Generalized Hyperalgesia in Chronic Low-Back Pain

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PhD Thesis by

Søren O'Neill

Center for Sensory-Motor Interaction (SMI),
Department of Health Science and Technology,
Aalborg University, Aalborg, Denmark

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In Memorandum

Oda Gade O'Neill
a stoic who knew musculoskeletal pain far too well.
1938 – 2012

Dedicated

to my son Erik Emil O'Neill

ABSTRACT

Generalized hyperalgesia has been demonstrated in cross-sectional studies in a range of chronic pain disorders, including low-back pain. It is not clear, whether the increased sensitivity to experimental pain stimuli in chronic low-back pain sufferers develops early with acute pain, later with chronification, or whether it actually represents pre-existing, high pain sensitivity in a susceptible subgroup of the background population. Assessing experimental pain sensitivity is not routine practice in the management of low-back pain.

The current thesis consists of five studies, which were conducted in order to clarify the temporal association of generalized hyperalgesia and low-back pain. In three studies, the experimental pain sensitivity in acute low-back pain patients was compared to that of pain-free controls. Similarly, in three studies, the pain sensitivity of chronic low-back pain patients was compared to controls and in a single study, the relative risk of developing future low-back pain when displaying a high pain sensitivity (low pressure pain threshold) was investigated. Furthermore, two novel methods of experimental pain stimulation were assessed.

The results support an association between generalized hyperalgesia and chronic, but not acute low-back pain. A high baseline pain sensitivity in pain-free participants did not constitute a risk factor for the future development of low-back pain.

Generalized hyperalgesia, appears to develop over time in step with the progression from acute/subacute low-back pain to chronic low-back pain. This may have clinical implications for the future assessment and management of low-back pain.

RESUMÉ

Generaliseret hyperalgesi er blevet påvist i tværsnitsstudier i en række kroniske smertetilstande, herunder lænderygsmerter. Hvorvidt den forøgede sensitivitet for eksperimentelle smerter i gruppen af kroniske lænderyg patienter udvikler sig tidligt i forløbet med akutte smerter, senere i forbindelse med kroniske smerter, eller om der i realiteten er tale om en forud-eksisterende høj smerte sensitivitet i en sub-gruppe af baggrundsbefolkning, med øget risiko for kronicitet, er ikke klart. Vurdering af eksperimentel smerte sensitivitet er ikke en del af den almindelige udredning af lænderyg patienter.

Aktuelle afhandling består af 5 studier, som er gennemført for at afklare den temporale association mellem generaliseret hyperalgesia og lænderygsmerter. I tre studier, er den eksperimentelle smerte sensitivitet i akutte lænderyg patienter blevet sammenholdt med en smertefri kontrolgruppe. Tilsvarende er kroniske lænderyg patienters eksperimentelle smerte sensitivitet blevet sammenholdt med en smertefri kontrol gruppe i 3 studier. Og i et enkelt studie er det undersøgt om en høj smertesensitivitet (lav tryk smertetærskel) udgør en seperat risiko for udviklingen af rygsmerter fremadrettet. Endeligt, er anvendeligheden af to nye eksperimentelle smerte stimuli, blevet vurderet.

Resultaterne understøtter en association mellem generaliseret hyperalgesi og kroniske, men ikke akutte lænderygsmerter. En høj smertesensitivitet i en forsøgsgruppe fra baggrundsbefolkningen, uden lænderygsmerter havde ikke øget risiko for at udvikle rygsmerter senere.

Generaliseret hyperalgesi synes at udvikle sig over tid, sideløbende med progressionen fra akutte/subakutte lænderygsmerter til kroniske lænderygsmerter. Dette kan have kliniske implikationer for den fremtidige udredning og håndtering af lænderygsmerter.

PUBLICATIONS

The present thesis is based on the following works

I O'Neill, S., Manniche, C., Graven-Nielsen, T., Arendt-Nielsen, L., 2007. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. Eur J Pain 11 (4), 415–420.

II O'Neill, S., Graven-Nielsen, T., Manniche, C., Arendt-Nielsen, L., 2009. Ultrasound guided, painful electrical stimulation of lumbar facet joint structures: an experimental model of acute low back pain. Pain 144 (1-2), 76–83.

III O'Neill, S., Kjær, P., Graven-Nielsen, T., Manniche, C., Arendt-Nielsen, L., 2011. Low pressure pain thresholds are associated with, but does not predispose for, low back pain. Eur Spine J 20 (12), 2120–2125.

IV O'Neill, S., Graven-Nielsen, T., Manniche, C., Arendt-Nielsen, L., 2012 Association between a composite score of pain sensitivity and clinical parameters in low-back pain. Submitted to Clinical Journal of Pain

V O'Neill, S., Graven-Nielsen, T., Manniche, C., Arendt-Nielsen, L., 2012 A simple, clinically applicable and reliable pain stimulus: sustained mechanical pressure with a spring-clamp. Submitted to European Journal of Pain

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I will also acknowledge the support of my family for the time spent working nights and weekends. More so, I am fortunate to also thank my wife Lotte Dyhrberg O'Neill, M.Med.Ed, Ph.D. for her valuable academic input — we never talk about the weather. Many thanks to my Father Joe O'Neill for reviewing my spelling, punctuation and general abuse of the English language.

Experimental pain research inherently involves pain and I am indebted to the many patients and controls who have subjected themselves to a variety of painful experiences in the course of these studies.

I would also like to acknowledge the financial support of *Fonden til fremme af kiropraktisk forskning og post-graduat uddannelse* and *IMK Almene fond*.

This thesis and the five papers on which it is based have been prepared using opensource software almost exclusively – from the Linux OS to the statistical software system R. I thank the FOSS community for providing excellent software and support.

ABBREVIATIONS AND ACRONYMS

CNS	Central nervous system
CPM	Conditioned pain modulation
CPT	Cold-pressor test
IASP	International Association for the Study of Pain
*i*CPM	Inhibitory CPM
*f*CPM	Facilitatory CPM
*f*MRI	Functional magnetic ressonance imaging
LBP	Low-back pain
NRS	Numerical (verbal) rating scale
PAG	Peri-aquaductal grey
PPT	Pressure pain treshold
QST	Quantitative sensory testing
RVM	Rostral ventromedial medulla
VAS	Visual analogue (pain) scale

HYPERALGESIA The term '*hyperalgesia*' has been used throughout this thesis in agreement with the IASP [1] taxonomy to denote *Increased pain from a stimulus that normally provokes pain* with an emphasis on the clinical phenomenon, as opposed to the assumed or interpreted neurophysiological mechanisms underpinning hyperalgesia.

