory abnormalities in 38% of all members of the healthy control group. This number is in line with previous

findings reporting 41% abnormalities using the QST protocol (Maier et al 2010).

In our healthy volunteers, abnormalities were observed across all QST parameters with the exception of DMA. The detected sensory abnormalities reflected gain of function for the most part, some loss of function and in a minority fraction both gain and loss of function (Fig 2-1).

Although previously reported otherwise (Maier et al 2010), in the present study, PHS >1 occurred in 1.4% at the test side "dorsal hand" and in 9.3% at the test side "dorsal foot". The presence of abnormal PHS in our study could be associated with a greater likelihood of sensory dysfunction with an increase in age ($r=0.193$; $p<0.01$).

4.2. Sensory signs at the affected, painful side of neuropathic pain patients

As expected, the large majority (91%) of neuropathic pain patients showed sensory abnormalities at their affected side. Maier and colleagues (2010) (Maier et al 2010) reported a similar percentage (92%) of patients with at least one QST abnormality. Given the fact that for 9% of the patients, no abnormality could be detected, QST and the cut-off of 95% CI of the mean reference values might possibly be more stringent than clinical examination.

In accordance with previous studies, sensory loss was predominantly found in non-nociceptive parameters (Maier et al 2010; Scholz et al 2009) which could be associated with central or peripheral neuronal damage which might lead to ongoing pain via increased ectopic activity (Liu et al 2000; Ochoa et al 2005; Serra et al 2009). Sensory gain was predominantly found in nociceptive parameters which could be associated with peripheral sensitisation and/or altered central processing (Baron 2000; Baumgartner et al 2002; Sandkuhler 2009; Treede et al 1992; Wasner et al 2004).

Maier and co-workers (2010) (Maier et al 2010) reported abnormal QST values for the affected side across the different clinical neuropathic pain entities ranging between 8%-36% (compared to 7%-48% in this study). There was good agreement between our estimates of the expected range of sensory abnormalities in the general neuropathic pain patient population and those reported by Maier (Maier et al 2010). Only estimate ranges for the occurrence of sensory abnormalities for CDT, HPT, TSL, MDT, VDT and CPT in the present study differed slightly but were still in close proximity to the values reported previously (Maier et al 2010).

4.3. Contralateral sensory signs in neuropathic pain patients

Contralateral sensory changes in patients with chronic pain have been acknowledged in a number of clinical studies (Baron & Saguer 1994; de la Llave-Rincon et al 2009; Fernandez-de-las-Penas et al 2009; Huge et al 2008; Maleki et al 2000; Oaklander et

al 1998; Shenker et al 2008). For instance it was reported that 5% of the patients with complex regional pain syndrome (CRPS) present bilateral symptoms (Veldman & Goris 1996). Despite reports of the existence of bilateral changes in chronic pain patients no elaborate quantitative data have been published. In the present QST study, sensory abnormalities at the contralateral side were observed for all QST parameters.

Comparing the overall sensory findings from the contralateral side with those obtained from the healthy controls, a significant difference was shown indicating abnormal sensory function at the contralateral side in patients with unilateral neuropathic pain. In addition, a significant correlation was found for abnormal sensory function at the contralateral sides compared to the affected side. The pattern of sensory abnormalities for nociceptive and non-nociceptive parameters at the contralateral side was in line with that at the affected side but less severe. All patients had unilateral pain causing event and most showed bilateral sensory abnormalities. This finding points at a central component in processing the pain and controlling sensory function bilaterally.

Preclinical studies have also found evidence for bilateral sensory changes upon unilateral induction of pain and these studies correlated the severity of pain with occurrence of bilateral changes. Hubbard and colleagues (2008) demonstrated in a rat model using painful cervical nerve root compression that the occurrence of contralateral allodynia depended on the load of compression (Hubbard & Winkelstein 2008). In another study, zymosan induced sciatic neuritis in rats, causing a dose-dependent bilateral allodynia (Chacur et al 2001).

In healthy volunteers and patients with rheumatoid arthritis an intradermal administration of capsaicin induced mechanical hyperalgesia and allodynia at the side contralateral to the injection area (Shenker et al 2008). Studies using capsaicin revealed that short-lasting but high intensity pain induces contralateral sensory changes [7; 21]. These results suggest that pain intensity may play a prominent role in contralateral sensory changes. Potential underlying conditions which may lead to contralateral sensory changes in unilateral pain condition are currently investigated. Koltzenburg et al. (Koltzenburg et al 1999) suggested the involvement of nerve growth factors (NGF) to explain the contralateral peripheral responses in rats with unilateral neural injuries. Other studies suggested the involvement of altered glial activation and spinal pro-inflammatory cytokines (tumour necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6)) (Gao et al 2010; Hansson 2006; Milligan et al 2003; Watkins & Maier 2002).

In line with these findings, in the present study we have also found a significant correlation between background pain and QST abnormalities at the contralateral side in patients who experienced a unilateral pain-causing event. This supports previous suggestions that high pain intensity can induce sensory abnormalities at the contralateral side in

patients with unilateral pain. Additional studies are needed to evaluate for instance if the severity of pain determines the onset of contralateral changes and if ongoing pain is the driving force for the maintenance of contralateral abnormalities in chronic pain patients.

4.4. Correlation between sensory changes at affected and contralateral side

An interesting finding is that the presence of sensory gain or loss at the affected side was related to sensory gain or loss for the same QST parameter at the contralateral side, ranging from 25% to 58% dependent on the QST parameter. In particular for the group of mechanical stimuli the estimated presence of sensory abnormalities at the non-affected side was substantial (ranging from 35%-52%). Although sensory abnormalities at the contralateral side were less pronounced compared to those at the affected side, there was a significant correlation between the numbers of sensory abnormalities at both sides in patients.

Contrary to recommendations to use the contralateral side as a reference to identify sensory abnormalities in patients (Haanpaa et al 2010; Haanpaa et al 2009) our data indicate that this is not advisable since the sensory function at the contralateral side stands a reasonable chance to be altered. The interpretation of sensory signs and its clinical manifestations using the contralateral side or reference values from healthy subjects may vary (see Table 2-4 for examples).

Table 2-4: Diagnostic consequence of using either the contralateral side or normative data from healthy volunteers. The difference between the last two columns shows that the choice of reference is not trivial and that using the contralateral side in the same patient can lead to misinterpretation of sensory function.

observation affected side	observation contralateral side	clinical result using contralateral side as reference	clinical result using healthy volunteers as reference
0	0	0	0
+	0	+	+
-	0	-	-
0	+	-	0
0	-	+	0
+	+	0	+
+	-	++	+
-	+	--	-
-	-	0	-

The interpretation of sensory function and its clinical manifestation at the affected side using the contralateral side or reference values from healthy subjects. The observation at the affected side and contralateral side indicate the sensory response for a Quantitative Sensory Testing (QST) parameter in patients. Clinical results using the contralateral side as reference or healthy volunteers as reference indicate sensory interpretation for the affected side. '0' indicate normal sensory function, '+' indicate sensory gain such as hyperalgesia/allodynia, '-' indicate sensory loss such as hypesthesia, '++' or '- -' indicate overestimation of sensory gain or sensory loss, respectively.

Since most (n=77) patients in the present study continued their pain medication it cannot be excluded that the medication itself might have influenced the onset or maintenance of somatosensory changes seen bilaterally.

These results firmly establish evidence for a cautious use of the contralateral side as a reference site in clinical practice. A way to overcome this problem is the use of reference values for either normative response or for pathological response to QST parameters to allow a precise identification of sensory abnormalities in patients.

In conclusion, our data provide detailed evidence for bilateral sensory abnormalities in unilateral neuropathic pain patients using a standardized, elaborate QST protocol. Our results show that in these patients, the contralateral side should not be regarded as normal or healthy per se. This has implications for appropriate diagnostic evaluation in clinical practice.

Acknowledgement
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Chapter 3

Somatosensory profiles but not numbers of somatosensory abnormalities of neuropathic pain patients correspond with neuropathic pain grading

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submitted

3. Somatosensory function and neuropathic pain grading

Abstract

Due to the lack of a specific diagnostic tool a grading system to categorize pain as 'definite', 'probable', 'possible' and 'unlikely' neuropathic pain was proposed. Somatosensory abnormalities are common in neuropathic pain and it has been suggested that a greater number of abnormalities would be present in patients with 'probable' and 'definite' grades. To test this hypothesis, we investigated the presence of somatosensory abnormalities by means of QST in patients with a clinical diagnosis of neuropathic pain and correlated the number of sensory abnormalities and sensory profiles to the different grades.

Of patients who were clinically diagnosed with neuropathic pain, only 60% were graded as 'definite' or 'probable', while 40% were graded as 'possible' or 'unlikely' neuropathic pain. Apparently, there is a mismatch between a clinical neuropathic pain diagnosis and neuropathic pain grading. Contrary to the expectation, patients with 'probable' and 'definite' grades did not have a greater number of abnormalities. Instead, similar numbers of somatosensory abnormalities were identified for each grade. The profiles of sensory signs in 'definite' and 'probable' neuropathic pain were not significantly different, but different from the 'unlikely' grade. This latter difference was due to a different frequency of a mixture of sensory gain and loss and of sensory loss only.

The grading system allows a separation of neuropathic and non-neuropathic pain based on profiles but not on the total amount of sensory abnormalities. Our findings indicate that patient selection based on grading of neuropathic pain may provide advantages iselecting homogenous groups for clinical research.

3. Somatosensory function and neuropathic pain grading

1. Introduction

The International Association for the Study of Pain (IASP) defined neuropathic pain as a direct consequence of a lesion or disease affecting the somatosensory system (Treede et al 2008). Neuropathic pain has traditionally been classified based on the underlying aetiology (Hansson 2003); (2001); (Woolf & Mannion 1999). Due to the lack of a specific diagnostic tool for neuropathic pain, a grading system of 'definite', 'probable', 'possible' and 'unlikely' neuropathic pain was proposed (Treede et al 2008). This grading system aims to determine with a greater level of certainty whether a pain condition is neuropathic, especially when including patient's in clinical trials. Briefly, the grade 'unlikely' is applicable when patients lack a history of a lesion or disease with a plausible neuroanatomical distribution of their pains. The grade 'possible' could be regarded as a working hypothesis, which does not exclude, neither diagnoses neuropathic pain. Patients who fall into the category 'possible' neuropathic pain can be transferred into the grades 'probable' and 'definite' if neurologic examination and the presence of a positive confirmatory test reveal confirmatory evidence.

Although the proposed grading system is intended for clinical and research purposes and has been available for several years, studies investigating somatosensory similarities between the clinical neuropathic pain entities and the new grading system in large patient cohorts are not available. Quantitative sensory testing (QST) has been used to identify somatosensory abnormalities in patients with neuropathic pain. The ultimate goal of identifying differences in the response to sensory stimuli in neuropathic pain patients is the identification of differences in the mechanisms responsible for generating sensory abnormalities and their subsequent mechanism-based therapy. A recent QST study showed that specific profiles (along thirteen different QST parameters) correspond to the different clinical entities of neuropathic pain (Maier et al 2010). The authors suggested that in case of a patient showing many sensory abnormalities, the grading of this patient would fulfil the criteria for 'probable' or 'definite' neuropathic pain.

Previously, we showed that bilateral somatosensory abnormalities were common in patients with unilateral neuropathic pain (Konopka et al) (submitted). We did not account differences in the quantities of sensory abnormalities at the affected side between the clinical entities of neuropathic pain of our study population. In the present study, we hypothesized that the number of somatosensory abnormalities in patients with clinically diagnosed neuropathy do not differ within the 'definite', 'probable', 'possible' and 'unlikely' neuropathic pain grading groups. We also aimed to find QST profile - based corroboration of the new grading system.

We selected a large cohort of patients with clinically confirmed neuropathic pain and subsequently categorized each patient according to the neuropathic pain grading. We examined the painful area using the standardized (German Research Network on

Neuropathic Pain) DNFS QST protocol comparing values with those obtained from age- and gender-matched healthy volunteers.

2. Methods

The study adhered to the declaration of Helsinki was approved by the medical ethical committee "Stichting Beoordeling Ethiek Bio-Medisch Onderzoek, P.O. Box 1004, 9400 BA Assen, The Netherlands". The study includes patients and healthy controls from the local region. All participants signed an informed consent form.

2.1. Description of healthy controls

Healthy subjects were identified according to medical history. Subjects were specifically questioned regarding previous injuries or diseases. The healthy subjects did not use analgesics regularly and were free of medication at the time of the assessments. In total, 209 age- and gender-matched healthy volunteers (age range 20-73 years), of which 138 females (age 45.3 ± 13.4 years) and 71 males (age 48.7 ± 14.0 years) underwent QST assessments on both, the dorsal hand and foot. These body locations have been proposed as reference sites for QST (Rolke et al 2006a). Since there are no significant differences in QST parameters between the right and left sides of the body in healthy volunteers, we obtained QST reference values from one side of the body. In total, 418 QST references from the upper and the lower extremity were obtained.

2.2. Description of the patient cohort

Patients with neuropathic pain lasting for more than three months were recruited from the outpatient Department of the Pain Management Unit of the University Medical Center Groningen, The Netherlands. Patients were diagnosed with neuropathic pain by the physicians of the Unit. Neuropathic pain diagnosis was made based on coherent patient history, medical history and physical examination which included neurological function tests. Each clinical diagnosis was additionally confirmed by an experienced pain specialist of the Pain Management Unit based on patient's files. In total, 108 neuropathic pain patients (age range 22-75 years), of which 54 females (age 52.7 ± 12.8 years) and 54 males (age 50.9 ± 13.0 years). Prior to the QST assessments, patients were asked to rate their ongoing pain level using a Numerical Rating Scale (NRS) of '0' indicating "no pain", and '100' indicating "most intense pain imaginable". Patients did not discontinue their regular pain treatment if applicable. Patients underwent the QST assessment, at the area where the most profound pain was experienced (leg: n=59, arm: n=25, thorax: n=9, groin: n=4, back: n=3, cervix: n=3, abdomen: n=2, shoulder: n=2, flank: n=1).

2.3. Quantitative sensory testing (QST)

The QST battery consisted of seven tests, measuring thirteen parameters and was applied according to the standardized protocol (Rolke et al 2006a). QST was performed by two research nurses, who underwent a comprehensive training at the DNFS in Germany. All tests were performed at the same research facility of PRA Int., Groningen, The Netherlands. The average room temperature was 23.1° C ± 1.7° C.

Thermal QST tests were performed using the Pathway System (Medoc, Israel) and consisted of six parameters: threshold assessments for warm and cold detection (WDT, CDT) and heat pain and cold pain (HPT, CPT). In addition, subjects were asked about paradoxical heat sensations (PHS) during the thermal sensory limen (TSL) procedure of alternating warm and cold stimuli.

Mechanical QST tests consisted of seven different parameters. The mechanical detection threshold (MDT) was determined with modified von Frey filaments (Optihair2-Set, Marstock Nervtest, Germany). The mechanical pain threshold (MPT) was measured with seven weighted pinprick devices (cylindrical, 0.2 mm in diameter flat contact area) with fixed stimulus intensities forces of 8, 16, 32, 64, 128, 256, and 512 mN. Mechanical pain sensitivity (MPS) was assessed using the same pinprick devices to obtain a stimulus–response relation. Dynamic mechanical allodynia (DMA) was assessed as part of the test above, using a set of three light tactile stimulators as dynamic innocuous stimuli: cotton wisp, cotton wool tip fixed to an elastic strip and a standardized brush (SENSElab No.5, Somedic, Sweden). Vibration detection threshold (VDT) was performed with a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale) that was placed over a bony prominence. The wind up ratio (WUR) test was assessed with a pinprick intensity of 256 mN. The pressure pain threshold (PPT) was determined over muscle with a pressure gauge device (FDN200, Wagner Instruments, CT, USA).

2.4. Neuropathic pain grading

For each of the neuropathic pain patients the diagnosis of neuropathic pain was confirmed using the grading system that categorizes neuropathic pain as "definite", "probable", "possible" or "unlikely" neuropathic pain (Treede et al 2008). If a patient's pain complaints do not have a plausible neuroanatomical distribution and lack a history which suggests a relevant lesion or disease they are regarded as 'unlikely' neuropathic. If both requirements were fulfilled the working hypothesis 'possible' neuropathic pain was applied. If confirmatory tests such as positive or negative sensory signs confined to the innervations area of the relevant nerve structure and a diagnostic test confirming the lesion or disease were both positive, patients were graded as 'definite' neuropathic pain. In case of only one positive confirmatory test, a patient's pain was graded as 'probable' neuropathic. If both confirmatory tests were inconclusive, a patient's pain was regarded as unconfirmed and patients were assigned 'possible' neuropathic pain. All patients in the present study were allocated to one of the four neuropathic pain grades.

2.5. Data analysis and statistics

2.5.1. Z-transformation of QST data

QST data of patients with neuropathic pain were compared with reference data from gender and age matched healthy subjects. Both, patients and healthy subjects were divided into two age groups each (20-45 years of age and 46-75 years of age). QST values of chronic pain locations on the upper extremities were compared to QST reference values obtained from the dorsal hand of healthy controls (n=63 for females and n=29 for males for age group 20-45 years; n=75 for females and n=42 for males for age group 46-75 years), whereas values from chronic pain locations on lower extremities were compared to reference values obtained from the dorsal foot of healthy controls (n=63 for females and n=29 for males for age group 20-25 years; n=75 for females and n=42 for males for age group 46-75 years). QST values from each patient were transformed to z-scores. A score above 1.96 or below -1.96 falls outside the 95% confidence interval of the mean reference value and was considered as a sensory abnormality. Abnormalities were subsequently categorized as either a sensory gain or a sensory loss.