GENERALIZED HYPERALGESIA The term '*generalized hyperalgesia*' is not defined in the IASP terminology. It has been used to denote hyperalgesia which is evident in tissues unrelated and seperate to a painful lesion, which is assumed to be the cause of changes in pain modulation such as hyperalgesia. The terms '*generalized*', '*spreading*' and '*widespread*' hyperalgesia seem to be used interchangeably in the literature.

1 `http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm`

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Part I

THESIS

1

INTRODUCTION

The primary objective of this thesis and the scientific investigations on which it is based is to examine the apparent association of *generalized hyperalgesia* and *low-back pain* (LBP), specifically to investigate the temporal development of generalized hyperalgesia in *chronic* LBP.

The thesis is based on five manuscripts, each of which are based on seperate investigations.

The Ph.D. has been a collaboration between the *Spine Center of Southern Denmark*, Lillebaelt Hospital and *Center for Sensory-Motor Interaction*, University of Aalborg. The two primary care chiropractic clinics *Hartvigsen & Hein*, Odense and *Kiropraktisk Klinik*, Kolding collaborated on studies IV and V, and the Institute of Forensic Medicine, University of Southern Denmark assisted in study II.

2

BACKGROUND

2.1 LOW-BACK PAIN

Low back pain is a *symptom*, and is commonly defined as *pain perceived in the region of the lumbar and gluteal areas*, i.e. between the lower costal margin and the gluteal folds (see figure 1).

When LBP is a secondary symptom related to a specific serious pathology such as malignancy, infectious disease, gross traumatic injury or systemic connective tissue disorders, it is not categorized as LBP, but diagnosed according to the underlying pathology.

As a *diagnostic category*, LBP includes non-specific LBP and LBP related to a range of structural musculoskeletal abnormalities which may or may not be clinically relevant in a given case. These include degenerative changes, arcolytic spondylolisthesis, intervertebral disk herniation and many others.

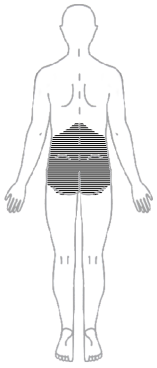

Figure 1

2.2 FACTORS CONTRIBUTING TO LBP CHRONICITY

LBP can not be assumed to spontanously resolve in the majority of cases, as is often suggested[34], in fact a recent review on the natural course of LBP concludes that *'improvement (becoming pain free) was never reported to be a common finding'*[49] and more than a third of the Danish population reports having a specific spinal disorder and/or spinal pain within the last 2 weeks[47]. Although LBP can be shrugged off as simply an intermittent reminder of advancing age in some instances. For others, LBP becomes a debilitating chronic pain condition, which undermines quality of life, social relations, and ability to work. The socio-economic burden of LBP is immense, amounting to 13 billion Danish kroner in 2005, more than half of which is due to reduced productivity[47]. Arguably, the important issue in relation to LBP is prognosis and the bio-psycho-social complications following *chronic* LBP.

The distinction between *acute*, *sub-acute* and *chronic* LBP is not immediately obvious, however. The usual approach is to define *chronic* somewhat arbitrarily, as pain which has persisted beyond a specified period of time, e.g. 3 months. But the natural course of LBP is one of fluctuating symptoms; intermittent periodes of exacerbations and remissions[33] and a simple cutoff-point in time fails to take this into account. In addition, 1) there are no obvious arguments for choosing

one arbitrary cutoff-point in favour of another, 2) patients' ability to accurately recall previous LBP over longer periods of time is poor[43] and 3) patients often (mis-)interpret chronic as meaning *irreversible*, rather than simply long-lasting pain.

It is not entirely clear what determines the prognosis of LBP and it is likely multifactorial in most cases. Some psychosocial factors like distress, low job-satisfaction and pain-catastrophizing seem to increase the risk of a poor prognosis[40,51,64,65], but so does heavy physical work, working in forward flexion, repetitive monotonous work and other biomechanical factors[30,39,42].

While it is difficult for researchers and clinicians alike to disentangle the relationships of biological, psychological and social factors in LBP prognosis, patients are often quite clear in identifying their *pain* as the primary problem and the ensuing cascade of bio-psycho-social issues as '*simply*' secondary complications to the pain.

An illustrative example from clinical practice, was the well-intended suggestion to a chronic, bedridden patient, that if only he would get out of bed and move about, his LBP might get better. To which he sourly replied, that *"..if only the pain would get better, he would most certainly get out of bed and move about!"*.

2.3 PAIN ASSESSMENT IN THE MANAGEMENT OF LBP

It is striking, that clinicians go to great lengths to identify structural abnormalities, quantify biomechanical function and investigate psychosocial issues in LBP, whereas *pain*, the primary focus of the patient, is regarded almost nonchalantly as simply an indicator that something *else* is afoot: Patients are typically questioned as to whether the onset of LBP was gradual, sudden, traumatic or unprovoked, etc as this is assumed to hint at the underlying cause. Similarly, pain location and intensity, as well as factors which exacerbate or improve pain are investigated in order to cast light on the probable tissue site and mechanism of pain. These are meaningful and worthwhile clinical questions, but pain itself and the sensory nervous system which transduces, conveys and modulates the noxious input is, by and large ignored.

Yet, the clinical and experimental pain research of the last few decades has demonstrated, that modulation of nociception is an important determinant of the pain experience and arguably, the modulation of nociception may therefore be an important factor in determining LBP prognosis.

It has become increasingly clear that such nociceptive modulation plays an important role, not least in chronic pain conditions, and that the clinical presentation of pain is not a simple reflection of the nociceptive stimuli.

2.4 MODULATION OF NOCICEPTION

Current understanding of *the pain system* is far removed from the original Cartesian model of pain as a simple, one-way conduction system: Pain is dynamically and adaptively modulated by a complicated integrative system of neural networks, in which facilitatory and inhibitory feed-back loops continually modify the processing and relaying of nociceptive signals.

Nociceptive modulation occurs at several levels; even from *before* the onset of an anticipated noxious stimulus[5], and the modulatory mechanisms can affect the intensity, quality, location and duration of pain. Indeed nociceptive modulation may determine whether a stimulus is perceived to be painful at all.

2.4.1 *Sensitization and hyperalgesia*

Arguably, *sensitization* simply means increased neuronal sensitivity to stimulation. This may include nociceptive pathways, but also nociceptive inhibitory pathways, sympathetic pathways and motorsystems. In pain research however, the term is often used implicitly to mean increased neural excitability of *nociceptive pathways* and thus potentially an increased pain perception in response to a given stimuli.