As it never occurs in healthy volunteers that dynamic innocuous stimuli become painful, the QST parameter "dynamic mechanical allodynia" (DMA) could not be used for z-score analyses. In this case, ratings greater than NRS 10 (scale 0-100) were regarded as clinically relevant and identified as abnormal.

For the QST parameter "Wind-Up Ratio" (WUR), eighteen patients rated the single pinprick stimulus as "0" making ratio calculations (painfulness of one pinprick stimulation vs. painfulness of a train of ten pinprick stimulations) for Wind-Up impossible. For these patients WUR was not used for subsequent analyses. Similar, 31 healthy subjects rated the single pinprick stimulus as "0" making ratio calculations for Wind-up impossible.

2.5.2. Proportions of sensory signs for the different neuropathic pain grades

To investigate the differences in the proportions of sensory loss, sensory gain or mixture of sensory loss and gain for the different neuropathic pain grades we calculated the 95% confidence intervals of the proportions using the 'Wilson Estimate' of proportion (Moore & McCabe 2003).

2.5.3. Correlation between the number of sensory abnormalities and neuropathic pain grades

For each grading numbers of sensory abnormalities were compared using ANOVA. The total numbers of sensory gain and sensory loss as well as the overall numbers of sensory abnormalities across the thirteen QST parameters for patients were correlated to the different neuropathic pain grades using Spearman correlations.

2.5.4. Correlation between background pain and neuropathic pain grades

To identify a possible relationship between neuropathic pain grade and background pain of each patient, Pearson correlation was used. P-values <0.05 were regarded as significant for each statistical test performed.

3. Results

3.1. QST observations in healthy controls

From the healthy volunteer cohort (n=209) investigated in this study, a total of 418 locations were assessed and 5403 measurements were analysed by means of z-score profiling. The total of 1412 measurements for the most affected area were analysed by means of z-score profiling.

3.1.1. Sensory loss and/or gain of function

Although the majority of the QST results obtained in healthy subjects confirmed normal sensory function for this cohort, incidental sensory abnormalities (4.3%) were observed for all QST parameters with the exception of DMA.

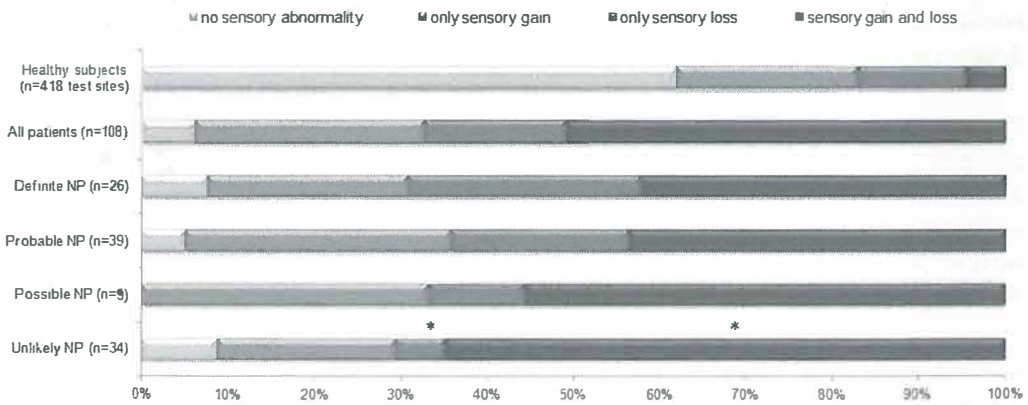

Fig. 3-1: Sensory findings (gain and/or loss of sensory function) in % for healthy controls (n=209 with 418 test sides), for patients (n=108) overall and ordered according to their likelihood to be neuropathic pain. "No sensory abnormalities": none of the Quantitative Sensory Testing (QST) parameters were outside the 95% CI. "Only sensory gain": at least one QST parameter indicating thermal or mechanical hyperesthesia or hyperalgesia without the presence of hypesthesia or hypoalgesia. "Only sensory loss": at least one QST parameter indicating thermal or mechanical hypesthesia or hypoalgesia without the presence of hyperesthesia or hyperalgesia. "Sensory gain and loss": at least one positive sign combined with one negative sign. Wilson estimates of proportions between the groups of definite and probable neuropathic pain and the group of unlikely neuropathic pain for only sensory loss and sensory gain and loss parameter (* $p<0.05$).

Out of the total of 418 different body areas that were tested across all healthy controls 62% (259 locations) showed normal sensory function and 38% (159 locations) showed a sensory abnormality for at least one QST parameter. Sensory abnormalities were regarded as sensory gain in 21%, sensory loss in 13% and a mixture of sensory gain and sensory loss in 4% of the cases (Fig.3-1).

3.2. Demographics of patients

Demographic data of the patients are shown in Table 3-1. Apart from two patients, all patients reported ongoing spontaneous pain ranging from 3 to 100 (Mean 63.2 ± 22.8 SD) on a 0-100 NRS just before the QST assessment took place.

3.2.1. Clinical diagnose of neuropathic pain

The aetiology of patient's pain in our sample was diverse. The largest subgroup developed pain after a surgical intervention (33) followed by patients who had a trauma (18). Other causes of pain were polyneuropathy (12), failed back surgery (10), pain after fracture (7), Herniated Nucleus Pulposus (HNP) (6), spinal cord injury (4), peripheral nerve entrapment (4), central pain (3), amputation (3), Herpes Zoster infection (3), Radiotherapy (3), and pain after infection (2). The clinical diagnoses of patients included peripheral nerve injury (83), polyneuropathy (14), spinal cord injury (4), central pain (3), postherpetic neuralgia (3) and complex regional pain syndrome (CRPS) (1) (see Table 3-1).

Table 3-I: Patient characteristics

ID	Gender	Age	Pain VAS (0-100)	Cause of Pain	Clinical Diagnose	Grading 1	Grading 2	Grading 3	Grading 4	Grading: Conclusion	Numbers of abnormalities
1	M	62	50	Polyneuropathy	polyneuropathy	yes	yes	yes	positive	definite NP	3
2	F	43	60	Post stroke pain	central pain	yes	yes	yes	positive	definite NP	6
3	M	52	75	Spinocerebellar ataxia	central pain	yes	yes	yes	positive	definite NP	4
4	F	57	80	Diabetic polyneuropathy	polyneuropathy	yes	yes	yes	positive	definite NP	1
5	F	55	90	Herniated nucleus pulposus	peripheral nerve injury	yes	yes	yes	positive	definite NP	2
6	F	53	50	TH12 fracture	spinal cord injury	yes	yes	yes	positive	definite NP	4
7	F	52	80	Sepsis and organ failures	polyneuropathy	yes	yes	yes	positive	definite NP	5
8	F	71	60	Failed back surgery	peripheral nerve injury	yes	yes	yes	positive	definite NP	4
9	F	51	75	Peripheral nerve entrapment	peripheral nerve injury	yes	yes	yes	positive	definite NP	4
10	F	72	50	Failed back surgery	peripheral nerve injury	yes	yes	yes	positive	definite NP	1
11	M	41	60	Failed back surgery	peripheral nerve injury	yes	yes	yes	positive	definite NP	3
12	M	49	40	Accident with trauma	peripheral nerve injury	yes	yes	yes	positive	definite NP	2
13	F	43	80	Postsurgical pain	CRPSII	yes	yes	yes	positive	definite NP	5
14	F	48	60	Lesion of cervical myelum	spinal cord injury	yes	yes	yes	positive	definite NP	7
15	M	53	70	Polyneuropathy	polyneuropathy	yes	yes	yes	positive	definite NP	4
16	M	36	50	Accident with trauma	peripheral nerve injury	yes	yes	yes	positive	definite NP	5
17	M	52	75	Myelopathy	spinal cord injury	yes	yes	yes	positive	definite NP	1
18	M	46	0	Cruris fracture	peripheral nerve injury	yes	yes	yes	positive	definite NP	2
19	M	66	75	Polyneuropathy	polyneuropathy	yes	yes	yes	positive	definite NP	2
20	M	58	40	Herniated nucleus pulposus	peripheral nerve injury	yes	yes	yes	positive	definite NP	0
21	F	65	70	Herniated nucleus pulposus	peripheral nerve injury	yes	yes	yes	positive	definite NP	5
22	F	42	70	Peripheral nerve entrapment	peripheral nerve injury	yes	yes	yes	positive	definite NP	5
23	M	38	90	Accident with trauma	peripheral nerve injury	yes	yes	yes	positive	definite NP	1
24	F	43	100	Cervical myelopathy	peripheral nerve injury	yes	yes	yes	positive	definite NP	6
25	F	75	80	Herniated nucleus pulposus	peripheral nerve injury	yes	yes	yes	positive	definite NP	4
26	M	46	65	Failed back surgery	peripheral nerve injury	yes	yes	yes	positive	definite NP	0
27	F	71	3	Herpes zoster	postherpatic neuralgia	yes	yes	yes	none	probable NP	6
28	F	37	90	Postsurgical pain	peripheral nerve injury	yes	yes	yes	none	probable NP	4
29	F	48	65	Accident with trauma	peripheral nerve injury	yes	yes	yes	negative	probable NP	0
30	F	46	70	Accident with trauma	peripheral nerve injury	yes	yes	yes	negative	probable NP	1
31	M	56	80	Postsurgical pain	peripheral nerve injury	yes	yes	yes	none	probable NP	1
32	M	55	40	Accident with trauma	peripheral nerve injury	yes	yes	yes	none	probable NP	2
33	F	53	80	Radiotherapy	peripheral nerve injury	yes	yes	yes	none	probable NP	4
34	M	54	80	Postsurgical pain	peripheral nerve injury	yes	yes	yes	none	probable NP	2
35	M	26	75	Accident with trauma	peripheral nerve injury	yes	yes	yes	none	probable NP	4
36	F	56	3	Postsurgical pain	peripheral nerve injury	yes	yes	yes	none	probable NP	2
37	F	59	60	Postsurgical pain	peripheral nerve injury	yes	yes	yes	none	probable NP	4
38	F	25	70	Accident with trauma	peripheral nerve injury	yes	yes	yes	none	probable NP	3
39	F	41	70	Postsurgical pain	peripheral nerve injury	yes	yes	yes	negative	probable NP	5
40	F	67	85	Herniated nucleus pulposus	peripheral nerve injury	yes	yes	yes	negative	probable NP	3
41	F	66	70	Postsurgical pain	peripheral nerve injury	yes	yes	no	positive	probable NP	2
42	M	40	60	Amputation	peripheral nerve injury	yes	yes	yes	negative	probable NP	2
43	M	23	70	Postsurgical pain	peripheral nerve injury	yes	yes	yes	none	probable NP	3
44	F	62	80	Failed back surgery	peripheral nerve injury	yes	yes	yes	none	probable NP	6
45	F	46	85	Postsurgical pain	peripheral nerve injury	yes	yes	yes	negative	probable NP	2
46	F	54	65	Diabetic polyneuropathy	polyneuropathy	yes	yes	yes	none	probable NP	4
47	F	46	40	Amputation	peripheral nerve injury	yes	yes	yes	none	probable NP	3
48	M	63	80	Postsurgical pain	peripheral nerve injury	yes	yes	yes	negative	probable NP	1
49	M	26	85	Accident with trauma	peripheral nerve injury	yes	yes	yes	negative	probable NP	4
50	F	27	70	Femur fracture	peripheral nerve injury	yes	yes	yes	negative	probable NP	8
51	M	62	70	Accident with trauma	peripheral nerve injury	yes	yes	yes	negative	probable NP	2
52	M	58	80	Postsurgical pain	peripheral nerve injury	yes	yes	yes	negative	probable NP	0
53	F	58	90	Postsurgical pain	peripheral nerve injury	yes	yes	yes	none	probable NP	3
54	M	73	10	Herpes zoster	postherpatic neuralgia	yes	yes	yes	none	probable NP	1
55	F	41	70	Metacarpal fracture	peripheral nerve injury	yes	yes	yes	none	probable NP	2
56	M	57	75	Tibia fracture	peripheral nerve injury	yes	yes	yes	none	probable NP	6
57	M	44	35	Postsurgical pain	peripheral nerve injury	yes	yes	yes	none	probable NP	2
58	M	57	40	Polyneuropathy	polyneuropathy	yes	yes	yes	none	probable NP	5
59	M	73	70	Polyneuropathy	polyneuropathy	yes	yes	yes	none	probable NP	1
60	M	24	50	Postsurgical pain	peripheral nerve injury	yes	yes	yes	none	probable NP	9

to be continued on page 56

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Table 3-I: Patient characteristics

ID	Gender	Age	Pain VAS (0-100)	Cause of Pain	Clinical Diagnose	Grading 1	Grading 2	Grading 3	Grading 4	Grading: Conclusion	Numbers of abnormalities
61	F	61	20	Diabetic polyneuropathy	polyneuropathy	yes	yes	yes	none	probable NP	3
62	F	75	50	Failed back surgery	peripheral nerve injury	yes	yes	yes	negative	probable NP	5
63	F	73	25	Herpes zoster	postherpatic neuralgia	yes	yes	yes	none	probable NP	3
64	F	44	45	Postsurgical pain	peripheral nerve injury	yes	yes	yes	none	probable NP	4
65	F	51	70	Postsurgical pain	peripheral nerve injury	yes	yes	yes	none	probable NP	2
66	M	47	50	Postsurgical pain	peripheral nerve injury	yes	yes	no	none	possible NP	4
67	M	43	90	Postsurgical pain	peripheral nerve injury	yes	yes	no	none	possible NP	6
68	M	70	10	Postsurgical pain	peripheral nerve injury	yes	yes	no	none	possible NP	6
69	M	50	75	Spontaneous rib fracture	peripheral nerve injury	yes	yes	no	none	possible NP	6
70	M	51	70	Postsurgical pain	peripheral nerve injury	yes	yes	no	none	possible NP	3
71	M	50	80	Postsurgical pain	peripheral nerve injury	yes	yes	no	none	possible NP	4
72	M	59	60	Accident with trauma	peripheral nerve injury	yes	yes	no	negative	possible NP	2
73	M	57	80	Postsurgical pain	peripheral nerve injury	yes	yes	no	none	possible NP	1
74	F	52	100	Failed back surgery	peripheral nerve injury	yes	yes	no	none	possible NP	4
75	M	43	60	Accident with trauma	peripheral nerve injury	yes	no	yes	negative	unlikely NP	6
76	F	43	75	Meralgia paresthetica	peripheral nerve injury	yes	no	yes	none	unlikely NP	0
77	M	75	65	Postsurgical pain	peripheral nerve injury	no	yes	no	none	unlikely NP	2
78	M	54	75	Postsurgical pain	peripheral nerve injury	no	yes	no	none	unlikely NP	3
79	F	66	75	Accident with trauma	peripheral nerve injury	no	yes	no	none	unlikely NP	1
80	F	59	75	Ischemic CVA	central pain	yes	no	no	none	unlikely NP	1
81	M	37	60	Accident with trauma	spinal cord injury	no	yes	no	negative	unlikely NP	4
82	F	65	50	Amputation	peripheral nerve injury	no	yes	no	negative	unlikely NP	4
83	M	59	55	Borrelia infection	polyneuropathy	no	yes	no	none	unlikely NP	8
84	F	36	70	Cruris fracture	peripheral nerve injury	no	no	no	none	unlikely NP	4
85	M	51	80	Failed back surgery	peripheral nerve injury	no	no	no	negative	unlikely NP	2
86	M	46	65	Herniated nucleus pulposus	peripheral nerve injury	no	no	no	negative	unlikely NP	3
87	F	41	55	Postsurgical pain	peripheral nerve injury	no	no	no	none	unlikely NP	5
88	F	39	80	Postsurgical pain	peripheral nerve injury	no	no	no	none	unlikely NP	3
89	M	32	40	Postsurgical pain	peripheral nerve injury	no	no	no	negative	unlikely NP	4
90	M	49	85	Sternum fracture	peripheral nerve injury	no	no	no	none	unlikely NP	3
91	M	42	80	Accident with trauma	peripheral nerve injury	no	no	no	negative	unlikely NP	1
92	M	42	70	Failed back surgery	peripheral nerve injury	no	no	no	none	unlikely NP	2
93	F	47	80	Accident with trauma	peripheral nerve injury	no	no	no	none	unlikely NP	5
94	F	66	90	Postsurgical pain	peripheral nerve injury	no	no	no	none	unlikely NP	7
95	M	71	20	Polyneuropathy	polyneuropathy	no	no	no	none	unlikely NP	3
96	F	46	75	Accident with trauma	peripheral nerve injury	no	no	no	none	unlikely NP	2
97	M	50	70	Radiotherapy	peripheral nerve injury	no	no	no	none	unlikely NP	4
98	F	22	0	Postsurgical pain	peripheral nerve injury	no	no	no	none	unlikely NP	2
99	F	49	50	Accident with trauma	peripheral nerve injury	no	no	no	negative	unlikely NP	1
100	F	50	10	Radiotherapy	peripheral nerve injury	no	no	no	none	unlikely NP	7
101	F	75	90	Polyneuropathy	polyneuropathy	no	no	no	positive	unlikely NP	4
102	F	61	80	Postsurgical pain	peripheral nerve injury	no	no	no	negative	unlikely NP	7
103	M	73	10	Peripheral nerve entrapment	peripheral nerve injury	no	no	no	negative	unlikely NP	0
104	M	62	80	Polyneuropathy	polyneuropathy	no	no	no	none	unlikely NP	7
105	M	29	60	Postsurgical pain	peripheral nerve injury	no	no	no	none	unlikely NP	5
106	F	49	30	Failed back surgery	peripheral nerve injury	no	no	no	negative	unlikely NP	0
107	M	60	80	Postsurgical pain	peripheral nerve injury	no	no	no	negative	unlikely NP	4
108	M	57	50	Polyneuropathy	polyneuropathy	no	no	no	negative	unlikely NP	2

Demographic patient overview; Quantitative Sensory Testing (QST) area indicates assessment location. Clinical diagnose indicate the different neuropathic pain entities. For allocating patients pain complaints as neuropathic pain a grading system was applied (Treede et al 2008). This grading determine with a greater level of certainty whether a pain condition is neuropathic. To increase likelihood of neuropathy grading requires that pain in plausible neuroanatomical distribution (Grading 1), that there is a history for a lesion or disease (Grading 2), sensory signs are in a neuroanatomical plausible distribution (Grading 3) and the presence of a positive confirmatory test (Grading 4) (none indicates that no test was performed). Number of sensory abnormalities reflects sensory gain sensory loss based on QST parameter exceeding CI 95% of z-scores.

3.2.2. Grading of neuropathic pain

Patient's pain was graded into 'definite neuropathic' (n=26), 'probable neuropathic' (n=39), 'possible neuropathic' (n=9) and 'unlikely neuropathic' (n=34) according to the classification by Treede and colleagues (Treede et al 2008). Thus, of the 108 neuropathic pain patients investigated, 60% were graded as having 'definite' and 'probable' neuropathic pain. Out of this group 40% were accounted as 'definite' neuropathic. For patients graded as 'probable' neuropathic pain, 67% (n=26) a diagnostic test was not performed and 33% (n=13) had a negative outcome of the diagnostic test. Interestingly, in one patient with 'probable' neuropathic pain grading the diagnostic test was positive but the confirmatory test was negative (Table 3-1).

All nine patients graded as 'possible' neuropathic pain did not have their sensory signs in a neuroanatomical confined territory. For this patient group more confirmatory and diagnostic work would be necessary to advance this group to 'probable' neuropathic pain. 31% of the clinically diagnosed neuropathic pain patients were graded as 'unlikely' neuropathic pain. This was due to the fact that there was a lack of history of patient's lesion or disease and their pain complaints were not in a plausible neuroanatomical distribution (Table 3-1).

3.3. Type of sensory abnormalities in relation to neuropathic pain grading

3.3.1. Sensory loss and/or gain of function

For the 108 patients investigated in this study, 1404 QST data measurements were obtained. In patients with neuropathic pain, sensory abnormalities were observed in all QST parameters. In our patient cohort, 94% had at least one QST abnormality. From these patients 51% had a mixture of sensory gain and loss, 26% had only sensory gain (hyperalgesia) and 16% had only sensory loss (hypesthesia) (Fig. 3-1).

The profiles of sensory signs in 'definite' and 'probable' neuropathic pain were not significantly different, but different from the 'unlikely' grade. This latter difference was due to an increase of a mixture of sensory gain and loss and a decrease in frequency of sensory loss only for the 'unlikely' grade compared to the 'definite' and 'probable' neuropathic pain grade (all $p<0.05$) (Fig. 3-1).

These results indicate that profiles of sensory signs for 'definite' and 'probable' neuropathic pain differ from the profiles for the 'unlikely' grade.

3.3.2. Individual QST parameters

For the different grading groups of neuropathic pain similar patterns of the distribution of sensory abnormalities were observed. Since the different neuropathic pain grades

showed comparable profile only the two most distant opponents i.e. 'definite' and 'unlikely' neuropathic pain, are displayed for illustration in Figure 3-2. All neuropathic pain grades showed predominantly sensory gain changes for nociceptive QST parameters (CPT, HPT, PPT, MPS, WUR) reflecting hyperalgesia, whereas the non-nociceptive parameters (CDT, WDT, TSL, MDT, VDT) reflected hypesthesia (Fig. 3-2).

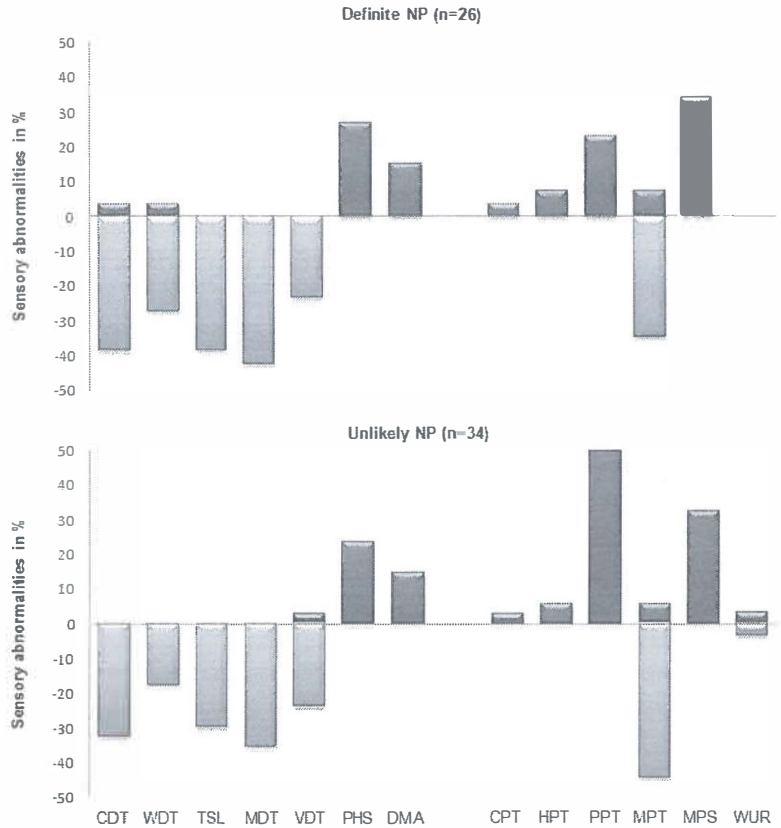

Fig 3-2: Quantitative Sensory Testing (QST) z-score abnormalities in % for 'definite' neuropathic pain (top) and 'unlikely' neuropathic pain (bottom) grading in 108 neuropathic pain patients. QST parameter are ordered as sensory parameters: Cold Detection Threshold (CDT), Warm Detection Threshold (WDT), Thermal Sensory Limen (TSL), Mechanical Detection Threshold (MDT), Vibration Disappearance Threshold (VDT), Paradoxical Heat Sensation (PHS), Dynamic Mechanical Allodynia (DMA) and nociceptive parameters: Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Pressure Pain Threshold (PPT), Mechanical Pain Threshold (MPT), Mechanical Pain Sensitivity (MPS) and Wind Up Ratio (WUR). Z-scores with positive sensory signs (gain of sensory function) plotted rightwards and negative sensory signs (loss of sensory function) plotted leftwards. Absence of DMA is normal and therefore no negative sign possible.

For the nociceptive parameters CPT and HPT, thermal pain thresholds were decreased indicating thermal hyperalgesia. An increased pain due to blunt pressure (PPT) and an increased sensitivity to mechanical pain (MPS) were observed indicating only hyperalgesia for these parameters. For MPT a greater incidence for mechanical hypo- than hypersensitivity was detected. WUR was more frequently increased than decreased indicating a greater incidence for hyper- than hyposensitivity. For almost every patient sensory loss was only observed for the non-nociceptive CDT indicating a thermal hypesthesia. In addition, thermal hypesthesias were observed in most of the patients for WDT and TSL. For MDT predominantly a sensory loss was observed indicating a mechanical hypesthesia. Except for two patients, it was not possible to detect hyperesthesia for VDT as the maximal value of 8/8 measured by the tuning fork was within the normal range. PHS and DMA were found to be increased within all grading of neuropathic pain.

These results show that sensory abnormalities for the individual QST parameters are remarkably similar between the grades of neuropathic pain. These similarities were also reflected in the distribution for nociceptive and non-nociceptive QST parameters for the different neuropathic pain grades.

3.4. Number of sensory abnormalities in relation to neuropathic pain grading

The number of sensory abnormalities in neuropathic pain patients varied between 0 and 9 for the thirteen QST parameters (see Table 3-1). In three out of the four grading categories, i.e. 'unlikely', 'definite' and 'probable' neuropathic pain, a small fraction of patients did not show any sensory abnormality upon undergoing the complete QST monitoring.

When comparing the number of sensory abnormalities in the different categories of graded patients, the mean number of abnormalities for the group of patients graded as 'definite' neuropathic pain was 3.3 (SD ± 2.0). Similar numbers were also found for the group of patients with 'probable' and 'unlikely' neuropathic pain, 3.1 (SD ± 2.0) and 3.4 (SD ± 2.1) respectively. Slightly higher was the number of abnormalities observed for the group of patients graded as 'possible' neuropathic pain (4.0, SD ± 1.8). This increase is not significant compared to patient groups graded as 'definite', 'probable' or 'unlikely' neuropathic pain using ANOVA (Fig. 3-3).

3.5. Background pain in relation to neuropathic pain grading

Except for two patients, all patients reported ongoing spontaneous pain (NRS mean 63.2, SD ± 22.8) before the QST assessment took place (see Table 3-1). For patients graded as 'definite' neuropathic pain the mean NRS score for spontaneous pain were 65.2 (SD ± 20.3). Slightly higher pain levels were reported by patients graded as 'possible' neuropathic pain (68.3, SD ± 26.5). Patient's graded as 'probable' and

'unlikely' reported slightly lower pain levels of 60.9 (SD ± 23.8) and 62.8 (SD ± 23.0), respectively. However, these differences were not significant (ANOVA).

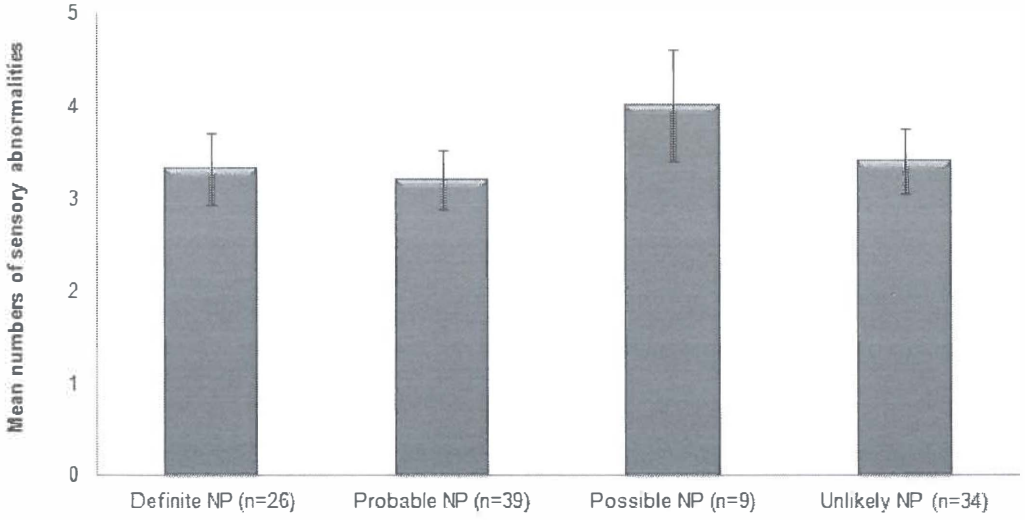

Fig. 3-3: Numbers of sensory abnormalities (sensory again and loss) for patients (n=108) graded as 'definite', 'probable', 'possible' and 'unlikely' neuropathic pain (NP); Mean values ± SEM.

4. Discussion

Investigating the somatosensory profiles of patients using QST showed that somatosensory abnormalities are a common feature in neuropathic pain. Applying the grading system for neuropathic pain revealed similar numbers of somatosensory abnormalities across the four different grading categories. Analysing the profile of sensory signs showed that overall the 'definite' and 'probable' neuropathic pain groups have an indistinguishable similar profile. The presence of a mixture of sensory gain and loss as well as for sensory loss only differed significantly for these groups compared to the 'unlikely' grade. There was no significant correlation between background pain and the different neuropathic pain grades.

The grading system allows a separation of neuropathic and non-neuropathic pain based on profiles but not on the total amount of sensory abnormalities. Thus, the suggestion that patient selection based on grading of neuropathic pain may provide a more homogenous group of neuropathic pain patients for research and for clinical studies is only partly supported by the findings of this study. A more useful criterion for homogenous patient selection is the grading system since it allows a separation of neuropathic and non-neuropathic pain based on somatosensory profiles.

4.1. Clinical diagnoses and grading of neuropathic pain

All patients investigated in the present study were diagnosed with neuropathic pain based on clinical presentation. Neuropathic pain is notoriously difficult to diagnose and due to the lack of a specific diagnostic tool a grading system to categorize pain as 'definite', 'probable', 'possible' and 'unlikely' neuropathic was proposed (Treede et al 2008). For 67% of the patients investigated, a direct history of a relevant lesion or disease and plausibly distributed pain was confirmed. These patients were subsequently graded at least as 'possible' neuropathic pain. In 26% of the patients such a plausible distribution of their pains was not identified, therefore these patients were graded as 'unlikely'. For 29% of the patients no direct history of a relevant lesion or disease was identified. For these patients a greater degree of certainty than 'unlikely' could not be reached. Overall, 32% of patients gained the neuropathic pain grade 'unlikely'.

A small group of patients (8%) were graded as 'possible' neuropathic pain. Here confirmatory tests were either negative or had not yet been performed, therefore this group of patients is regarded as having 'unconfirmed' neuropathic pain. This status is difficult to judge since clinical investigations determine this category. Any additional positive confirmatory test could change the status to neuropathic pain e.g. 'probable' and/or 'definite'. On the other hand, it has not been described how to proceed with the grading if future confirmatory tests were negative. For that reason the comparison of 'definite' and 'probable' versus 'unlikely' neuropathic pain grading is the most valuable for this paper.

According to the classification criteria only definite and probable grades are to be regarded as neuropathic pain (Treede et al 2008). Therefore, 40% of patients investigated should be regarded as having non-neuropathic pain. Apparently, there is a mismatch in the outcome 'neuropathic pain' between the clinical observations / diagnosis and the grading system. Reason for such differences could lie in the fact that the grading system relies on a direct relationship between cause of pain and its neuroanatomical plausible distribution to exclude 'unlikely' neuropathic pain grade. It could be argued that the grading system is "biased" towards precisely defined neuropathic pain entities. Once a distinct clinical entity is confirmed an increase in the certainty of neuropathic pain is almost an "epiphenomenon" since confirmatory evidence is often part of the assessment. Examples include neuropathic pain after a known surgical nerve lesion or postherpetic neuralgia after shingles. From a clinical perspective such a direct relationship is sometimes difficult to establish. For example, a large group in the present study are postsurgical pain patients (n=33) which were diagnosed clinically with peripheral nerve injury. Out of this pool, seventeen patients were graded as 'definite' and 'probable', six patients as 'possible' and ten patients as 'unlikely' neuropathic pain. For grading purposes, it has been suggested that the distribution of pain or hyperalgesia does not necessarily need to be identical to the innervations area of a peripheral nerve or root,

but it should be in a distribution that is typical for the underlying disorder (Treede et al 2008). This is easy to recognise in well defined diseases such as postherpetic neuralgia where central sensitization might influence the distribution of sensory abnormalities. In contrast it is less clear in patients with postsurgical pain since it has been not established if damage to tissues other than nerves causes neuropathic pain after surgery (Macrae 2008).

Overall, 60% of the patients were graded as 'definite' and 'probable' neuropathic pain. Interestingly, different clinical neuropathic pain entities were found consistently within the grades of neuropathic pain. Only patients with postherpetic neuralgia were consistently graded as neuropathic pain.

4.2. Somatosensory function in healthy controls

Z-score transformation of QST data revealed one or more somatosensory abnormalities in 38% of the healthy control group. This number is in line with previous findings of 41% abnormalities using the QST protocol (Maier et al 2010).

For healthy volunteers, abnormalities were observed across all QST parameters with the exception of DMA. The detected sensory abnormalities reflected gain of function for the most part, some loss of function and in a minority a mixture of gain and loss of function (Fig 3-2).

4.3. Somatosensory function in neuropathic pain patients

As expected, the large majority (93%) of neuropathic pain patients showed sensory abnormalities. Previously, a similar percentage (92%) of patients with at least one QST abnormality were reported (Maier et al 2010). Given the fact that for 7% of the patients, no abnormality could be detected, QST and the cut-off of 95% CI of the mean reference values might be more stringent than clinical examination.

In accordance with previous studies, sensory loss was predominantly found in non-nociceptive parameters (Maier et al 2010; Scholz et al 2009), which could be associated with central or peripheral neuronal damage leading to ongoing pain via increased ectopic activity (Liu et al 2000; Ochoa et al 2005; Serra et al 2009). Sensory gain was predominantly found in nociceptive parameters which could be associated with peripheral sensitization and/or altered central processing (Baron 2000; Baumgartner et al 2002; Sandkuhler 2009; Treede et al 1992; Wasner et al 2004). Overall, there was good agreement between our estimates of the expected range of sensory abnormalities in the general neuropathic pain patient population and those reported by Maier (Maier et al 2010).

4.3.1. Somatosensory function across the grading of neuropathic pain

The pattern of sensory abnormalities for nociceptive and non-nociceptive parameters did not differ for the different neuropathic pain grades. A similar distribution of nociceptive and non-nociceptive parameters was previously reported in neuropathic pain patients (Maier et al 2010).