Sensitization of nociceptors is not the same as hyperalgesia, but the two are most likely related, with sensitization assumed to be *the* important underlying neurophysiological mechanism explaining the psychophysical characteristics of hyperalgesia. Indeed there are obvious similarities between the lowered thresholds, increased responsiveness, extension of receptive field and unmasking of stimulation modalities seen at both the cellular level in laboratory animals (sensitization) and behavioural level in human volunteers (hyperalgesia). Central sensitization would explain many of the *hyperalgesic* clinical observations in clinical pain, and is likely to be an important factor in the development of chronicity. See Cervero[12] and Woolf[84] for reviews.

Nociceptive modulatory mechanisms are complicated however and may involve both local hetero- and homosynaptic mechanisms, ascending and descending feed-back systems, and circulating substances with neuromodulatory effects. In order to aid clarity, nociceptive sensitization is often said to occur *peripherally*, *segmentally* and at *supraspinal* levels. For a review on nociceptive pathways, see Almeida et al.[1].

2.4.2 *Peripheral sensitization*

A range of pro-inflammatory substances are released in injured tissues; serotonin, histamine, prostaglandins, bradykinin and many others. This *inflammatory soup* causes sensitization of nociceptors in the injured tissue, thus lowering the activation threshold and increasing stimulation

responses. Depolarisation of nociceptor terminals, will in turn also cause the release of inflammatory mediators such as Substance P and CGRP, causing neurogenic inflammation. For review, see Woolf and Ma[85].

In addition to increased responsiveness of nociceptors, peripheral sensitization may also lead to the activation of previously unresponsive, mechano-insensitive afferents (silent nociceptors).

2.4.3 *Primary hyperalgesia*

The link between peripheral neuronal sensitization and primary hyperalgesia has been reseached extensively. Primary hyperalgesia is the increased pain sensitivity observed in an area of noxious input, e.g. in tissue injury or inflammation. In primary hyperalgesia, stimuli which would otherwise be innocous may become painful and stimulation which would be painful even under normal circumstances, will be perceived as more painful than they otherwise would be, reflecting a *left-shift* of the stimulus-response curve. Primary hyperalgesia is evident in the injured tissue within a short period of time, but the characteristics of primary hyperalgesia is dependent on the type noxious input[46].

2.4.4 *Central sensitization*

Nociception is not only modulated within an injured tissue. Prolonged nociceptive input from un-myelinated C-fibres may increase the excitability of second order neurons, particularly *Nocioceptive specific* (NS) neurons and *Wide dynamic range* (WDR) neurons in the spinal cord dorsal horn. When sensitized, these neurons become more responsive to stimuli, both noxious and innocous, their receptive fields become enlarged and they may become excitable by stimulation modalities, which would otherwise not cause activity. For review, see Sandkühler[70].

Central sensitization is driven primarily by nociceptive input from the periphery, i.e. it is activity dependent, but up-regulation of membrane NMDA receptors, increased number and strength of synaptic connections and other structural changes may cause more persistent sensitization.

As with peripheral sensitization, central sensitization is observed at the neuronal level and is not directly observable outside of experimental animal research, but it is believed to be associated with the observation of *referred pain*, *secondary hyperalgesia* and *generalized hyperalgesia*.

2.4.5 *Referred pain*

Plurisegmental convergence of sensory input onto sensitized WDR neurons from a variety of deep and superficial structures with unmasking of otherwise *'silent'* receptive fields, causes pain to be perceived in

superficial areas distant from the (deep) source of nociception. There is evidence that nociception from deep tissues is more capable of inducing central sensitization than superficial nociception, and clinically referred pain is observed to stem almost exclusively from deep somatic structures. For review see Graven-Nielsen[24].

2.4.6 *Secondary hyperalgesia*

Central sensitization is also the most likely cause of *secondary hyperalgesia*, which is increased pain sensitivity in areas extending beyond the area of noxious input and primary hyperalgesia. The area of secondary hyperalgesia may include contralateral homologue areas.

Secondary hyperalgesia can be demonstrated to be initiated by peripheral noxious input, but is maintained centrally[76].

Secondary hyperalgesia is induced within minutes of injury and it may last days, weeks or longer. Central sensitization of NS and WDR neurons is also observed to last days or weeks once established.

2.4.7 *Supra-spinal modulation*

Modulation of noxious input extends beyond the periphery and segmental innervation. Nuclei in the *rostral ventromedial medulla* (RVM) extend descending connections in the dorsolateral funiculus to NS and WDR neurons in laminae I, II and V of the dorsal horns. Through these connections, the RVM can exert a nociceptive modulatory effect at the spinal level. The RVM in turn receives major input from the *peri-aquaductal gray* (PAG), onto which input converges from both the spinal cord and higher brain centres such as the amygdala, the cingulate cortex, the thalamus and hypothalamus. For reviews, see Staud[78] and Porreca et al.[66].

The PAG-RVM complex, thus integrates ascending nociceptive input from the spinal cord with input from higher brain centres underlying emotion, behaviour, memory and other higher functions, and excerts a modulatory effect on nociception at the spinal level.

The descending modulation of the PAG-RVM complex on spinal nociception may be concommitantly inhibitory and facilitatory, and it is the balance between these modulatory effects which determine the net descending modulation. Evidence suggests, the net-effect of initial descending modulation after acute inflammatory pain is facilitatory for a period of hours. With persistent nociception however, the net descending modulation gradually shifts towards inhibition after a period of hours or days. For review see Ren and Dubner[68].

It has been suggested, that neurons in the PAG-RVM complex can be subdivided into *on*, *off* and *neutral cells*, depending on whether they excert a facilitatory, inhibitory or no modulatory effect on spinal nociception. It has also been suggested, that individual on and off cells have

whole-body receptor and effector fields. While this has been contested, and there appears to be a substantial number of *atypical on/off cells*[73], the whole-body receptor and effector field of supra-spinal nociceptive modulation as a whole, is plausible.

Again, the neurophysiological mechanisms of descending nociceptive modulation are not directly observable in human pain research or a clinical setting, but the phenomenon of *conditioned pain modulation* and *generalized hyperalgesia* are thought to reflects supra-spinal nociceptive modulation.

2.4.8 *Conditioned pain modulation*

The supra-spinal descending modulation of nociception is often (presumably) evoked and studied by quantifying *conditioned pain modulation* (CPM). For reviews, see Yarnitsky[86] and Lewis et al.[50].

CPM is based on the *'pain-inhibits-pain'* paradigm and is examined by applying a tonic, painful *conditioning* stimulus of some intensity (e.g. cold-pressor test) and observing the effect it has on a phasic *test* stimulus, e.g. pressure pain threshold.

The ability of supra-spinal networks to excert descending inhibition was previously termed *diffuse noxious inhibitory control* (DNIC). In line with recent recommendations on pain terminologi, the terms *inhibitory* or *facilitatory* conditioned pain modulation (*i*CPM vs. *f*CPM) have been adopted instead.