Recently, Maier and colleagues reported in a QST study of 1236 neuropathic pain patients that profiles of sensory abnormalities differ in the neuropathic pain conditions (Maier et al 2010). Differences in profiles of sensory abnormalities were also observed in our study based on the grading system of neuropathic pain. The presence of sensory gain and loss and only sensory loss was similar for the grade of 'definite' and 'probable' but was significantly different to the grade 'unlikely' neuropathic pain.

Our results indicate that the grading system allows a separation of neuropathic and non-neuropathic pain based on profiles of sensory abnormalities.

4.4. Background pain, number of sensory abnormalities and neuropathic pain grading

QST revealed that the numbers of sensory abnormalities did not differ between the different neuropathic pain grades. This observation challenges the hypothesis that the number of sensory abnormalities is positively related to neuropathic pain grades using the grading system (Maier et al 2010).

In a study with 618 neuropathic- and non-neuropathic pain patients, Dworkin and colleagues showed that pain intensity, unpleasantness, quality, and spatial characteristics differed significantly between these groups (Dworkin et al 2007a). In the present study we have assessed the intensity of background pain prior to QST. There was no correlation between background pain intensity and numbers of somatosensory abnormalities in patients clinically diagnosed as neuropathic pain or for the different grades of neuropathy.

The majority of patients investigated (93%) used their regular medication when the QST assessment took place. The medication could have influenced the sensory profiles detected. This is not ideal, but it reflects the most common situation in which QST testing is performed, clinically. Furthermore, all categories of the neuropathic pain grading include patients with medication. Apart from the ethical aspect of drug withdrawal leading to increased pain, many neuropathic pain medications have long elimination times and possible active metabolites, making drug withdrawal prior to testing both unwarranted and unpractical.

In conclusion, our results indicate that there is a mismatch between clinical neuropathic pain diagnoses and neuropathic pain grading outcome. Only 60% of patients with clinically diagnosed neuropathy were categorized as 'definite' and 'probable' neuropathic pain patients. Even if such a stringent grading system may provide advantages in selecting homogenous groups for clinical research, numbers of somatosensory abnormalities within the different certainties of neuropathic pain are remarkably similar. The only significant finding to differentiate "true" neuropathic pain from "unlikely" neuropathic pain was the difference in somatosensory profiles, in particular with regard to the presence of the mixture of sensory gain and loss and only sensory loss. Neuropathic pain grades as well as numbers of sensory abnormalities were not correlated with patients reported background pain intensity.

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Chapter 4

A single QST parameter as a tool for mechanism-based investigation of neuropathic pain

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submitted

4. QST and neuropathic pain mechanisms

Abstract

Quantitative sensory testing (QST) allows the somatosensory profiling of patients with neuropathic pain. The ultimate goal of identifying differences in the responsiveness to sensory stimuli is the identification of differences in the mechanisms responsible for generating sensory abnormalities and their subsequent mechanism-based therapy. Recently, it was shown that distinct somatosensory patterns using a battery of QST tests are present in the different clinical entities of neuropathic pain. Until now, it has not been investigated whether the responsiveness to a single QST parameter would reveal different patient subgroups. Thus, we studied patients with neuropathic pain for their responsiveness to a single QST parameter "Mechanical Pain Sensitivity" (MPS). Abnormal MPS score reflects hypersensitivity for mechanical stimulation, which occurs in ~30% of the neuropathic pain patient population. The MPS test obtains stimulus-response function to seven pinprick devices exerting forces between 8-512mN to identify abnormalities for pinprick pain. In this study we found that patients with MPS abnormalities showed two distinctive patterns of altered stimulus-response function to pinpricks. 40% of patients reported a stimulus dependent pain response whereas 60% of patients did not show such stimulus dependent behaviour and rated all pinprick intensities equally painful. Both types of responses were found within different clinical entities of neuropathic pain. Hence, we show that even a single QST parameter can reveal additional, more detailed information of sensory abnormalities in neuropathic pain. Further evaluation might lead to the identification of differences in the mechanisms responsible for these distinct MPS abnormalities.

4. QST and neuropathic pain mechanisms

1. Introduction

The International Association for the Study of Pain (IASP) defined neuropathic pain as a direct consequence of a lesion or dysfunction affecting the somatosensory system (Treede et al 2008). Neuropathic pain has traditionally been classified based on its underlying aetiology (Hansson 2003); (Jensen et al 2001); (Woolf & Mannion 1999). Until now, neuropathic pain classification according to the aetiology has been the basis for its pharmacological treatment, including tricyclic antidepressants, anticonvulsants and opioids (Attal et al 2010; Baron et al 2010; Dworkin et al 2007b; Wong et al 2007). However, improvement of pain complaints of more than 50% is achieved in less than one-third of neuropathic pain patients studied (Argoff et al 2006; Farrar et al 2001; McQuay et al 1996; Sindrup & Jensen 1999; Ziegler 2008). A way to provide more insight in the distinct underlying mechanisms for the different types of neuropathic pain patients is to investigate symptoms and sensory signs in greater detail. Ideally, this could lead to a mechanistic understanding of the disease with subsequent improved treatment.

With the development of standardized quantitative sensory testing (QST) protocols such as was provided by the DFNS group in Germany (Rolke et al 2006b), a methodology has emerged to characterise a full profile of somatosensation in each patient with neuropathic pain. Recently, Maier and colleagues reported in a study of 1236 neuropathic pain patients using this DFNS QST protocol that profiles of sensory abnormalities along 13 different QST parameters differ in the different neuropathic pain entities such as in postherpetic neuralgia, peripheral nerve injury, polyneuropathy and others (Maier et al 2010). This study provides valuable information to generate understanding and concepts reflecting different sensory presentations of neuropathic pain.

Because the convergence of multiple mechanisms into only one clinical symptom is probably the case for many of the different symptoms and signs in patients with neuropathic pain (Woolf & Mannion 1999), an additional contribution to mechanistic studies of neuropathic pain could be the identification of somatosensory subgroups of patients based on a single QST parameter. Even for a single QST parameter, there might be differences in response within the group of patients that show abnormalities for this particular QST test.

One of the parameters of the DFNS QST battery is Mechanical Pain Sensitivity (MPS). Abnormal MPS score reflects hypersensitivity for mechanical stimulation, a cumbersome phenomenon, which occurs in ~30% of the neuropathic pain patient population (Maier et al 2010). The MPS test obtains stimulus-response functions to identify sensory abnormalities for pinprick pain.

In the present study we investigated whether a single QST parameter, i.e. MPS,

can be used to identify relevant subgroups of neuropathic pain patients, in this case characterised by altered mechanical pain sensitivity. According to the DFNS QST protocol, the geometric means of the numerical pain ratings for the different pinprick stimuli are taken for further analysis (Konopka et al a; Maier et al 2010; Rolke et al 2006a; Rolke et al 2006b). As an addition to the QST protocol, we performed stimulus response analyses, since these can be very informative and have been widely used to assess hypo- and hyperalgesic cutaneous reaction in clinical pain models (Fuchs et al 2001; Magerl et al 2001; Segerdahl 2006) and in patients (Stiasny-Kolster et al 2004).

2. Method

The study adhered to the declaration of Helsinki and all procedures have been approved by the medical ethical committee "Stichting Beoordeling Ethiek Bio-Medisch Onderzoek, P.O. Box 1004, 9400 BA Assen, The Netherlands", including patients and healthy controls from the local region. All participants signed an informed consent form.

2.1. Description of healthy controls

In total, 185 age-matched healthy volunteers (age range 25-75 years), 119 females (age 48.9 ± 10.5 years) and 66 males (age 51.9 ± 12.4 years) underwent the QST assessments on their dorsal hand and dorsal foot. These body locations are indicated by Rolke et al., 2006 as reference sides for QST (Rolke et al 2006a). A previous study concluded that there were no significant differences in QST parameters between the right and left sides of the body in healthy volunteers (Rolke et al 2006a), thus we obtained QST reference values from one side of the body. In total, 370 QST reference values were obtained. Healthy subjects were identified according to medical history. Subjects were specifically questioned about previous injuries or diseases. The healthy subjects did not use pain medication regularly and were free of medication at the time of the assessments.

2.2. Description of the patient cohort

Patients were recruited from the outpatient Department of the Pain Management Unit of the University Medical Center Groningen, The Netherlands. All patients were diagnosed as suffering from neuropathic pain by the physicians of the pain management unit. Neuropathic pain diagnosis was made on grounds of coherent patient history, medical history, physical examination, including neurologic function tests. Each clinical diagnosis was additionally confirmed by an experienced pain specialist of the Pain Management Unit based on patient's files. In total, 127 neuropathic pain patients (65 females age 52.4 ± 12.1 years and 62 males age 51.45 ± 12.4 years) underwent the QST assessment, each at the area where the most profound pain was experienced (leg: n=70, arm: n=29, thorax: n=12, back: n=4, abdomen: n=3, cervix: n=3, groin: n=2,

shoulder: n=2, flank: n=2). Patients did not discontinue their regular pain treatment, if applicable.

2.3. Quantitative sensory testing (QST)

The MPS testing procedures were applied according to the standardized protocol of Rolke et al., 2006 (Rolke et al 2006a). QST was performed by two research nurses, who underwent a comprehensive training at the DNFS in Germany. All tests were performed at the same research facility of PRA International, Groningen, The Netherlands. The average room temperature was 22.9°C; SD ± 1.9°C.

Mechanical pain sensitivity (MPS) was assessed using a set of seven pinprick devices (flat contact area of 0.2 mm in diameter) with fixed stimulus intensities that exerted forces of 8, 16, 32, 64, 128, 256, and 512 mN stimuli to obtain a stimulus–response function for pinprick-evoked pain, which activates Aδ-nocipectors (Ziegler et al 1999). A total of 35 pinprick stimuli were delivered. As part of the QST protocol, MPS test was intermixed with the assessment of Dynamic Mechanical Allodynia (DMA). For DMA, three innocuous dynamic allodynia tools, cotton wisp, cotton bud and brush were applied (see Rolke et al., 2006) These stimuli were given in runs of 7 (five runs each), and each run consisted of a different pseudorandom sequence of seven pinprick stimuli and three dynamic allodynia stimuli. All stimuli were applied with a ~10 s inter-stimulus interval – well below the critical frequency for wind-up (temporal pain summation).

After each stimulus application, subjects were asked to give a pain rating for each stimulus on a '0–100' numerical rating scale (NRS) ('0' indicating "no pain", and '100' indicating "most intense pain imaginable").

2.4. Data analysis and statistics

2.4.1. Z-transformation of QST data

Pain rating to the seven different intensities of punctuates mechanical stimuli obtained from healthy subjects and patients are expressed as arithmetic mean and 95% confidence intervals. Both, patients and healthy subjects were divided into two age groups each (25-44 years of age and 45-74 years of age). MPS data of patients with neuropathic pain were compared with reference data from gender and age matched healthy subjects. QST values of neuropathic pain locations at the upper extremities were compared to QST reference values obtained from the dorsal hand of healthy controls, whereas values from neuropathic pain locations at lower extremities were compared to reference values obtained from the dorsal foot of healthy controls. MPS values from each patient were transformed to z-scores as described by Rolke et al., 2006 (Rolke et al 2006a). A score above 1.96 or below -1.96 falls outside the 95% confidence interval of the mean reference value and was considered as a sensory abnormality. Abnormalities were subsequently categorised as either a sensory gain or a sensory loss.

2.4.2. Stimulus-response function for MPS in patients

Only patients who exceeded the 95% CI of the z-score transformation were eligible for further analyses of their stimulus-response functions for MPS. For patients with abnormal MPS z-score values, the stimulus-response function of the seven pinpricks, based on the mean of five stimuli each, were analysed. To identify differences in the pattern of the stimulus-response function the median of all seven pinprick forces was calculated. Each patient's median out of the seven pinprick ratings was calculated and compared to mean of five stimuli per pinprick intensity NRS rating. If the variance was greater than NRS ±10 of the median for two out of the seven pinprick intensities the presence of a stimulus-response function was recorded. If patients did not exceed the variance of pain ratings of greater than NRS ±10 for six out of seven pinprick stimuli, the absence of a stimulus-response function for MPS was reported.

2.4.3. Statistical analyses

For healthy subjects, data were analysed using repeated measures ANOVA with 'age group' (25-44 years, 45-74 years) as within subject variables and 'gender (male/female) and location (arm/leg)' as between subject variables.

Patients were divided into two groups according to their differences in the stimulus-response function to pinpricks. For each individual, the slope of the stimulus-response function was analysed using a least square regression. The slopes between the two groups were tested using t-test.

All data are presented as group mean scores with Standard Error of the mean (SE). For statistical analysis SPSS 16.0 (SPSS Inc, Chicago (IL), USA) was used.

3. Results

3.1. Stimulus-response function in healthy subjects

In healthy volunteers, the painfulness of the different stimulus intensities for the pinprick forces was significantly different ($F(1,181) = 12.93$, $p < 0.001$), indicating that pain ratings increased with the increase in pinprick force (see Table 4-1). Taking gender, age and location as variables, only for location there was a significant effect found ($F(6,1086) = 3.57$, $p = 0.02$) showing that the pinprick forces were rated more painful at the leg compared to the arm. Therefore, for z-score transformation of MPS values in patients, MPS values for each of the two test locations were pooled with respect to the different gender and age groups of healthy controls.

Table 4-1: Overview of pain ratings for Mechanical Pain Sensitivity (MPS) in healthy subjects

Pinprick Force	Pain	F < 45 hand n=40 test sites	F > 45 hand n=79 test sites	F < 45 foot n=40 test sites	F > 45 foot n=79 test sites	M < 45 hand n=19 test sites	M > 45 hand n=47 test sites	M < 45 foot n=19 test sites	M > 45 foot n=47 test sites
8mN	Mean NRS	0.31	0.70	0.30	0.72	0.45	0.51	1.02	0.99
	95% CI	(-0.19)-(0.82)	(-0.03)-(1.44)	(0.07)-(0.53)	(0.18)-(1.26)	(-0.17)-(1.07)	(-0.02)-(1.05)	(-0.19)-(2.24)	(0.29)-(1.69)
16mN	Mean NRS	0.42	1.01	1.65	1.78	0.52	0.51	1.39	1.56
	95% CI	(-0.01)-(0.84)	(0.28)-(1.75)	(0.78)-(2.52)	(0.90)-(2.66)	(0.02)-(1.02)	(-0.01)-(1.03)	(0.16)-(2.61)	(0.40)-(2.71)
32mN	Mean NRS	0.78	1.07	2.21	2.18	0.96	1.09	1.69	1.79
	95% CI	(0.16)-(1.40)	(0.39)-(1.74)	(1.14)-(3.28)	(1.14)-(3.23)	(-0.08)-(2.01)	(0.19)-(1.99)	(0.01)-(3.36)	(0.26)-(3.32)
64mN	Mean NRS	2.57	2.44	3.61	3.54	1.40	2.43	2.95	3.98
	95% CI	(1.37)-(3.77)	(1.49)-(3.39)	(2.09)-(5.14)	(2.29)-(4.78)	(0.43)-(2.37)	(0.86)-(4.00)	(0.93)-(4.96)	(2.03)-(5.93)
128mN	Mean NRS	4.28	4.41	6.25	5.91	4.32	4.15	7.06	6.47
	95% CI	(2.70)-(5.87)	(2.88)-(5.93)	(4.23)-(8.27)	(4.26)-(7.57)	(2.67)-(5.97)	(2.33)-(5.96)	(3.13)-(10.99)	(4.31)-(8.64)
256mN	Mean NRS	5.28	5.41	7.68	6.37	5.76	5.69	7.40	7.89
	95% CI	(3.57)-(6.99)	(3.80)-(7.01)	(4.99)-(10.36)	(4.66)-(8.07)	(3.02)-(8.49)	(2.96)-(8.42)	(3.49)-(11.31)	(5.35)-(10.42)
512mN	Mean NRS	7.93	7.85	10.17	9.49	7.53	8.07	7.71	10.40
	95% CI	(5.47)-(10.39)	(5.81)-(9.89)	(6.91)-(13.44)	(7.12)-(11.85)	(4.74)-(10.31)	(5.10)-(11.04)	(4.34)-(11.09)	(7.27)-(13.54)
Mean MPS	Mean NRS	0.75	1.08	1.26	1.61	0.95	0.70	1.46	1.42
	95% CI	(0.37)-(1.13)	(0.38)-(1.78)	(0.76)-(1.76)	(0.85)-(2.37)	(0.24)-(1.66)	(0.23)-(1.17)	(0.29)-(2.63)	(0.59)-(2.25)

Mechanical Pain Sensitivity (MPS) stimulus-response functions for healthy controls (n=185). Controls are divided in two age groups (<45: age range 25-44 years and >45: age range 45-74 years). MPS assessment took place at dorsal hand (hand) and dorsal foot (foot). Stimulus-response functions were assessed by seven pinpricks exerting forces of 8mN, 16mN, 32mN, 64mN, 128mN, 256mN and 512mN. Each subject rated the painfulness of each stimulus by Numerical Pain Rating (NRS) (0 no pain – 100 most imaginable pain). Geometric means of each value of five stimulations for each pinprick force were pooled and 95% CI are presented.

3.2. Z-score transformation for MPS in patients

From the 127 chronic pain patients investigated, 87 (68.5%) patients did not exceed the CI 95% of the z-score transformation and were regarded as normal responders to the test of MPS. 40 patients (31.5%) exceeded the CI 95% of the z-score transformation. None of the patient's z-score was greater than -1.96 indicating the presence of only sensory gain for MPS.