2.4.9 *Generalized hyperalgesia*

Generalized hyperalgesia, i.e. widespread, heterotopic increased pain sensitivity is a common finding in chronic pain conditions, and may reflect a gradual *spreading sensitization* caused by abberations in supra-spinal nociceptive modulation. The timeframe for changes in general pain sensitivity with chronic clinical pain is not well understood, but there is some clinical evidence that it is activity dependent and reversible[32,83].

Generalized hyperalgesia offers one explanation for the increased incidence of painful co-morbidity seen in chronic LBP[2,35]. Similarly, diffuse pain conditions such as fibromyalgia often start out as more localized pain complaints, which gradually develop into widespread, diffuse pain.

2.5 QUANTITATIVE SENSORY TESTING — QST

Hyperalgesia and CPM are thus presumably the psychophysical reflections of underlying neurophysiological phenomenon such as sensitization and descending nociceptive modulation. Whilst direct observation of the neurophysiological processes remains the domain of laboratory

animal research, psychophysical responses can readily be examined by quantitative sensory testing (QST), which is used extensively in experimental human pain research.

In its simplest form, QST consists of a controlled stimulus and a standardized method of quantifying the response. For review, see Graven-Nielsen and Arendt-Nielsen[25].

The response is obviously affected by the modality of the noxious stimulus and the intensity with which it is applied, but several other aspects need to be controlled also: The tissue type and area/volume to which the stimulus is applied, the manner and rate at which it is applied, the sequence and interval between consecutive stimuli, etc. may all affect the pain response.

Also, different aspects of the response can be quantified, e.g. intensity, distribution and quality of pain. Each of these in turn, can be quantified with different tools. Pain intensity e.g. can be quantified by means of a visual analogue pain scale, a numerial rating scale or an ordinal Likert scale with pain descriptors.

Most pain stimuli in QST can be grouped into 1) mechanical, 2) thermal, 3) chemical and 4) compound modalities such as ischemic pain and direct electrical stimulation. Most response measures quantify 1) pain threshold, 2) pain intensity, 3) pain distribution, 4) pain quality and 5) pain duration.

The studies on which this thesis is based, have made use of a variety of QST stimuli and response measures to examine the development of generalized hyperalgesia in chronic LBP.

2.6 QST EVIDENCE OF DISTURBED PAIN MODULATION IN CHRONIC PAIN

2.6.1 *Generalized hyperalgesia in chronic pain*

There is no systematic review or meta-analysis of generalized hyperalgesia in chronic pain conditions, but the literature is compelling. Using QST, generalized hyperalgesia has been demonstrated in a range of different painful clinical disorders, from non-specific *syndrome*-disorders to specific pathologies, both musculoskeletal and viceral. The following list is not exhaustive:

- Chronic fatigue syndrome[54]
- Cox-arthrosis[48]
- Gen-arthrosis[3,41]
- Endometriosis[6,32]
- Fibromyalgia[16,77]
- Irritable bowel syndrome[82]

- Lateral epicondylalgia[19]
- Low-back pain[23,67]
- Pancreatitis[11]
- Reumatoid arthritis[37,55]
- Temporomandibular disorder[71]
- Tensiontype headache[4]
- Whiplash[15,44,74]

A smaller number of studies have demonstrated, that generalized hyperalgesia is reversible and disappears when the associated painful disorder remits. This suggests that aberrations in descending nociceptive modulation are maintained by noxious input.

He et al.[32] examined 100 woman suffering from endometriosis and 70 healthy controls, and found generalized hyperalgesia in the patient group, in line with previous findings in endometriosis[6]. The patient group was re-examined 3 and 6 months after surgery, and the authors reported a significant, progressive reduction in clinical pain (dysmenorrhea) and experimental pain sensitivity (electrical pain threshold and ischemic pain intensity of the non-dominant arm)[32].

The study by Verne et al.[83] reported reversibility of generalized hyperalgesia (heat stimulation of the left foot) in 10 patients with irritable bowels syndrome (IBS) following rectal administration of either lidocaine or placebo, in a double-blinded cross-over design. Remarkably, the change in both local and general pain sensitivity was evident within 5-15 minutes after lidocaine treatment, despite the IBS having been present for 5+ years.

A randomized, double-blind, placebo-controlled study by Staud et al.[79] demonstrated attenuation on heat-hyperalgesia on the forearm of fibromyalgia patients when tonic painful pressure on the trapezius muscle was treated by licaine injection. Placebo injections did not affect heterotopic heat hyperalgesia and clinical fibromyalgia pain was not affected by the licaine injection.

Generalized hyperalgesia, thus is demonstrably 1) a common feature in chronic pain and is associated with a variety of heterogenous clinical disorders, 2) is apparently maintained by tonic noxious input from the disorder it is associated with and 3) is apparently modifiable by changes in the tonic noxious stimuli, possibly within minutes.

2.6.2 *Conditioned pain modulation in chronic pain*

A recent systematic review and meta-analysis by Lewis et al.[50] concluded that aberrations in CPM is a common finding in chronic pain.

The review identified 30 studies on 664 controls and 778 patients with diagnoses as diverse as Parkinsons disease and irritable bowel syndrome. No studies on LBP were included, however.

A significant difference was found in 29 of 42 CPM-comparisons in the reviewed studies. In all cases, the chronic pain patients demonstrated facilitation (or impaired net inhibition) of pain.

The authors reported that the choice of QST protocol and diagnostic category did not influence the results of the individual studies.

Like generalized hyperalgesia, it would seem that attenuated *i*CPM responses (or accentuated *f*CPM), is a common feature in chronic pain and is associated with a variety of heterogenous clinical disorders.

2.6.3 *Generalized hyperalgesia in non-painful disorders*

Abnormalities in pain modulation have also been demonstrated in a number of chronic, non-painful clinical conditions. Holst et al.[38] demonstrated increased secondary hyperalgesia in experimental pain induced by intradermal capsaicin injection in patients with *multiple chemical sensitivity*. Marsala et al.[53] reported lower pain thresholds and tolerance in patients with Parkinsons disease irrespective of painful comorbidity, compared to healthy controls. There are also reports in the literature of abnormal pain sensitivity in clinical depression[81] and post traumatic stress disorder[80]. In recent years, QST has been used to provide important new information on how the pain system is affected in patients with such disorders.

2.7 CHRONIC LBP AND GENERALIZED HYPERALGESIA

A number of publications have investiagted the association between generalized hyperalgesia and LBP, with different conclusions being reported.