3.3. Differences in pattern of stimulus-response function

Investigating the stimulus response function of patients with MPS abnormalities revealed two distinctive groups of responders to pinprick stimulations. 40% of patients with abnormal z-score showed a stimulus-response function for MPS (Fig. 4-1). Generally, in these patients an increase in the pinprick force resulted in an increase in pain response (NRS). In contrast, such stimulus dependent response in pain ratings was absent in 60% of patients with MPS abnormalities (Fig. 4-2). Instead, patients consistently rated each individual pinprick force equally painful indicating an "all or none" phenomenon. Both patterns of pinprick responses in patients indicate a left-ward shift in painfulness compared to healthy controls and can be regarded as pinprick hyperalgesia.

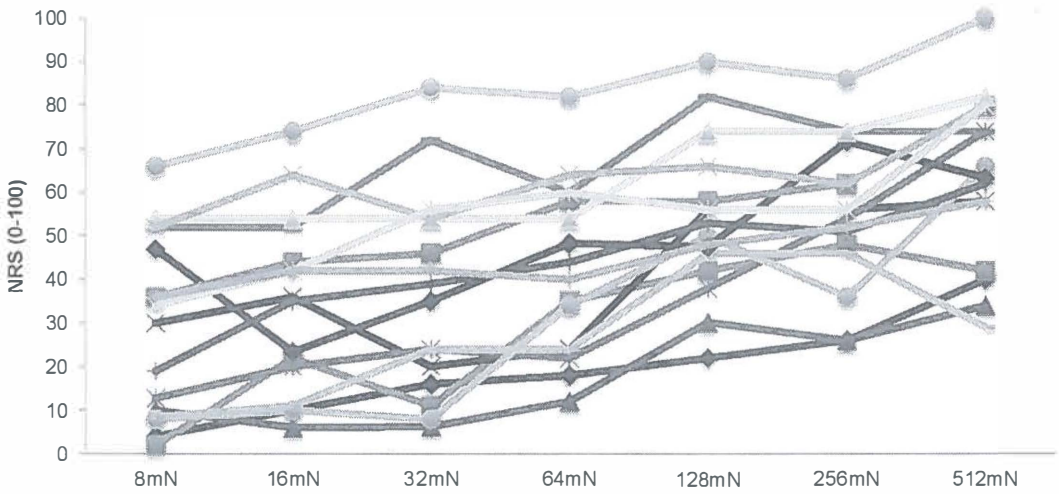

Fig. 4-1: Mechanical Pain Sensitivity (MPS) stimulus-response functions for neuropathic pain patients (n=16). Patients with MPS z-score values outside of the 95% CI showed a stimulus-response function to pinpricks. Stimulus-response functions were assessed by seven pinpricks exerting forces of 8mN, 16mN, 32mN, 64mN, 128mN, 256mN and 512mN. Each data point represents mean value for numerical rating scale (NRS (0-100)) for the painfulness of five stimulations for each pinprick force.

The two groups of patients with differences in their stimulus-response function were further evaluated. The linear fit analyses for each subject identified differences in the slope for the stimulus response function. For patients with a stimulus-response function the mean slope of the NRS for pain was 5.78 and for other patient group the NRS mean slope was 1.31 (Fig. 4-3). Significant differences between these slopes was confirmed by t-test ($t=7.532$, $df = 39$, $p < 0.001$). This result shows that two different types of responders to the pinprick stimulus-response function are present within the neuropathic pain patient population that show abnormal function in the MPS test.

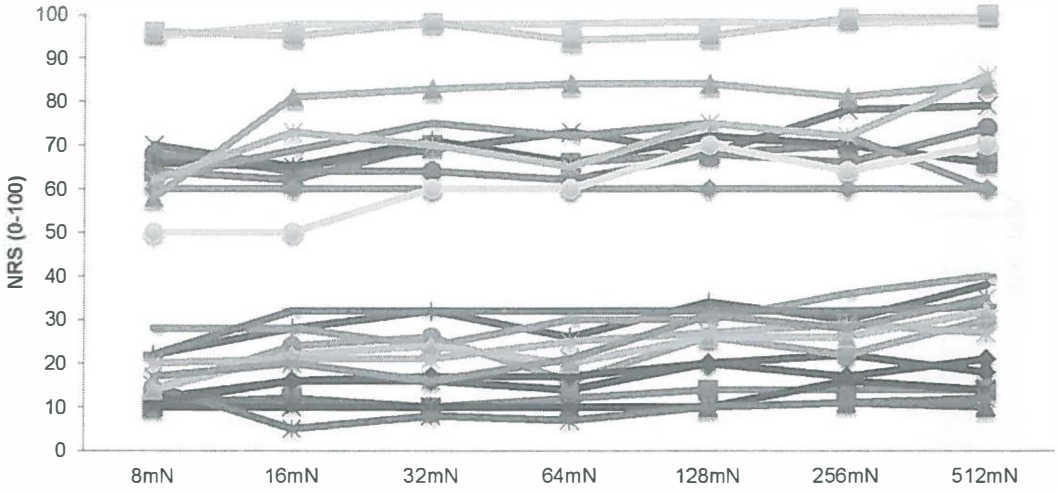

Fig. 4-2: Mechanical Pain Sensitivity (MPS) stimulus-response functions for neuropathic pain patients (n=24). Patients with MPS z-score values outside of the 95% CI showed an absence of stimulus-response function to pinpricks. Stimulus-response functions were assessed by seven pinpricks exerting forces of 8mN, 16mN, 32mN, 64mN, 128mN, 256mN and 512mN. Each data point represents mean value for numerical rating scale (NRS (0-100)) for the painfulness of five stimulations for each pinprick force.

3.4. Clinical diagnoses of patients with MPS abnormalities and different stimulus-response functions for pinpricks

All patients with MPS abnormalities have been diagnosed with neuropathic pain. Patients with stimulus-response function for MPS included peripheral nerve injury (n=13), complex regional pain syndrome (CRPS)-II (n=1) and central pain (n=2). Similar clinical entities are reflected in the group of patients with a lack of a stimulus-response function for MPS. In this group, patients were diagnosed with peripheral nerve injury (n=14), polyneuropathy (n=6), central pain (n=3) and postherpatic neuralgia (n=1). Disease duration for each of these two groups ranged between 1 year and 15 years. Similar clinical entities of neuropathic pain patients were for both groups of MPS abnormalities indicating that the phenomenon of different responder to pinprick pain is not restricted to the clinical entity.

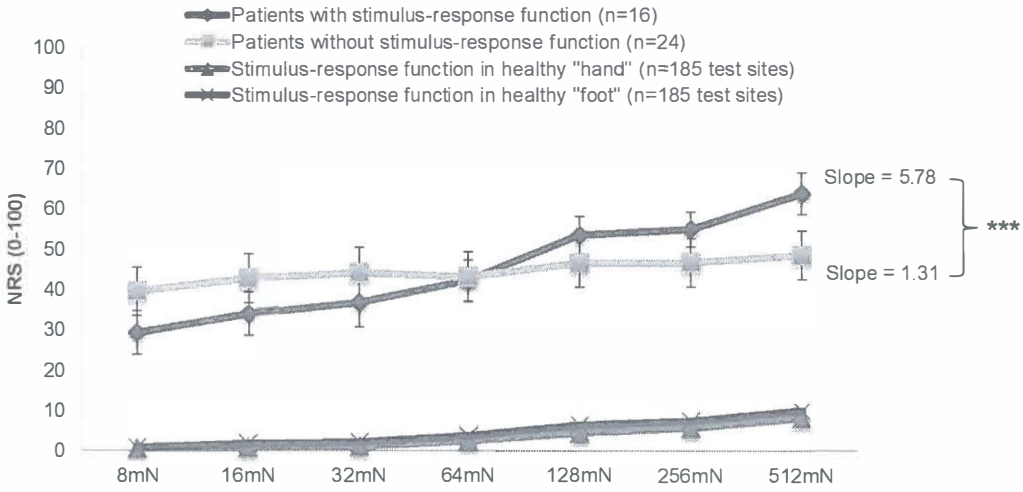

Fig. 4-3: Mechanical Pain Sensitivity (MPS) stimulus-response functions for healthy controls (n=185) and neuropathic pain patients (n=40). Patients with MPS z-score values outside of the 95% CI showed either a stimulus-response function to pinpricks (n=16) or absence of stimulus-response dependent function (n=24). Stimulus-response functions were assessed by seven pinpricks exerting forces of 8mN, 16mN, 32mN, 64mN, 128mN, 256mN and 512mN. Each data point represents mean value for numerical rating scale (NRS (0-100)) for the painfulness of five stimulations for each pinprick force. A significant difference between the slopes of the two stimulus-response functions in patients is indicated by *** ($p < 0.001$). Error bars indicate SE.

4. Discussion

QST has been used to identify somatosensory abnormalities in patients with chronic pain including neuropathic pain. The ultimate goal of identifying differences in the responsiveness to sensory stimuli in neuropathic pain patients is the identification of differences in the mechanisms responsible for generating sensory abnormalities. A QST study recently published by Maier and colleagues, showed that sensory abnormalities along the thirteen different QST parameters can be categorised into specific patterns of abnormal sensory function and furthermore, that these patterns are represented in the different clinical entities of neuropathic pain (Maier et al 2010).

An aspect which cannot be recognised in studies of patterns of sensory abnormalities along a series of QST parameters is the potential presence of differences in the responsiveness to a "single" QST parameter. In the present QST study we show that even a single QST parameter which is found to be abnormal in a subgroup of neuropathic pain patients compared to healthy controls can reveal additional, more detailed information of sensory abnormalities. Investigating the stimulus-response function in patients with abnormal MPS values revealed two distinctive groups. 40% of patients with MPS

abnormalities showed as expected a stimulus dependent pain response whereas 60% of patients unexpectedly did not show such stimulus dependent behaviour and rated all pinprick intensities equally painful. Both distinctive groups of different responsiveness to MPS were found in different clinical entities of neuropathic pain.

Thus, our results indicate that within the group of neuropathic pain patients who show abnormalities in the MPS test, distinct differences in the responsiveness to this single QST parameter exist. Further evaluation might lead to the identification of differences in the mechanisms responsible for these distinct MPS abnormalities.

4.1. MPS abnormalities in neuropathic pain patients

MPS was assessed as part of our QST screen of neuropathic pain patients. The occurrence of MPS abnormalities was 31.5% and reflected only sensory gain. Similar, the presence of sensory gain for MPS was reported to be 29.2% in a previous study in 1236 neuropathic pain patients (Maier et al 2010). On the other hand, we found a slightly lower prevalence (24.7%) of sensory gain for MPS in patients selected on the basis of their unilateral neuropathic pain (Konopka et al a).

4.2. Stimulus-response function for pinprick

Static or punctuate hyperalgesia assessed by pinprick stimuli is mediated by nociceptive Aδ-fibre high-threshold mechanoreceptors (LaMotte et al 1991; Magerl et al 2001; Ziegler et al 1999). In patients with spontaneous pain and hyperalgesia and in healthy subjects who were sensitised by an injection of capsaicin it was shown that by assessing the pinprick stimulus-response function also the degree of central sensitisation as measured by the shift in stimulus-response pain can be identified (Baumgartner et al 2002). Such a left-ward shift in the stimulus-response function to pinpricks was also observed in patients with restless-leg syndrome (Stiasny-Kolster et al 2004).

Central sensitisation refers to the increased synaptic efficacy established in neurons in the dorsal horn of the spinal cord following intense peripheral noxious stimuli such as tissue injury or nerve damage (Koltzenburg et al 1994; Schaible 2007; Woolf 2010; Ziegler et al 1999). This enhanced synaptic transmission leads to a reduction in pain threshold and an amplification of pain responses. Pharmacological intervention studies showed that central sensitisation seen in patients with neuropathic pain and in healthy subjects using clinical pain models can be reduced (Belfrage et al 1995; Chizh et al 2007; Gottrup et al 2004; Segerdahl 2006).

QST studies investigating mechanical pain sensitivity regularly use only the geometric mean value out of the 35 stimuli to identify sensory abnormalities compared to the healthy controls (Magerl et al 2010; Maier et al 2010; Rolke et al 2006a; Rolke et al 2006b). Investigating the QST parameter MPS in greater detail, e.g. dose-response

function as we did in the present study gives more detailed insight in the abnormalities. Part of the patients (40%) with an abnormal MPS parameter showed a dose-response function for the different pinprick intensities which reflects a left-ward shift when compared to dose-response function of healthy subjects. The other part, i.e. 60% of the patients, did not have a dose-response function to pinprick stimuli and rated each of the pinprick intensity equally painful. Such "all or none" response has been not reported previously. The observation of a loss of stimulus-response function in neuropathic pain patients with MPS abnormalities raises the question if the perception threshold and the maximum nociceptive activity are identical for this group of patients. In this context it is not clear if we have actually "missed out" the starting point of a stimulus-response function by not lowering the pinprick force. A further reduction in pinprick intensities is technically difficult and the usefulness is questionable since a state of pinprick hyperalgesia is confirmed. Whether or not the observation of a minimal perceptive stimulus which already induces a maximum nociceptive activity represents itself as a disease continuum in neuropathic pain patients with pinprick hyperalgesia could be investigated in longitudinal studies.

We have observed different levels of "all or none" response in our study population. Some patients consistently rated their painfulness for pinpricks as relatively mild (NRS 10-30) whereas others displayed high pain levels (NRS 60-95). Since QST is psychometric testing, it could be argued that the maximum pain response for each patient is also reflected in their rating. It could be presumed that in larger patient cohorts the "gap" between these responders can be filled.

The majority of patients with MPS abnormalities (85%) used their regular medication when the QST assessment took place. The medication could have influenced the MPS abnormalities detected. This is not ideal, but it reflects the most common situation in which QST testing is performed, clinically. Furthermore, all MPS pattern include patients with and without medication. Apart from the ethical aspect of drug withdrawal leading to increased pain, many neuropathic pain medications have long elimination times and possible active metabolites, making drug withdrawal prior to testing both unwarranted and unpractical.
The present QST study confirms that even a single QST parameter which is known to be abnormal compared to healthy reference values can reveal additional, more detailed information of sensory abnormalities.

4.3. QST for mechanism-based studies in neuropathic pain patients

QST data can be regarded as a rich source of valuable information of sensory abnormalities in chronic pain patients such as neuropathic pain. It is striking that sensory abnormalities for certain parameter such as Pressure Pain Threshold (PPT) or Mechanical Pain Sensitivity (MPS) of the QST battery were by far more frequently observed than others. The prevalence of sensory gain for PPT and MPS overall in neuropathic pain patients was reported to be 36.4% and 29.2%, respectively (Maier et al 2010).

The identification of somatosensory phenotypes based on single QST parameter such as MPS can contribute to the viability of mechanism-based understanding of neuropathic pain. We showed that different "responders" to MPS exist in the population of neuropathic pain patients. From a mechanistic point of view the identification of phenotypical homogenous groups of different "responders" for even a single QST parameter e.g. MPS might be useful. Future studies could evaluate if these different responders show differences in pharmacological responsiveness using different classes of pharmacological agents, e.g. sodium-channel blocker, antidepressants. In addition, if differences in responders to other QST parameters could be identified, with again distinct reactions to pharmacological interventions, a truly mechanistic picture of the somatosensory of neuropathic pain patients could be emerging. As previous mentioned, looking at QST profiles instead of a single parameter has shown its value to generate a mechanistic understanding of somatosensory abnormalities in neuropathic pain (Maier et al 2010). Our results add to that finding that one can even further subdivide the patients based on more detailed testing as we did using our specific MPS analysis approach.

Our results indicate that multiple mechanisms e.g. different causes of neuropathic pain, can lead to the same sensory sign e.g. MPS abnormalities. Moreover, that distinct different pattern of sensitisation to pinprick pain is common in different neuropathic pain aetiologies. This observation raises the question if these mechanistic differences in sensitisation could also explain the lack of efficacy of pharmacotherapy in neuropathic pain patients.

In summary, a single QST parameter, i.e. MPS, can be used to identify distinct subgroups of neuropathic pain patients, characterised by altered mechanical pain sensitivity. Part of the patients showed a clear stimulus-response to pinprick stimuli, while in the other part a stimulus-response to pinprick stimuli was completely absent. Both types of responses were found within different clinical entities of neuropathic pain. Further evaluation is necessary to identify potential differences in the mechanisms responsible for these distinct MPS abnormalities and their subsequent mechanism-based therapy.

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Chapter 5

Do patients with chronic patellar tendinopathy have an altered somatosensory profile? – A Quantitative Sensory Testing (QST) study

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5. QST in patients with tendinopathy

Abstract

The prevalence of tendinopathies in sports is high. The aetiology and pain mechanisms of tendinopathies are not completely understood. Currently, little is known whether, or to which degree, somatosensory changes within the nervous system may contribute to the pain in tendinopathies. We conducted a patient controlled study in which we used the standardized QST protocol developed by the German Research Network on Neuropathic Pain. This protocol consists of 7 different tests that measures 13 somatosensory parameters and can be seen as the gold standard to measure somatosensory function. Twelve athletes with clinically diagnosed chronic patellar tendinopathy (PT) with a mean duration of symptoms of 30 months (range 6 - 120) and 20 control athletes were included in the study. In two of the thirteen QST parameters namely mechanical pain threshold ($p < 0.05$) and vibration disappearance threshold ($p < 0.05$) injured athletes were significantly more sensitive for the applied stimuli compared to controls. None of the athletes had signs of dynamic mechanical allodynia. Reduced mechanical pain thresholds or pinprick hyperalgesia reflects the involvement of central sensitisation upon the myelinated (Aδ-fibre) nociceptive input. From this explorative study we conclude that sensitisation may play a prominent role in patella tendinopathy patients.