Naliboff et al.[56] and Cohen et al.[14] reported *increased* thresholds to radiant heat stimuli and uncomfortable noise in LBP patients, compared to pain-free controls and Peters et al.[63] hypothesised higher electrical pain tresholds in 12 LBP patients with daily, idiopathic LBP for more than a year, but found no statistically significant group differences. Conversely, Schmidt and Brands[72] and Brands and Schmidt[9] reported greater pain intensity and less pain tolerance with cold-pressor test in chronic, idiopathic LBP, compared to controls.

A later paper by Giesecke et al.[23] also reported generalized hyperalgesia in chronic LBP. The authors compared chronic, idiopathic LBP with fibromyalgia patients and healthy controls. Manual tender point count was performed, followed by experimental pain stimuli consisting of mechanical pressure to the thumbnail with calibrated weights. Experimental pain was assessed using an NRS (0-20). The authors reported no increased tender point count, but increased thumbnail pain sensitiv-

ity in both patient groups compared to controls. Furthermore, *f*MRI was performed during experimental thumbnail pain of *'equal pressure'* (2kg) and *'equal pain'* (slightly intense pain). For *'equal pressure'*, the pain scores were greater (mean=6) for LBP and fibromyalgia patients, compared to controls (mean=1), and for *'equal pain'* the required pressure was lower for patients (mean 3.6 and 3.9 kg) compared to controls (mean=5.6kg). During *'equal pain'* *f*MRI was similar across all three groups, but during *'equal pressure'* stimulation, *f*MRI overlapped for LBP and fibromyalgia patients in 5 areas, but only 1 with healthy controls. I.e. *f*MRI confirmed the QST findings.

The recent study by Blumenstiel et al.[7] also compared fibromyalgia patients, chronic LBP patients and healthy controls and concluded, in contrast to Giesecke et al.[23], that whereas fibromyalgia patients exhibited generalized hyperalgesia, LBP patients had the '*profile of a localized pain condition with a decreased threshold only for deep pain and only at the affected area*'. The study by Blumenstiel et al.[7] used the comprehensive QST profile of the German Research Network on Neuropathic pain[69] and performed QST on the most painful area of the back and on the dorsum of the hand. The authors reported a significantly lower PPT on the painful area of the back, but not on the dorsum of the hand, in chronic LBP patients. The test sites differed between groups for the *most painful area of the back* (exclusively lumbar region for LBP patients, exclusively cervical region for controls and predominantly cervical region of fibromyalgia patients), which makes direct comparison questionable. However, no difference was reported in pain sensitivity on the dorsum of the hand between LBP patients and controls, suggesting no generalized hyperalgesia in that study population.

Contrary to the findings by Blumenstiel et al.[7], the recent study by Puta et al.[67] reported generalized hyperalgesia in chronic LBP patients compared to pain-free controls, in a study which shared many characteristics with the study by Blumenstiel et al. Participants were tested for pain sensitivity to mechanical punctate pressure in the *most painful body site* and in two neutral, pain-free sites. Age and gender matched controls were included and, unlike Blumenstiel et al. the same test sites were used in both groups – paraspinally in the lumbar region and on the dorsal and palmar aspects of both hands.

Overall, conflicting findings on the association between generalized hyperalgesia and chronic LBP, have been reported. This may to some extend, have been influenced the choice of experimental stimuli, the experimental pain parameter measured and the populations studied.

Most of the studies investigating generalized hyperalgesia in chronic pain (including LBP), are *cross-sectional* designs. Single cross-sectional studies however can not reveal the temporal association between two factors such as chronic pain and generalized hyperalgesia. Generalized hyperalgesia may develop early in the course of pain, which is the case

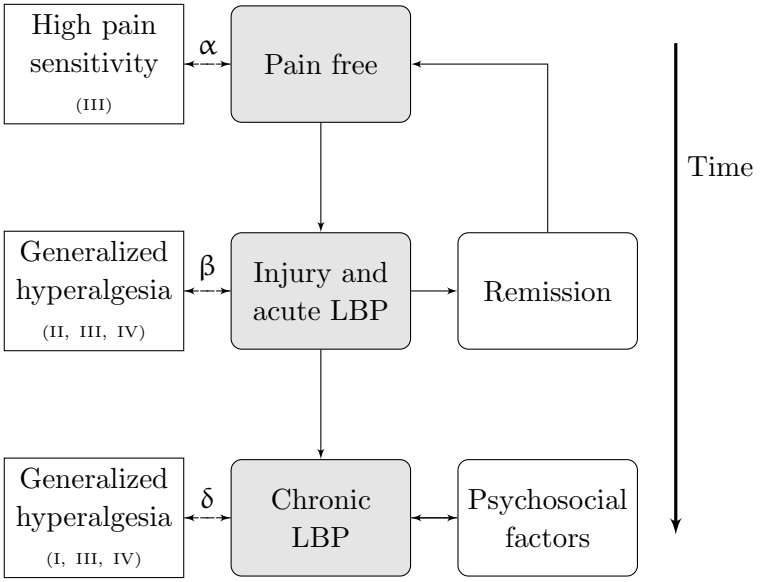

Figure 2: The current thesis examines three related hypothesis: That generalized hyperalgesia develops over time in sync with the *chronification* LBP (δ-arrow), that generalized hyperalgesia develops in the acute phase of LBP (β-arrow), and that a high-pain-sensitivity sub-group exists within the group of LBP free individuals, who are thus at greater risk of developing LBP (α-arrow).
The gray boxes illustrate progression of clinical LBP over time, from pain-free, over acute pain to chronic pain. Acute LBP may remit or progress into chronic LBP, in which case it is often associated with disability, psychosocial- and work-related issues.

with primary and secondary hyperalgesia, or it may be a pre-disposing trait or characteristic of a susceptible subgroup, which is then more likely to become chronic once exposed to acute pain.

2.8 THE AIM OF THIS THESIS

The aim of the current thesis was to examined whether generalized hyperalgesia is present in LBP and to investigate the temporal association of generalized hyperalgesia and LBP. Three hypotheses were tested:

Hypothesis α Pain-free individuals with a low threshold for experimental pressure pain, are at greater risk of developing LBP.

Hypothesis β Generalized hyperalgesia develops within a short time-frame (minutes to days) following acute pain.

Hypothesis δ Generalized hyperalgesia develops over time, in step with chronification of LBP, i.e. weeks or months.

See figure 2 for illustration.

3

SUMMARY OF METHODOLOGY

Data was collected in five different study designs, all of which were *primary* (empirical).

Study I *Matched-groups comparison* of experimental pain responses of chronic LBP patients and healthy controls

Study II *Within-participant comparison* of pain thresholds before, during and after acute experimental LBP in healthy volunteers

Study III *Longitudinal cohorte study* comparing pain thresholds and LBP status in a random background population sample.

Study IV *Cross-sectional survey* of the correlation of pain sensitivity and clinical parameters in a heterogenous group of LBP patients.

Study V *Methodology study* of the reliability and construct validity of sustained mechanical pressure with a spring-clamp.

Hypothesis α, that high pain sensitivity is a pre-existing characteristic of some pain-free individuals, which poses a risk factor for development of LBP was investigated in study III.

Hypothesis β, the relation between generalized hyperalgesia and acute/-subacute LBP was investigated in studies II, III and IV.

Hypothesis δ, the relation between generalized hyperalgesia and chronic LBP was invesitgated in studies I, III and IV.

The aims and methodology of each study is summarized briefly below. For more detail, refer to the individual manuscripts in appendix A.

3.1 SUMMARY OF STUDY I

AIM The aim of the study was to examine whether generalized hyperalgesia of deep musculoskeletal structures was evident in a group of chronic LBP patients with a *specific* diagnosis, when compared to matched healthy controls.

MATERIALS AND METHODS The study was cross-sectional and included 12 consecutive patients with chronic LBP and sciatica, neurological evidence of ipsilateral nerveroot inflammation and a corresponding, MRI confirmed lumbar disc herniation. At the time of QST, the acute nerve-root inflammation was judged to have receeded (negative straight leg raise test). The patient group thus consisted of chronic LBP patients with a *specific* pathoanatomical diagnosis.

A control group of age and gender matched, pain-free individuals was recruited.

Pain sensitivity was examined by QST of the tibialis anterior and infraspinatus muscles, ipsilateral to sciatic pain and consisted of:

- Pressure pain threhold
- Pain intensity with pressures of 120% and 140% of individual PPT
- Pain intensity with injection of 0.5 ml sterile, hypertonic saline solution (1 mmol/ml)
- Pain distribution following injection of hypertonic saline

3.2 SUMMARY OF STUDY II

AIM The aim of the study was to determine whether generalized hyperalgesia develops within a few minutes of acute pain, such as the case is with primary and secondary hyperalgesia.

METHODS A group of 13 healthy pain-free volunteers were followed over time from before onset of pain, during acute, experimental LBP and after it had receeded again.

The following QST was performed:

- Pressure pain threshold before, during and after acute, experimental LBP at:
  - gastrocnemius (bilatarally)
  - infraspinatus (bilaterally)
  - paraspinally at T_{12}
  - paraspinally at T_7
  - paraspinally at T_1
  - paraspinally at C_1

The acute *'LBP episode'* was induced by electrical stimulation of the right L_3-L_4 facet joint.

ERRATUM In section 2.4.1 of paper II (see page 55) line 10 of the second paragraph: "... (over 12 s)...", should read "... (over 1–2 s)...".

In section 3.4 (see page 56) reference is made to table 2 which lists summary data of VAS scores with continuous stimulation, and it is stated that VAS data was normally distributed, confirmed by Shapiro-Swilk test, "$p < 0.05$". The text should read "$p > 0.05$" (which supports normality).

3.3 SUMMARY OF STUDY III

AIM The aim of the study was three-fold:

- To re-examine previous findings of generalized pressure pain hyperalgesia in *long-lasting* (i.e. chronic) LBP
- To re-examine previous findings of no generalized hyperalgesia in *recent* (i.e. subacute) LBP
- To examine whether a high pain sensitivity in pain-free individuals increases the risk of developing future LBP

METHODS 264 participants of the longitudinal cohorte study "*Backs on Funen*" participated.

Low back pain status at baseline, 4-year and 8-year follow-up was categorized as: *Long-lasting LBP*, *recent LBP* or *No-or-remitted LBP*. This categorization was based on available data and differs from the usual definition of chronic as LBP for 3+ months.

QST at baseline and 8-year follow-up consisted of:

- PPT at the brachioradialis and tibialis anterior muscles (bilaterally) (*distant-PPT*)
- PPT in the mid-line over spinous process of L_4 (*local-PPT*)

Important differences in PPT methodology at baseline and 8-year follow-up, meant that direct within-subject comparison of PPT over time was not possible.

3.4 SUMMARY OF STUDY IV

AIM The study had the following aims:

- To re-examine previous findings of generalized pressure pain hyperalgesia in *chronic* LBP
- To re-examine previous findings of no generalized hyperalgesia in *acute* LBP
- To examine the correlation of a composite score of pain sensitivity and LBP duration
- To examine the correlation of a composite score of pain sensitivity and a number of different clinical parameters, relevant in LBP.

METHODS To ensure a heterogenous mix of LBP patients, participants were recruited from a hospital spine center (n=119) and from two primary care chiropractic clinics (n=79). 44 pain-free individuals were included as control group.

Quantitative sensory testing consisted of:

- PPT of the left infra spinatus muscle
- Ten seconds of sustained mechanical pressure on the left thumbnail using a spring-clamp.
- Cold-pressor test (0-2°C for 60 seconds), right hand.
- Conditioned pain modulation (CPT as conditioning stimulus and spring-clamp pain as test stimulus)

A *composite pain sensitivity score* was calculated, reflecting:

- Pain threshold
- Pain intensity
- Pain tolerance
- Conditioned pain modulation

Clinical data was collected on clinical pain presentation, work situation, quality of life, a psychological screening profile and functional status (disability).

3.5 SUMMARY OF STUDY V

AIM The aim of the study was to investigate whether a simple, mechanical spring clamp could be a useful standard pain stimuli in future pain research.

METHODS The spring clamp used in study IV, was re-tested in the hospital patients on their first subsequent visit.

Furthermore, a group of 20 healthy volunteers (senior clinical interns) were recruited to examine the test/re-test pain scores and stimulus-response proporties of a set of 6 spring-clamps of varying strengths.

3.6 SUMMARY OF PARTICIPANTS

A total of 563 participants toke part in the five studies; both patients with specific (I) and non-specific LBP (III-V), acute (III-V) and chronic (I,III-V) LBP and participants recruited from the background population (III), primary care (IV-V) and a hospital setting (I,IV-V), as well as pain free participants (I-V).