5. QST in patients with tendinopathy

1. Introduction

The prevalence of tendinopathies in sports is high, well known sports related tendinopathies are achilles tendinopathy in runners, patellar tendinopathy (PT) in volleyball and basketball players and supraspinatus tendinopathy in swimmers (Chaudhry & Maffulli 2007; Lian et al 2005; Sein et al 2010). The aetiology and pain mechanisms of tendinopathies are not completely understood. A tendinopathy is considered to be an 'overuse injury' with a failing intratendinous healing response, with neoangiogenesis and/or neural reorganization (Rees et al 2009; Tan & Chan 2008). In the assessment of PT, pain following manual palpation of the tendon, together with a characteristic history of increased pain during and after (sport) activities are the key elements for the diagnosis, and can be confirmed with additional imaging techniques such as Color Doppler Ultrasonography or Magnetic Resonance Imaging (Warden et al 2007). However, not all symptomatic athletes show tendon abnormalities on these imaging techniques (Malliaras & Cook 2006).

An interesting question is why pain occurs during or after exercise in both athletes with tendons showing abnormalities on ultrasound scans but also without abnormalities. A possible explanation for pain in tendons may be the changes in somatosensory function within the nervous system itself i.e. sensitisation of the nervous system, rather than damage within the tendon itself (Rees et al 2009; Webborn 2008). In the (sub-) acute phase, sensitisation is a physiologic mechanism that forces the patient to guard the affected body part, in order to enable tissue healing. However, sometimes sensitisation persists beyond the normal healing time; the pain becomes chronic. In PT pain typically occurs during or after exercise. This type of ongoing pain represents a more or less irreversible state of hyperexcitability within the central nervous system and could be considered as an important aspect in the development of neuropathic pain (Woolf & Mannion 1999). Sensitisation results in the clinical symptoms allodynia – pain due to a stimulus which does not normally provoke pain, e.g. pain upon the light stroking of the skin (dynamic allodynia) or pain during training or exercise (mechanical or kinetic allodynia) and hyperalgesia – an increased response to a stimulus which is normally painful, e.g. intense pain following a moderate pain stimulus (Merskey & Bogduk 2004; Svensson et al 2008; Treede et al 2008).

Clinically, the identification of signs of pain tenderness following a manual palpation is one of the essential diagnostic criteria of tendinopathy. Recently, Webborn proposed in a review that if no signs of ongoing nociception or persistent inflammation can be found in tendinopathies the presence of persistent pain can explained by neuropathic pain or by a psychogenic cause (Webborn 2008). If nociception and inflammation cannot be defined as plausible cause for a tendinopathy, it is reasonable to consider the possibility that an altered somatosensory profile i.e. sensitisation mechanisms may contribute or even trigger the occurrence of the pain in PT. With Quantitative Sensory Testing

(QST) it is possible to assess perceptual functioning of somatosensory modalities that correspond with distribution areas to peripheral nerve fibres and CNS pathways (Hansson et al 2007; Rolke et al 2006a). QST examines large fibre function (Aβ), and nociceptive small fibre (Aδ, C) functions, all of which may be involved in peripheral and central pain syndromes (Rolke et al 2006a). As QST is a form of psychophysical testing, alertness and cooperation of the patient is required for obtaining reliable test results. The cause of abnormal results may lie anywhere along the sensory pathway; from the peripheral receptor to the highest cortical regions in the brain (Chong & Cros 2004; Hansson et al 2007; Shy et al 2003).

Currently, little is known whether, or to which degree, somatosensory changes may contribute to the pain in tendinopathies and other sports injuries. Jensen et al. investigated the presence of neuropathic pain mechanisms in 91 patients with chronic patellofemoral pain syndrome (Jensen et al 2008). They used somatosensory testing's and found significant hypesthesia on the affected side as opposed to the patients' own unaffected, contralateral side. In a clinical pilot study in patients with general chronic sports injuries we found signs of sensitisation in 27 % of the athletes and additional 13 % showed signs of hypoalgesia (van Wilgen & Keizer 2011).

The primary goal of this study is to investigate whether somatosensory changes represent a plausible explanation for pain in patient with chronic patellar tendinopathies and secondly to investigate if psychological co-morbidities may contribute to pain in tendinopathy.

2. Methods

2.1. Participants

In this patient controlled study we included only male athletes with PT and male volleyball, basketball and soccer-players without PT in a control group. We included only male participants as gender differences have been reported for several QST parameters (Rolke et al 2006a). Patients with PT, diagnosed by an experienced sports medicine physician or sports physical therapists were asked to participate in the study. The diagnostic criteria for PT included a characteristic history of knee pain in the proximal patellar tendon related to exercise and tenderness upon palpation of the patellar tendon. Patients with PT were included if their pain had been present for at least 6 months and if they scored lower than 80 points on the Victorian Institute of Sports Assessment – Patellar Questionnaire (VISA-P). The VISA-P is a validated, self-administered questionnaire that is frequently used to evaluate the severity of symptoms, knee function and sports participation of athletes with PT (Visentini et al 1998). The psychometric properties of this questionnaire and the Dutch version in injured athletes

are adequate (Visentini et al 1998; Zwerver et al 2009).
Healthy control athletes were recruited from local sports clubs and through advertisements on websites. Inclusion criteria for participation of this study were a VISA-P score had to be above 90. All subjects were asked neither to take analgesics 24h before participation in the study nor to take part in sport activities on the day of the study. Subjects with diseases or conditions associated with possible altered somatosensory function, such as a knee surgery, diabetes, fibromyalgia or neurological diseases were excluded. All participants signed an informed consent prior to their inclusion QST testing was approved by the Medical Ethical Commission (Stichting Beoordeling Ethiek Bio-Medisch Onderzoek Assen, The Netherlands).

2.2. Quantitative Sensory Testing

QST entails the measurement of the subjects' responses to standardized thermal and mechanical stimuli. QST is used to determine detection, disappearances and pain thresholds. The German Research Network on Neuropathic Pain – DFNS has developed a standardized QST protocol. This protocol consists of 7 different tests that measure 13 parameters, including various types of mechanical and thermal detection and pain thresholds for the hand, foot and face (Rolke et al 2006a). QST was performed by two research nurses, who had undergone a comprehensive training at the DNFS in Germany. All tests were performed in the same research facility. Thermal QST tests were performed using the Medoc Pathway System (Medoc, Israel) and consisted of threshold assessments for warm and cold detection (WDT, CDT) and heat pain and cold pain (HPT, CPT). Thermal measurements were obtained with ramped stimuli (1 °C/s) that were terminated when the subject pressed a button. Minimal and maximal temperatures were 0 and 50 °C. The baseline temperature was 32 °C. In addition, subjects were asked about paradoxical heat sensations (PHS) during the thermal sensory limen (TSL) procedure of alternating warm and cold stimuli.

Mechanical QST tests consisted of seven different parameters. The mechanical detection threshold (MDT) was determined with a standardized set of modified von Frey filaments (Optihair2-Set, Marstock Nervtest, Germany). The mechanical pain threshold (MPT) was measured using a set of seven pinprick devices with fixed stimulus intensities that exerted forces of 8, 16, 32, 64, 128, 256, and 512 mN. Mechanical pain sensitivity (MPS) was assessed using the same set of seven weighted pinprick stimuli to obtain a stimulus–response function for pinprick-evoked pain. Dynamic mechanical allodynia (DMA) was assessed as part of the test above, using a set of three light tactile stimulators as dynamic innocuous stimuli: cotton wisp, cotton wool tip fixed to an elastic strip and a standardized brush (SENSElab No.5 Somedic, Sweden). Vibration disappearance threshold (VDT) was performed with a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale) that was placed on the patellar tendon; the vibration is graded from 0 to 8 (max). The wind up ratio (WUR) test was assessed with a pinprick intensity

of 256 mN. The pressure pain threshold (PPT) was determined with a pressure gauge device (FDN200, Wagner Instruments, CT, USA). All PT patients and healthy controls were tested on the patellar tendon, directly distal to the apex of the patella.

2.3. Questionnaires

The DN-4 (Douleur Neuropathique 4 questions) was assessed in the patients with PT in order to assess the presence of neuropathic pain symptoms. The 'classical' DN4-questionnaire contains 10 items; the first 7 items, called the DN4-interview, are sensory descriptors that may be applicable to the patient's pain, the remaining 3 items are related to physical examination signs; touch hypoestesia, pricking hypesthesia and brushing. Since we assessed a physical examination through the QST protocol, we only used the 7-items DN-4-interview. For each positive item on the DN-4, one point is assigned. The cut-off score for neuropathic pain of the DN-4 interview was set at 4 or more positive items (Bouhassira et al 2005). The results from the 'classical' DN4-questionnaire have been compared with the diagnoses of expert clinicians, DN-4 showed 83% sensitivity and 90% specificity and the DN4-interview demonstrated similar results (Bouhassira et al 2005).

Since psychological factors may interfere with pain perception, two psychological questionnaires were included. All participants filled out the Symptom Check List-90 (SCL-90) and the Profile of Mood States (POMS). The SCL-90 is a multidimensional self-report inventory to assess various current psychological symptoms. The SCL-90 yields 9 symptom domains of which the dimensions phobic anxiety, anxiety, depression, somatisation, insufficiency of thinking and acting, interpersonal sensitivity, hostility and quality of sleep were used in this study. Participants were asked to rate on a 5-point scale from 1 (not at all) to 5 (extreme) how much each item had distressed or bothered them during the last 7 days, including the day of the examination. The SCL-90 is a questionnaire that is used world-wide, the psychometric properties have been considered adequate (Arrindel & Ettema 2003).

Furthermore the Dutch revised version of the (POMS) was used (Robinson et al 2001). The POMS has been used extensively over the last years to understand the emotional responses to injuries (Wiese-Bjornstal et al 1998) as well as to understand the relation between pre-competitive mood states and athletic performance (LeUnes 2002). Originally the POMS consisted of 65 items; after factor analysis, support was found for a shortened version with 24 items and 6 dimensions (Wicherts & Vorst 2004). For the Dutch POMS however, support was found for 5 domains and 32 items, namely: negative mood depression (8 items), anger (7 items), fatigue (6 items), positive mood vigour (5 items), and tension (6 items), with adequate reliability and validity (Wicherts & Vorst 2004).

2.4. Statistical analyses

The data of the thirteen measurements of QST in the injured athletes were compared to the healthy controls. Since some of the QST outcomes are ordinal data and most data were non-normally divided we used non-parametric tests (Mann Whitney U). The descriptive data of the social demographic parameters are presented. Because of non-normally divided data the SCL-90 and POMS dimensions were analyzed using non-parametric (Mann Whitney U) test to compare injured versus control athletes.

3. Results

3.1. Participants

The socio-demographic data are presented in Table 5-1; twelve PT patients and 20 control athletes were included in the study. All athletes were still training and or playing matches. The outcome on the VISA-P differed significantly between patients (VISA-P 62, SD 17.97) and controls (VISA-P 99, SD 1.68). The median duration of symptoms for the PT group was 30 months (range 6 - 120). The outcome of QST assessment is presented in Table 5-2.

Table 5-1: Socio demographic data of patients with a patella tendinopathy to healthy controls

	Patients (n=12)	**Controls (n=12)**
	Mean (SD)	Mean (SD)
Age (years)	23.3 (3.57)	24.7 (5.30)
BMI	23.2 (3.61)	22.3 (1.92)
Height	187.7 (7.40)	188.0 (7.64)
VISA-P	62 (17.97)* p<0.05 compared to controls	99 (1.68)
Sport	Basketball (3) Soccer (5) Volleyball (2) Squash Rowing	Basketball (7) Soccer (7) Volleyball (6)
Education	Highschool (9) College/University (3)	Highschool (10) College/University (10)

3.2. QST

In two of the thirteen QST parameters i.e. mechanical pain threshold and vibration disappearance threshold injured athletes were significantly more sensitive for the applied stimuli than for the control group (Table 5-2). None of the athletes showed signs of dynamic mechanical allodynia (DMA). The room temperature during QST testing was 23.7°C (SD 0.8).

Table 5-2: Results on the Mann Whitney test; comparing QST data of patients with a patella tendinopathy to healthy controls

QST parameters			Patients (n=12)	Controls (n=20)	Z scores	Mann Whitney U Asymp sign. (2 tailed)
		Units	*Median (range)*	*Median (range)*		*p-value*
Nociceptive parameters	CPT Cold Pain Threshold	°C	11.27 (0.00-26.47)	0.12 (0.00-25.90)	-1.25	0.21
	HPT Hot Pain Threshold	°C	46.35 (40.70-49.80)	47.13 (39.50-50.00)	-0.58	0.95
	PPT Pain Pressure Threshold	mN	78.00 29.33-122.00)	74.00 (37.33-130.67)	-0.04	0.97
	MPT Mechanical Pain Threshold	mN	59.86 (24.25-181.02)	90.51 (8.00-337.79)	-2.03	0.04
	MPS Mechanical Pain Sensitivity	NRS**	0.60 (0.15-2.14)	0.25 (0.01-1.91)	-1.83	0.07
	WUR* Wind-up ratio		2.17 (1.03-19.00)	2.13 (1.04-10.00)	-0.44	0.66
Non-nociceptive parameters	CDT Cold Detection Threshold	°C	4.40 (2.03-8.40)	3.20 (1.17-14.13)	-1.40	1.61
	WDT Warm Detection Threshold	°C	4.73 (2.47-13.53)	3.73 (2.30-13.80)	-0.97	0.33
	TSL Thermal Sensory Limen	°C	10.95 (7.40-26.47)	8.90 (5.67-16.67)	-1.09	0.28
	MDT Mechanical Detection Threshold	mN	2.77 (0.29-222.86)	2.46 (0.44-12.13)	-0.25	0.80
	VDT Vibration Disappearance Threshold	X/8	6.25 (4.83-7.83)	5.50 (4.17-6.83)	-2.53	0.01
	PHS Paradoxical Heat Sensation	X/3	0.00 (0.00-3.00)	0.00 (0.00-3.00)	-1.02	0.31

- * intensity of perception of series of 1Hz vs. single, ** numeric rating scale 0-100

3.3. Questionnaires

None of the injured athletes scored 3 points or higher on the DN-4. The SCL-90 and the POMS demonstrated no significant differences between injured and non-injured athletes (Table 5-3).

Table 5-3: Results on the Mann Whitney U test; SCL-90 and POMS.

SCL 90	**Patients (n=12)**	**Controls (n=20)**	**Z scores**	**Mann Whitney U Asymp sign. (2 tailed)**
	Median (range)	*Median (range)*		*p-value*
Agoraphobia	7 (7-7)	7(7-9)	-0.76	0.44
Anxiety	10(10-12)	11 (10-15)	-1.14	0.26
Depression	17 (16-23)	18 (16-26)	-0.86	0.39
Somatisation	13.5 (12-21)	13.5 (12-21)	-0.14	0.89
Insufficiency	11 (9-15)	10 (9-20)	-0.90	0.37
Sensitivity	19.5 (18-26)	20 (18-31)	-0.12	0.90
Hostility	6 (6-8)	6 (6-9)	-0.53	0.60
Sleep	3.5 (3-11)	3.5 (3-7)	-0.25	0.80
Psychoneurotic	102 (90-118)	100.5 (91-143)	-0.31	0.76
POMS	**Patients (n=12)**	**Controls (n=20)**	**Z scores**	**Mann Whitney U Asymp sign. (2 tailed)**
	Median (range)	*Median (range)*		*p-value*
Depression (0-4)	0.00 (0.00-0.50)	0.00 (0.00-1.12)	-0.24	0.81
Anger (0-4)	0.14 (0.00-1.29)	0.14(0.00-2.00)	-0.08	0.94
Fatigue (0-4)	0.33 (0.00-1.00)	0.50 (0.00-1.33)	-0.91	0.37
Positive mood vigour (0-4)	2.60 (1.40-3.40)	2.60 (1.40-3.80)	-0.6	0.95
Tension (0-4)	0.33 (0.00-0.83)	0.50 (0.00-1.33)	-1.10	0.27

4. Discussion

Although most quantitative sensory tests demonstrated similar results for the patient group and the control group, we found several interesting differences. We found significant differences in mechanical pain threshold and vibration disappearance threshold in athletes with a chronic PT compared to healthy controls. In patients with PT no signs of mechanical dynamic allodynia could be found. No psychological differences between the two groups could be detected.

Mechanisms of peripheral and central sensitisation have been described in several musculoskeletal disorders, such as chronic low back pain, fibromyalgia, whiplash, myofascial pain syndrome and other pain syndromes such as irritable bowel syndrome, chronic headache etc. (Nijs et al 2010; Winkelstein 2004; Yunus 2009). In sports injuries the role of sensitisation or lowered pain thresholds i.e. hyperalgesia has been described in patients with shoulder impingement (Hidalgo-Lozano et al 2010) and patellofemoral pain syndrome (Jensen et al 2008). In our study injured athletes showed considerable and significant aberrations of the mechanical pain threshold (MPT). This pinprick allodynia reflects the involvement of central sensitisation upon the peripheral input from the myelinated (Aδ-fibre) nociceptive input (Davis & Pope 2002; Keizer et al 2008). A reduced pain threshold of Aδ-fibre nociceptors is a plausible explanation why pain occurs during or shortly after sports activities. Such phenomenon is described to be very characteristic for (patellar) tendinopathy and is referred to in the classification of PT (Blazina et al 1973). A reduction of mechanical pain thresholds can be an explanation why sports activities that normally do not induce pain now become painful. Sensitisation accounts for the presence of a mechanical or kinetic allodynia in PT and is therefore a logical explanation for the occurrence of pain in the patellar tendon during or after activities.