3.7 SUMMARY OF QST PROCEDURES

The QST procedures employed in the 5 studies were:

1. Mechanical

   a) Pressure pain threshold, measured with an algometer (I-IV)
   b) Pressure pain intensity (applied with an algometer), quantified by visual analogue scale (I)
   c) Pressure pain intensity (applied with a spring-clamp), quantified by visual analogue scale (IV-V)

2. Chemical
   a) Intra-muscular injection of hypertonic saline, quantified by time-series VAS and pain drawing (I)

3. Electrical
   a) Electrical sensation, pain and referred pain threshold, quantified by verbal indication of phase change (II)
   b) Electrical referred pain distribution at threshold, quantified by pain drawing (II)
   c) Electrical pain intensity stimulation-response curve, quantified by verbal pain rating (II)
   d) Electrical pain intensity with continuous stimulation, quantified by time-series VAS, pain drawing and McGill questionnaire (II)

4. Thermal
   a) Cold pressor test tolerance, measured with a stopwatch (IV-V)
   b) Cold pressor test time from start of test until pain onset, measured with a stopwatch (IV-V)
   c) Cold pressor test pain intensity, quantified by visual analogue scale (IV-V)

Most of the QST procedures employed in the current studies are in common use, but the following were developed specifically for the current studies[1] and are described in more detail in the following subsections:

- electrical stimulation of lumbar facet joint structures
- sustained mechanical pressure with a spring clamp and
- the online visual analogue pain scale

1 The study by Egloff et al.[17] was published during data collection in studies IV and V. Egloff et al made novel use of a clothes peg to apply mechanical pressure in a manner quite similar to the spring-clamp in the present studies.

3.7.1 *Electrical facet joint stimulation*

Using a Sonosite Titan (L38 linear probe) ultrasound scanner, the right L_3-L_4 facet joint was located and the position was marked on the overlying skin. Two sterile electrode needles were inserted in a straight posterior-to-anterior direction, aimed at either side of the joint cleft (1 cm apart) and advanced until the needles tips met bony resistance.

The needles were teflon coated, except for the distal 2 mm of the tip, and when connected to a constant current stimulator, could stimulate the deep, periarticular tissues. Stimulation was delivered as 5 Hz, 1 ms, bi-directional square-wave stimuli of variable current.

3.7.2 *Sustained mechanical pressure with a spring-clamp*

In study IV, a simple and inexpensive woodworkers spring-clamp (see figure 3) was used to apply sustained, mechanical pressure on the thumb of study participants. The characteristics of the spring-clamp as an experimental pain stimulus was examined further in study V.

Figure 3

The spring-clamp was applied to the thumb nail-bed, ensuring that the pressure pads were positioned as far proximal as possible, but without overlapping the cuticula (nail-band). After ten seconds, the clamp was removed and participants indicated the pain intensity of the mechanical pressure.

3.7.3 *Online time-series VAS*

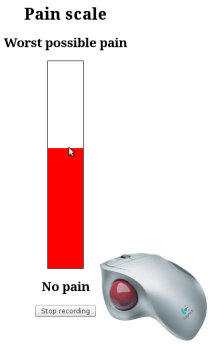

Figure 4

In studies I and II, there was a need to record pain intensity as it developed over time with injection of hypertonic saline (I) and sustained electrical stimulation (II). For those purposes, we developed an online VAS to be used with a commercially available ball-mouse (or a common computer mouse).

The online VAS displays a pain scale marked *'No pain'* at one end and *'Worst possible pain'* at the other. Moving the on-screen cursor vertically within those anchors, determines the level of the pain scale, which is illustrated in real-time as a red column of variable height. The position of the VAS is sampled with a frequency of 1 Hz and once the user clicks *'Stop recording'*, data collection is terminated and the sampled data is stored in the server database and presented in summarized form on-screen.

A test version has been made available at

`www.smerteforskning.dk/tools/phd_example/scale.php`.

3.8 STATISTICAL ANALYSIS – PARAMETRIC VERSUS NONPARAMETRIC

There is some discussion as to whether pain data such as VAS scores should be regarded as ratio or ordinal data[29,45]. A review of 112 research articles making use of VAS data, published in anaestesiology journals between 1991 and 1992, suggests that authors do not handle such data consistently: 76 articles summarized data as mean values and 24 reported median values. But conversely, 61 studies tested group differences with nonparametric tests and 38 used parametric t-test or ANOVA. Only 3 studies reported 95% confidence intervals, 2 for mean values and 1 for a median value[52].

While nonparametric tests generally have less power than their parametric counterparts, the power increases with increasing sample size and nonparametric tests are generally more robust, i.e. their validity are not unduly violated by departures from the underlying assumptions such as data distribution. Furthermore, nonparametric tests are less sensitive to outliers than parametric tests.

While transformation af skewed raw data may yield normally distributed data and *detecting and dealing with outliers* can improve the appropriateness of parametric group-difference testing, most of the statistical analyses used in the present studies are non-parametrical.

4

RESULTS

4.1 NEW QST PROCEDURES

ELECTRICAL FACET JOINT STIMULATION proved to be useful as a model of acute LBP:

- it could induce acute LBP in all study participants
- it induced non-painful sensation, pain and referred pain in the expected order with increasing stimulus intensity (see tabel I-1 on page 55)
- it could induce referred pain in 11 of 13 of participants (see figure I-1 on page 56)
- it induced LBP in a *stimulation-dependent* manner, i.e. increasing pain response with increasing stimulus intensity (see figure II-3 on page 56)
- continuous stimulation below the threshold for referred pain, induced referred pain in 9 of 13 study participants indicating central sensitization with temporal summation (see figure II-5 on page 57)
- it did not result in after-sensations, long lasting pain or serious complications, albeit several study participants reported muscular fatigue

THE SPRING-CLAMP also proved useful as a mechanical pain stimulus:

- a spring-clamp with a force of approximately 5kg induced mild to moderate pain in the majority of participants (see figure 5)
- a selection of different clamps induced pain in a *stimulation-dependent* manner, i.e. increasing pain response with increasing stimulus intensity (see figure V-4 on page 94)
- the clamp pain intensity correlated with other QST (see figure V-3 on page 93)
- the test/re-test pain intensity score and test/re-test force measurements were acceptable (see figure V-4 on page 94)

Furthermore, the spring-clamps were easy and expedient in use, are available commercially in a very large range of sizes and strengths and are inexpensive.