The vibration disappearance threshold (VDT) is a continuum measure, the differences found in VDT means that patients feel the vibration for a longer (median 6.25) period of time compared to the healthy subjects. This hyperesthesia could be regarded as a sign of an increased sensitivity in somatosensory function. The clinical relevance of this finding is difficult to interpret and has not been described previously. Further evidence that sensitisation might play a role in PT is that mechanical pain sensitivity was increased in patients.

Webborn (2008) indicated that the pain in tendinopathy can possibly be seen as neuropathic pain (Webborn 2008). According to the IASP definition neuropathic pain is related to lesions within the nervous system (diagnoses such as diabetes, herpes zoster, poly-neuropathy or post surgery neuralgias) or as a dysfunction (low back pain, fibromyalgia) (Merskey & Bogduk 2004). Treede et al. (2008) suggested replacing the word 'dysfunction' with 'disease'. Neuropathic pain should be demonstrated with

a clinical examination for positive (hyperalgesia, allodynia) and/or negative signs (hypaesthesia) in addition to continuous ongoing pain. In our study tendinopathies could not be related to negative signs. Furthermore the DN-4 interview did not demonstrate that neuropathic pain descriptors could be used to describe the pain. With QST, no obvious signs of dynamic allodynia were found, although static pinprick allodynia could be demonstrated. Furthermore the patients did not have ongoing pain in rest but only evoked by pressure and physical (sport) activities. We can therefore conclude that – according to the Treede (2008)-criteria, PT in our patient population is not associated with neuropathic pain.

However, sensitisation both centrally and peripherally may be a plausible explanation for the pain in (patella) tendinopathies. The question is why it arises and becomes chronic in some athletes but not in others. One explanation may be the extent of nociception that was originally present as a result of an extensive anatomical defect, severe and long-lasting nociception or (neurogenic) inflammation may cause more profound and irreversible sensitisation than relatively minor injury (Abate et al 2009; LaMotte et al 1991). However in general, athletes with chronic patella tendinopathy normally do not mention such an 'inciting event' causing severe nociception. Furthermore, genetic factors may be of importance, suggesting that some people tend to sensitises more vigorously than others (Magra & Maffulli 2008; Wang et al 2002; Zubieta et al 2003). Finally psychological and behavioral factors appear to play an important role in the maintenance of sensitisation (Gracely et al 2004). We did not find any differences in the psychological dimensions of the SCL-90 and POMS. The outcome of the psychological dimensions in our population was average or below average compared to norm figures of healthy subjects (Arrindel & Ettema 2003). Behavioral factors may be an underlying factor explaining sensitisation in chronic tendinopathies such as not taking adequate measures at the onset of pain e.g. overuse, playing or training with pain and not taking rest adequately. Injured athletes appear to experience fewer consequences from musculoskeletal pain and tend to accept pain during sports (van Wilgen et al 2010). This behavior could be a risk factor leading to physiological changes in the central nervous system. In contrast, another psychological risk factor, fear of movement, which we did not specifically measure in this study may also be a risk factor (Silbernagel et al 2011). Future research on this topic is warranted.

Explaining the pain in tendinopathy by sensitisation may give a better understanding of 'successful' treatments currently used for tendinopathy. The positive effects of slightly painful eccentric programs or painful shock wave treatment without anesthesia on pain relief may not have local effect on the tendon but a more central effect i.e. explained by desensitisation of the CNS (Rompe et al 2009).

The outcome of the present study showed a large variability in different threshold values as measured with QST. Although QST is the golden standard to measure somatosensory aberrations its success depends on the participant's perceptions and concentration which may induce heterogeneity. Furthermore, earlier studies found hypesthesia on the affected side in some athletes this may be a subgroup and explain the large variability within the groups (Jensen et al 2008; van Wilgen & Keizer 2011).

Further studies are needed to confirm whether the assessment for mechanical pain thresholds (myelinated Aδ-fibres) using standardized pinprick devices is adding to the clinical diagnosis of PT. A limitation of this study was that the diagnosis PT was based only on clinical examination by a sport medicine physician or sport physical therapist; no additional imaging techniques were used to investigate structural changes of the tendon which increases the likelihood of the diagnosis. On the other hand clinicians excluded patients with other knee pathology such as patella femoral pain syndrome, intra-articular pathology and ligament injuries. Furthermore, in the analyses of QST data mostly z-score transformations of data are used to identify sensory abnormalities with respect to controls (Rolke et al 2006a). Since z-score transformation and their interpretation is highly dependent on reference values we could not include such transformation due to the low numbers of participants, therefore in future studies larger groups should be included. Despite the fact that manual pressure pain thresholds for the clinical diagnose of PT has been used, the QST results for PPT showed no significant differences between the groups. The reason may be that we included patients with a long history of PT with pain evoked by sports activities. Furthermore all patients were measured on the same spot at the patella tendon and not on the most painful spot which is used in the clinical practice. In another study we measured athletes with PT and used an algometer (MicroFET2 Biometrics BV). This algometer was shaped like a fingertip an applied on the most painful spot of the patella tendon. In this study lower PPT's and significant differences between patients and controls were found (Kregel et al., submitted). Looking back at this study, a similar approach would have probably yielded more pronounced differences between the patient group and the control group in our study. Another limitation was that we recruited healthy controls through advertisements on websites, this procedure might have led to selection bias. Furthermore, we did not take into account if athletes participated in sports activities the day before the study, this may have interfered with the results of the study.

4.1. Conclusion

This is the first study investigating somatosensory aberrations in chronic patellar tendinopathy using a standardized QST protocol. Results of this explorative study should be interpreted as such as sensitisation might play an important role in the contribution of pain during and after sports activity in PT patients.

4.2. Perspectives

The pathophysiology of pain in chronic tendinopathy is largely unknown. We hypothesised that somatosensory changes may contribute to the pain in tendinopathies. From this explorative study we conclude that sensitisation may play a role in the explanation of pain during and after sports activity in patella tendinopathy patients. The diagnosis sensitisation may have consequences for the treatment and medical management of tendinopathies. Further studies however exploring the involvement of sensitisation in tendinopathy are warranted.

Chapter 6

General discussion and Summary

General discussion

The assessment of sensory signs in chronic pain is of major importance in clinical practice, in part to help to identify neuropathic pain. Standardized Quantitative Sensory Testing (QST) such as by the DNFS (German Research Network on Neuropathic Pain) protocol is not only advantageous in the clinic for diagnosis, where sensory signs in patients can now be described quantitatively and qualitatively, but QST also facilitates new opportunities for research. QST can be categorized as psychometric testing using both thermal and mechanical nociceptive as well as non-nociceptive stimuli. It allows the evaluation of different sub-modalities of nerve fibres involved in the transduction of sensory information from the periphery to the spinal cord such as Aβ-fibres, Aδ-fibres and C-fibres.

Originally developed to explore the prospects of a mechanism-based classification of neuropathic pain, in this thesis additional potentials of QST are investigated. As a research tool it provides valuable information of differences in somatosensory function between healthy subjects and chronic pain patients. We have shown that in a substantial number of patients with unilateral neuropathic pain bilateral somatosensory changes are found. This challenges the application of sensory testing as a clinical evaluation tool when the contralateral side is used as reference side. Therefore, we suggest that only reference values obtained from healthy controls can be used for the correct interpretation of sensory signs in neuropathic pain patients.

The results of our QST studies are also of relevance for the development of novel therapeutics in chronic pain, in terms of improved assay sensitivity. Examples are the selection of homogenous subpopulations based on specific QST parameters for the clinical evaluation of novel drugs, and the identification of distinct QST responders (e.g. Mechanical Pain Sensitivity) for mechanistic studies.

Implications of QST for clinical neuropathic pain practice

We demonstrated that by using QST values from healthy controls the interpretation of sensory function and its clinical manifestation for a patient with neuropathic pain may be different compared to the outcome based on bed side testing (chapter 2). In clinical practice, most often the contralateral, non-affected side of a patient is used as reference for the identification of sensory signs, such as hyperalgesia and allodynia, at the affected side. We have shown that in unilateral neuropathic pain bilateral somatosensory changes i.e. changes at the affected as well as the contralateral side occur frequently. Contralateral changes are in fact more rule than exception in unilateral neuropathic pain and could be attributed to plastic changes of the nervous system. These plastic changes might be "triggered" by pain since the presence of contralateral abnormalities was correlated with the ongoing pain intensity reported by patients. The observation of bilateral sensory abnormalities in unilateral neuropathic pain is very valuable clinically since it indicates that the contralateral side should be used cautiously as a control side in sensory examinations such as bedside tests. We have shown that the interpretation of

sensory function and its clinical manifestation can differ when either the contralateral side or the healthy volunteer data is used. To avoid potential misjudgement of the quality of sensory abnormalities we suggest that only QST reference values obtained from healthy controls are used.

In this context it is unknown to which extent the potential misinterpretation of sensory signs in neuropathic pain patients might have contributed to the lack of efficacy observed in the treatment of neuropathic pain. Based on our data, a direct comparison between the effects of treatment on sensory signs established with either bedside tests or the use of reference data would be useful.

Assessing patients using the elaborate QST protocol can be very time-consuming and demanding for both patient and physician. For the assessments, patients need to be repositioned frequently to allow a correct application of stimuli. Thus, commonly a complete evaluation of the affected site of neuropathic pain patients takes more than 45 minutes. Such time- and labour intensive evaluation of somatosensory abnormalities limits QST for regular usage in the clinic. Indeed, the QST protocol needs to be simplified to become a regular screening tool in a clinical setting. In this context, it is of interest to identify the most sensitive QST parameters to determine somatosensory specifics for each neuropathic pain entity.

To facilitate the diagnosis neuropathic pain, recently, a grading system was introduced by which the patient's pain can be categorized as definite, probable, possible or unlikely neuropathic pain (Treede et al 2008). This grading system is aimed to determine with a greater level of certainty whether a pain condition is neuropathic.
We applied this grading system in a group of neuropathic pain patients and compared the results with those of the standardized QST protocol (chapter 3). Our findings show that the number of sensory abnormalities do not correspond with a greater level of certainty whether a pain condition is neuropathic, i.e., the number of somatosensory abnormalities were not different between the various grades of neuropathic pain. This result is striking since the presence of somatosensory abnormalities is a major aspect of neuropathic pain, which would predict that the more certain the diagnosis of neuropathic pain the greater the number of abnormalities. However, our results indicate that irrespective of the degree of neuropathic pain the somatosensory response e.g. numbers of abnormalities is similar for all diagnosis levels of certainty. In this context it would be interesting to investigate somatosensory abnormalities in non-neuropathic chronic pain diseases such as fibromyalgia and complex regional pain (CRPS-1) in greater detail. Similarities in the frequency of QST abnormalities to those observed in neuropathic pain patients might point towards a "common final path" for the somatosensory system in chronic pain diseases.
Whereas similar numbers of sensory abnormalities for the different grades of neuropathic

pain were found in our study population, aspects of the pattern of sensory signs did differ between the highest and lowest level of certainty, i.e., between 'definite' and 'probable' neuropathic pain and 'unlikely' neuropathic pain. Previously, it was reported that profiles of sensory signs differ even in the different clinical entities of neuropathic pain (Maier et al 2010). Unfortunately, the 1236 neuropathic pain patients included in that study were not analysed with respect to their neuropathic pain grades (Maier et al 2010). Studies in large populations of patients with different clinical entities of neuropathic pain and recognized neuropathic pain grades could evaluate the presence of specific profiles of somatosensory signs. The identification of differences in patterns of sensory abnormality in neuropathic pain patients could lead to a mechanistic understanding of somatosensory abnormalities in neuropathic pain.

We reported earlier that in patients with unilateral neuropathic pain the presence of contralateral sensory changes was correlated with the intensity of ongoing pain *(chapter 2)*. This was confirmed in a second study describing a larger and more diverse neuropathic patient sample *(chapter 3)*. When we categorized the patients with respect to their certainty of neuropathic pain we found that this overall effect was driven only by the group of patients graded as 'definite' neuropathic pain ($r=0.642$; $p=0.01$) (unpublished data). This finding indicates that the greater the pain intensity the more contralateral abnormalities occur, but only for the group of patients graded as 'definite' neuropathic pain.
In the same study we have also identified a mismatch between clinical diagnosis of neuropathic pain and neuropathic pain grading. Only 60% of patients with clinically diagnosed neuropathy were categorized as 'definite' and 'probable' neuropathic pain. This is an interesting finding in the context of the recently revised neuropathic pain definition. Accordingly, neuropathic pain is a direct consequence of a lesion or disease affecting the somatosensory system (Treede et al 2008). The grading system complements this definition and consequently 60% of our patients diagnosed as neuropathic pain were also graded as neuropathic pain. To what extent abnormal function of the somatosensory system oblige to this definition is in the context of our findings unclear. Similar, it remains unclear if the neuropathic pain grading could improve the efficacy in the treatment of neuropathic pain. However, this grading system certainly allows a precise selection of patients for clinical research and is therefore an interesting tool to translate findings into clinical practice and potentially increase patient's treatment satisfaction.

Implications of QST for clinical neuropathic pain research
The third study was designed to determine if QST would be a valid instrument to identify somatosensory homogenous groups of patients with neuropathic pain (chapter 4). We found that a single QST parameter, i.e. mechanical pain sensitivity (MPS), can be used to identify distinct subgroups of neuropathic pain patients. A part of the patients

studied showed a clear stimulus-response to pinprick stimuli, while in the other part a stimulus-response to pinprick stimuli was completely absent. Both types of responses were found within different clinical entities of neuropathic pain indicating that multiple mechanisms e.g. different causes of neuropathic pain, can lead to the same sensory sign e.g. MPS abnormalities. Thus, distinct patterns of sensitisation to pinprick pain are common within different neuropathic pain aetiologies.

The identification of somatosensory phenotypes based on a single QST parameter also contributes to the viability of mechanism-based understanding of neuropathic pain. For this purpose, patients of both types of MPS responses could be further investigated using functional magnetic resonance imaging (fMRI). It has been already shown in human brain imaging studies that chronic pain induces structural changes and changes in brain function in different neural regions (Apkarian et al 2011; DaSilva et al 2008; Geha et al 2008; Gustin et al 2011; Schweinhardt & Bushnell 2010; Tracey 2007; 2008; Tracey & Bushnell 2009; Tracey et al 2002). FMRI studies of different MPS responders aimed to investigate potential group-specific changes in the brain might contribute to a mechanistic understanding of these differences. Pharmacological fMRI studies using different classes of drugs known to be efficacious in neuropathic pain should be utilised in this context. Knowledge of specifics in the efficacy of standard drugs for the different MPS responders could be translated into specific requirements for the pharmacokinetics and pharmacodynamics of novel compounds for clinical evaluation.

Drug discovery is a very high-risk endeavour, and the time and costs of developing the compounds, as well as the methodologies to translate the research effort into medicines that better meet the needs of pain patients are challenging. QST phenotypic characterization e.g. MPS response pattern, as a tool for patient selection for enrolment into clinical trials could be used to decrease variance and increase the power to detect meaningful drug effects. In addition, knowledge gained in pharmacological intervention studies of this patient population could also help to determine a mechanism-based therapy for neuropathic pain.

Implications of QST in non-neuropathic pain diseases

Several studies indicate that sensory testing can be used to identify pathophysiological mechanisms and sensory differences across anatomical boundaries in chronic pain diseases. Kleinbohl and colleagues found that responses to phasic and tonic heat pain not only distinguished chronic pain from healthy controls but also discriminated among types of chronic pain (e.g. headache, back pain) with good sensitivity and specificity (Kleinbohl et al 1999). A study in complex regional pain (CRPS) grouped patients based on the spatial extent of sensory deficits showed that patients with more widespread sensory deficits also exhibit greater mechanical hypersensitivity in the affected limb (Rommel et al 2001). Enhancement in the response to painful stimuli was also reported

in fibromyalgia (Staud et al 2004), temporomandibular disorders (Sarlani & Greenspan 2003), pelvic pain syndromes (Granot et al 2002) and headache disorders (Bendtsen 2000). Thus, somatosensory abnormalities are not limited to neuropathic pain (Cruccu et al 2004; Cruccu et al 2010). These studies indicate that QST can serve to objectify clinical findings and could be used to improve the selection of treatments. In this context, investigating if somatosensory changes contribute to the presence or absence of pain could be also valuable.

In an exploratory QST study we showed that patients with chronic patellar tendinopathies had signs of sensitisation e.g. decreased threshold for mechanical pain and an increased vibration disappearance threshold compared to age- and sports activity-matched pain-free controls (van Wilgen et al 2011; *chapter 5*). Thus, it was hypothesised that sensitisation might contribute to the presence of pain.
Currently, little is known whether, or to what degree, somatosensory changes may contribute to the pain in tendinopathies. The pathophysiology of pain in chronic tendinopathy is largely unknown. The presence of sensitisation observed in this study is contradictive to the result of hypesthesia seen in a previous study (Jensen et al 2008). The differences in these studies could be explained by methodological differences. First, it is not known if sensory changes on the contralateral knee as seen in neuropathic pain also take place in tendinopathies. Therefore, in our study reference values were obtained from matched controls rather than using the contralateral side of patients. This could have contributed to a different outcome in the identification of sensory signs between these studies. Secondly, our study was aimed to identify pain contributing abnormalities in somatosensory function. Thus, we have used age- and sports activity-matched pain-free controls for this investigation. Interestingly, overall impaired sensory function for these sport controls compared to healthy controls of our QST database were found (unpublished results). This result would suggest that high intense sports activity might influence sensory function, even if no pain was reported as by these controls.

From this study we conclude that sensitisation may play a role in the explanation of pain during and after sports activity in patella tendinopathy patients. Larger QST studies could provide more evidence to what extent somatosensory changes contribute to the pain in tendinopathies. If such studies confirm the diagnosis sensitisation, treatment and medical management of tendinopathies could be adapted.

Normative QST values in clinical research
Normative QST data are generated by evaluating sensory function in healthy volunteers, a process that generally takes about 30 minutes in which one body area is assessed using the DFNS QST protocol. Ideally, normative data should be collected from different areas of the body since QST data are region specific (Rolke et al 2006a). Also age- and gender-specific differences were observed for some QST parameter (Rolke et al 2006a).

6. General discussion and Summary

To harmonize the QST approach, standardized assessment areas such as dorsal hand and dorsal foot were introduced. For the purpose of our studies, we have followed these recommendations and used age- and gender-matched controls to compare QST data obtained from patients to identify somatosensory abnormalities.

Z-score transformation of QST data revealed that one or more somatosensory abnormalities are also present in healthy controls, but its frequency was considerable lower than in patients. The likelihood in a healthy subject that all QST parameters (with exception of DMA, which is not present in healthy controls) are within the normal range can be calculated to be 54% (0.95^{12}). In accordance, our data showed normal sensory function for 53% of the healthy controls (n=209). In contrast, only 9% of patients showed normal sensory function (see chapter 3). Although overall, our healthy volunteer data is in line with data reported by others, there are differences encountered (Rolke et al 2006a; Rolke et al 2006b). For instance, we found Paradoxical Heat Sensations (PHS) >1 occurred in 1.4% at the test site "dorsal hand" and in 9.3% at the test site "dorsal foot". PHS >1 in healthy subjects were not observed in previous studies (Rolke et al 2006a; Rolke et al 2006b). Such differences could be explained by the fact that z-score transformations depend on reference values. In this context minimum numbers needed as controls incorporating the complexity of the QST battery have not been established.

There is a considerable variation in the literature concerning the choice of percentiles used to define reference values (Shy et al 2003). Ultimately, the choice of percentiles is dependent on a combination of clinical, disease-specific, personal and financial factors (O'Brien & Dyck 1995). Exchange of QST reference data between institutes would be favourable allowing QST access to the research and clinical community. A certified QST training is advantageous in this context to expand the QST database in co-operation with different institutes. We have participated in the QST training provided by the DFNS and differences in QST values in healthy subjects between institutions observed could be based on numbers of controls and/or regional differences in somatosensory function. The exchange of reference values could address potential regional differences and ultimately increases overall numbers of references by reduced costs. Such a scenario might be also valuable to be implemented beyond European boundaries.
Furthermore, detailed insight into normative QST values could be helpful in a more objective testing of drug efficacy in various neuropathic pain states. For regulatory purposes the FDA suggests pain as primary outcome measure for the evaluation of novel pain compounds. In clinical practice a pain decrease > 50% is desirable, however, this is only achieved in less than one-third of the cases (Argoff et al 2006; Farrar et al 2001; McQuay et al 1996; Sindrup & Jensen 1999; Ziegler 2008). For approval of a novel pain treatment a pain reduction of >30% on the visual analogue pain scale (VAS) compared to placebo is required. Secondary outcome, which may play a major role in providing supportive evidence for approval of pain medication, can be, amongst others,

the positive influence on sensory signs such as hyperalgesia and allodynia. Improved knowledge of the subjective nature of pain and related sensory processes could help to optimize the choice of study population and appropriate measurements for proof-of concept trails with putative pain therapies.

Evidently, there is a need for normative QST values in the clinical evaluations of novel pain compound, which start with studies in healthy volunteers to provide safety, pharmacokinetic and possible pharmacodynamic information. In the latter case, subjects are exposed to acute pain tests such as pain threshold evaluation for thermal and mechanical stimuli. A subset of the standardized QST battery could be introduced to establish normative data of sensory function for clinical setting either with or without pharmacological intervention. The utility of different outcome measures in clinical trials could be investigated with the aim to maximise validity and reliability. Supportive to this idea is a study we performed investigating the test-retest variability of different acute pain tests for mechanical and thermal stimuli applied at the different body areas in healthy volunteers (Konopka et al d). In this study each subject underwent different acute pain tests on three occasions over two weeks time. Results of this study revealed high between-subject variability for some parameters but not for all and a low within-subject variability for the different tests and test locations (in preparation for publication).

High between-subject variability was also observed for some parameters of our QST database. For example, cold pain thresholds (CPT) range between 2.3 °C and 31.9 °C in healthy volunteers (n=209). It is obvious that with such a wide range of thresholds for cold pain a potential difference in efficacy of novel drugs compared to placebo might be difficult to establish. With an enriched study sample such as using only healthy subjects which have CPT's between 10 °C and 20 °C a potential drug effect would be more likely to be picked up. An approach like this would increase the assay sensitivity by reducing variability. Furthermore, using a standardized approach to obtain reference values from healthy controls for pharmaceutical research allows the direct comparison of efficacy of compounds between studies. Such approach might allow a direct identification of superiority of novel compounds over other drugs at an early stage of development and potentially reduce costs.
Another aspect of QST in clinical trials is bridging preclinical and clinical studies to increase our understanding of the predictability of preclinical research. For both preclinical and clinical evaluation of novel treatments evoked stimuli are used to evaluate efficacy. Increase predictability of preclinical studies could lead to an increased success rate of a drug candidate to be transferred into clinic research.

QST in clinical practice; general considerations

Studies suggest that up to 5% of individuals undergoing surgery will develop severe persisting pain (Kehlet et al 2006; Poleshuck & Green 2008). In a number of studies, pre-existing pain and high-intensity post-operative pain have been the predictors of development of persisting pain after surgery (Bisgaard et al 2005; Katz et al 2005; Pluijms et al 2006; Poleshuck et al 2006). Another patient study showed that assessing the sensory characteristics of cancer-induced bone pain prior and after radiotherapy allows the identification in alterations in sensory responses. Alterations in specific sensory characteristics (e.g. abnormal warm sensation and pinprick pain) were associated with an increased likelihood of successful analgesia from palliative radiotherapy (Scott et al 2011). Individual differences in evoked pain sensitivity as potentially important prospective predictors of the course of clinical pain complaints have been suggested also in other studies. For example, pre-operative supra-threshold pain stimuli at 44 °C - 48 °C responses, but not heat pain thresholds predicted post-operative pain scores in women undergoing caesarean section (Granot et al 2003).

Sensory testing can be also used as an outcome measure to document treatment-related changes in somatosensory function. For example, opioid-induced hyperalgesia refers to a phenomenon whereby opioid administration results in a lowering of pain thresholds, clinically manifest as apparent opioid tolerance and worsening pain despite accelerating opioid doses. Recently, we proposed that sensory testing could help to identify opioid-induced hyperalgesia and subsequently its differentiation from tolerance (Konopka & van Wijhe 2010). This is clinically important, since tolerance can be overcome by dose escalation, whilst opioid-induced hyperalgesia may be aggravated by the same intervention. We have suggested that sensory testing should be performed prior to the anaesthesia at an area distant from the surgery site and subsequently up to a few hours post-operatively. Another aspect which has not been investigated is the situation that disease progression induces changes of sensory thresholds. If such changes occur and sensory abnormalities are present pre-operatively this in turn could blur post-operative sensory outcome measures and therefore might compromise the investigation of opioid-induced hyperalgesia. In this context, reference values from healthy subjects could be used to establish normal sensory functioning in patients prior to anaesthesia.

In conclusion, utilizing QST as a tool to assess sensory function does make sense, not only in patients with chronic pain but also in healthy subjects. In this thesis we have investigated the applicability of QST in clinical practice and for research purposes. In these studies we provide evidence that QST can lead to an improved characterisation of sensory signs in unilateral neuropathic pain, an improved understanding of sensory function in patients with different neuropathic pain grades and an improved understanding of somatosensory function as a pain-contributing factor in patients with patellar tendinopathies. QST also allows the identification of homogenous patient

populations which in subsequent studies could help to clarify the relationships between the aetiology and somatosensory function. The results of these studies contribute to a better understanding of sensory function in patients and indicate a great potential for QST as a research tool for clinical practice and drug development aiming for improvements in assay sensitivities.

6. General discussion and Summary

Summary

With the development of a standardized Quantitative Sensory Testing (QST) protocol by the German Research Network on Neuropathic Pain (DFNS), a methodology is available to investigate somatosensory function in patients with neuropathic pain and healthy volunteers (for reference data). This QST battery tests different sub-modalities of nerve fibres involved in the transduction of sensory information. An increase in knowledge of somatosensory function is not only advantageous in the clinic, where sensory signs in patients can now be described quantitatively and qualitatively, but QST also facilitates new opportunities for research. Originally developed to explore the prospects of a mechanism-based classification of neuropathic pain, additional applications for QST are explored in this thesis.

In chapter 2 and 3 the presence of sensory signs in patients with neuropathic pain was evaluated and scrutinized in the context of their clinical relevance. It has already been recognised that somatosensory abnormalities are commonly present in patients with neuropathic pain. In addition, we have shown that in unilateral neuropathic pain bilateral somatosensory changes occur frequently (i.e. changes at the affected as well as the contralateral side). The observation of bilateral sensory abnormalities in unilateral neuropathic pain is clinically very valuable since it indicates that one should be cautious in using the contralateral site as a "healthy" control area in sensory examinations such as bedside tests. Thus, in chapter 2 we resumed that to avoid potential misjudgement of the quality of sensory abnormalities we suggest that QST reference values obtained from healthy controls should be used.

For diagnostic purposes a grading system categorizing patient's neuropathic pain as definite, probable, possible or unlikely neuropathic pain was introduced. This grading system is aimed to determine with a greater level of certainty whether a pain condition is neuropathic. In our study described in chapter 3, only 59% of patients with clinically diagnosed neuropathy were categorized as 'definite' and 'probable' neuropathic pain indicating a mismatch between clinical diagnosis of neuropathic pain and neuropathic pain grading. However, this result indicates that stringent grading of neuropathic pain may provide advantages in selecting homogenous groups for clinical research. QST evaluation revealed that the numbers of somatosensory abnormalities were not different between the grading groups but profiles of sensory signs differed between definite and probable neuropathic pain grades and unlikely neuropathic pain.

It has been suggested that investigations of the differences in patterns of sensory abnormalities could lead to a mechanistic understanding of neuropathic pain. Such a mechanistic understanding could also be derived from investigations of a single QST parameter. In this context, for the QST parameter Mechanical Pain Sensitivity (MPS) two distinctive patterns in the stimulus-response functions in neuropathic pain patients

were described in chapter 4. Since the MPS parameter can be used to identify distinct subgroups of neuropathic pain patients we indicate that these differences could be further investigated using functional magnetic resonance imaging (fMRI) combined with pharmacological interventions. Ultimately, knowledge from these studies could reveal mechanistic differences in neuropathic pain patients.

Somatosensory abnormalities are not specific to neuropathic pain. In chapter 5, we investigated if QST is sensitive to identify somatosensory changes contributing to the experience of pain in patients with patellar tendinopathies. We showed that patients with chronic patellar tendinopathies had signs of sensitisation for some QST parameters compared to age and sports activity matched pain-free controls. Thus, we hypothesised that sensitisation might be contributing to the presence of pain. We have shown that investigating somatosensory function in these patients can serve to objectify clinical findings and could be used to improve the selection of treatments.

Utilizing QST as a tool to assess sensory function is not limited to clinical practise and research. QST phenotypic characterisation can also be utilised for drug development to establish normative data and disease specific data. In turn, this could decrease variance and increase the power to detect meaningful drug effects in clinical studies. In conclusion, QST as a tool to assess sensory function does make sense in pain patients and healthy subjects.

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Nederlandse samenvatting

Met de ontwikkeling van gestandaardiseerde Kwantitatieve Sensorische Testen (KST), ontwikkeld door het Duitse Onderzoeksnetwerk voor Neuropathische Pijn (DFNS), is er een methode beschikbaar gekomen om het somatosensorisch functioneren bij patiënten met neuropathische pijn en gezonde vrijwilligers (voor referentiewaarden) te onderzoeken. Deze KST batterij test verschillende submodaliteiten van de zenuwvezels die betrokken zijn bij de geleiding van tastzintuiglijke informatie. Meer kennis over het somatosensorisch functioneren is van grote toegevoegde waarde in de kliniek waar tastzintuiglijke observaties bij patiënten nu zowel kwantitatief als kwalitatief kunnen worden beschreven. Tevens faciliteert KST ook nieuwe mogelijkheden voor onderzoek naar neuropathische pijn. Hoewel KST oorspronkelijk ontwikkeld is om een mechanistische classificatie van neuropathische pijn mogelijk te maken, zijn meerdere aanvullende toepassingen van KST onderzocht in dit proefschrift.

In hoofdstuk 2 en 3 van dit proefschrift hebben we het somatosensorisch functioneren van patiënten met neuropathische pijn geëvalueerd en kritisch gekeken naar de klinische relevantie van KST. Eerder onderzoek heeft aangetoond dat somatosensorische afwijkingen veelvuldig aanwezig zijn bij neuropathische pijn patiënten. Wij hebben laten zien dat er bij unilaterale neuropathische pijn vaak bilaterale sensorische veranderingen optreden (veranderingen die zowel aan de pathologische kant als de contralaterale "gezonde" kant van het lichaam optreden). Het voorkomen van bilaterale somatosensorische veranderingen in unilaterale neuropathische pijn is klinisch zeer relevant aangezien het duidelijk maakt dat men voorzichtig moet zijn met het gebruik van de contralaterale lichaamshelft als "gezond" controle gebied bij klinisch somatosensorisch onderzoek. Op basis hiervan stellen wij in hoofdstuk 2 voor om KST referentiewaarden van een gezonde controle populatie te gebruiken om een verkeerd oordeel over de kwaliteit van het somatosensorisch functioneren van patiënten te voorkomen.

Ter verbetering van de diagnostiek is er een classificatiesysteem ingevoerd dat patiënten met mogelijke neuropathische pijn indeelt in de categorieën absoluut, waarschijnlijk, mogelijk of onwaarschijnlijk neuropathisch. Dit classificatiesysteem is bedoeld om met een grotere mate van zekerheid te kunnen bepalen of pijnklachten neuropathisch van aard zijn of niet. In de studie beschreven in hoofdstuk 3 vinden wij dat slechts 59% van de patiënten met klinisch gediagnosticeerde neuropathische pijn werden geclassificeerd als absoluut of waarschijnlijk neuropathisch. Dit geeft aan dat er een discrepantie is tussen de klinische diagnose en het classificatiesysteem voor neuropathische pijn. Aan de andere kant zouden de strengere classificatierichtlijnen kunnen bijdragen aan het selecteren van meer homogene patiëntgroepen voor klinisch onderzoek. De evaluatie van de KST liet zien dat het aantal somatosensorische afwijkingen niet verschilde tussen de classificatie categorieën. Het somatosensorische profiel was echter wel verschillend

voor de categorie onwaarschijnlijk neuropathisch ten op zichte van de categorieën absoluut en waarschijnlijk neuropathisch.

Er is gesuggereerd dat het onderzoek naar verschillen in de patronen van somatosensorische afwijkingen kan resulteren in een beter inzicht in de fysiologische mechanismen die aan neuropathische pijn ten grondslag liggen. Een dergelijke mechanistische visie van neuropathische pijn kan ook gebaseerd worden op een enkele KST parameter. Binnen deze context hebben wij voor de KST parameter voor mechanische pijn twee verschillende patronen in stimulus-responsefunctie gevonden bij neuropathische pijn patiënten (Hoofdstuk 4). Aangezien de stimulus-responsefunctie van mechanische pijn gebruikt kan worden om verschillende subgroepen te identificeren binnen de groep neuropathische pijn patiënten lijkt het ons van belang deze subgroepen verder te onderzoeken met behulp van functionele Magnetische Resonantie Imaging (fMRI) gecombineerd met farmacologische interventies. Mogelijk zou met de verkregen kennis verschillende fysiologische mechanismen kunnen worden onderscheiden binnen deze patiënten groep.

Afwijkingen in het somatosensorisch functioneren zijn niet enkel van toepassing op neuropathische pijn patiënten. In hoofdstuk 5 is onderzocht of men met behulp van KST somatosensorische veranderingen kon detecteren die mogelijk bijdroegen aan de pijnklachten bij patiënten met patellatendinopathie ('springersknie'). Wij konden aantonen dat patiënten met chronische patellatendinopathie sensitisatie lieten zien op sommige KST parameters vergeleken met gezonde controles gematched voor leeftijd en hoeveelheid sportieve activiteiten. Op basis van deze resultaten is onze hypothese dat sensitisatie mechanismen mogelijk bijdragen aan de pijnklachten van deze patiënten. We konden laten zien dat het in kaart brengen van het somatosensorisch functioneren in deze patiënten kan bijdragen aan een het objectiveren van de klinische bevindingen en mogelijk de selectie van de juiste behandeling kan verbeteren.

Het gebruik van KST als instrument om het sensorisch functioneren in kaart te brengen hoeft zich niet te beperken tot de klinische praktijk en onderzoek. Het karakteriseren van verschillende QST profielen kan ook toegepast worden binnen de ontwikkeling van nieuwe medicijnen en om normatieve data voor gezonde controles en patiënten populaties te vergaren. Dit zou kunnen leiden tot minder variabiliteit en een toename in kracht om de effectiviteit van medicatie te kunnen detecteren in klinische studies.

Concluderend kan men stellen dat het gebruik van KST als instrument om somatosensorisch functioneren te meten nuttig is bij patiënten met pijnklachten en gezonde vrijwilligers.

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List of publications

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