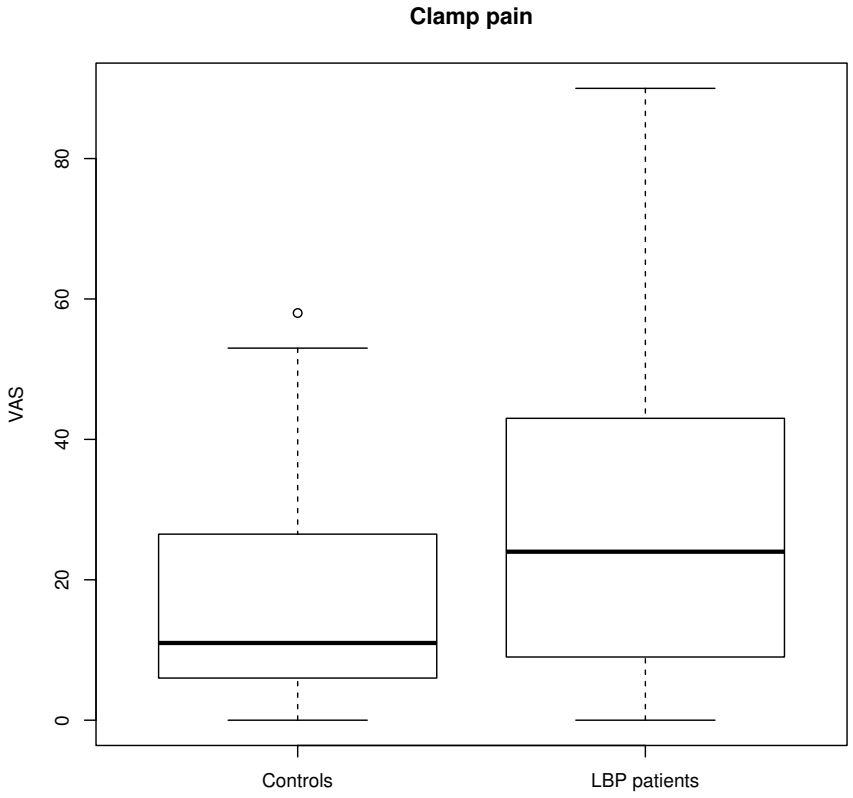

Figure 5: Distribution of pain responses with application of a spring-clamp (approximately 5 kg) on the thumb nail bed. LBP patients reported significantly greater pain with sustained mechanical pressure on the thumb, than healthy volunteers. $P < 0.01$ (from study IV).

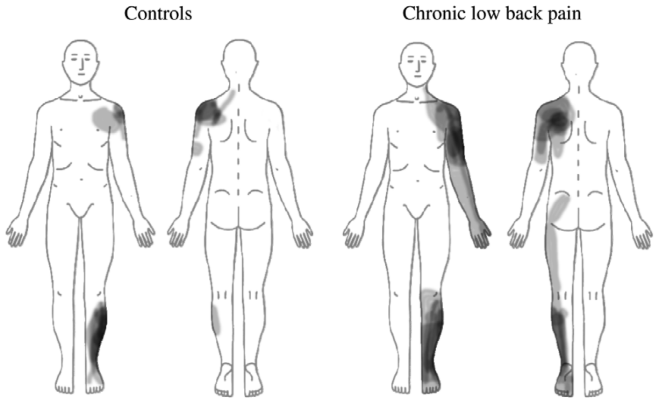

Figure 6: Pain evoked by injection of hypertonic saline in infraspinatus and tibialis anterior muscles. The evoked pain areas were significantly larger in the patients for infraspinatus ($P < 0.01$) and for both muscles combined, but not for tibialis anterior (ipsilateral to radicular pain)($P > 0.05$). Dark shading indicates overlapping pain areas among subjects. (from study I).

4.2 SUMMARY OF STUDY I

RESULTS The difference in infraspinatus PPT between chronic LBP patients and pain-free controls, was only just not-significant ($P = 0.052$). Neither was there a significant difference in the painful area with injection of hypertonic saline in the tibialis anterior muscle, see figure 6. In the other 12 pain measures, a significant difference was found, with LBP patients being more pain sensitive than controls. See table I-1 and I-2 on page 49.

4.3 SUMMARY OF STUDY II

RESULTS As described above (section 4.1), electrical stimulation of the L_3-L_4 facet joint induced acute LBP with evidence of central sensitization (referred pain), but no significant difference was found in the heterotopic PPTs before, during or after induction of acute, experimental LBP. See figure 7.

4.4 SUMMARY OF STUDY III

RESULTS Of the 264 participants recruited from the background population, 170 reported *no-or-remitted* LBP at baseline. Of these, the subgroup with low pressure pain thresholds did not have an increased risk of developing LBP compared to the rest of the group.

These were the findings irrespective of whether the relative risk was calculated for recent or long-lasting LBP, at 4-year or 8-year follow-up, and irrespective of whether a low pain threshold was defined in relation

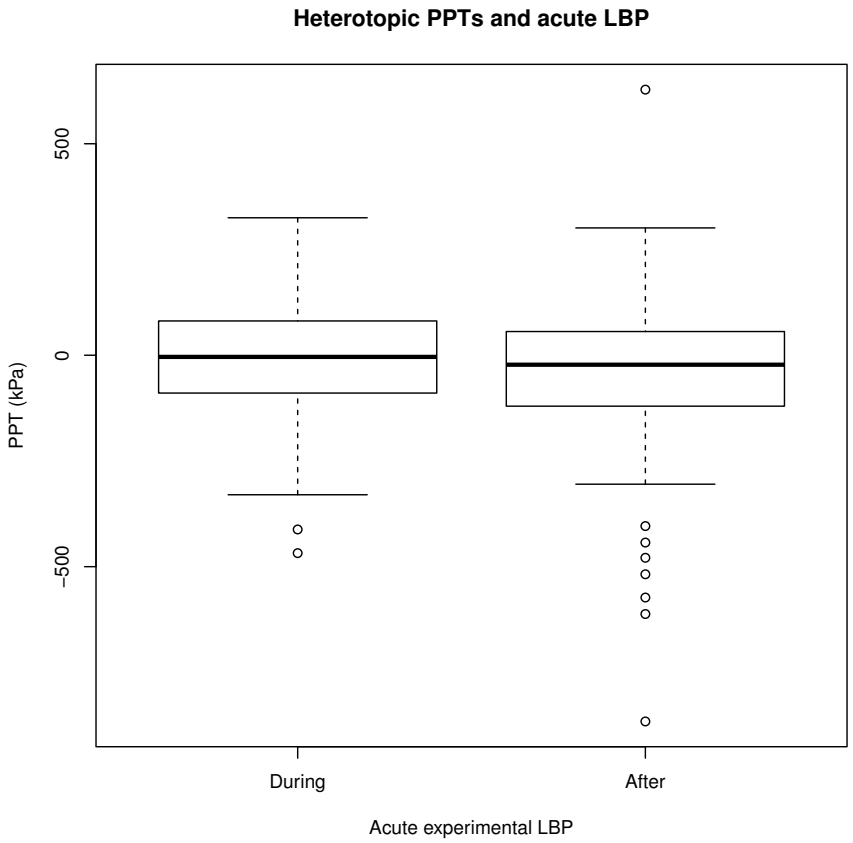

Figure 7: Boxplots of difference in PPT during and after acute experimental LBP induced by electrical facet joint stimulation, compared to the PPT measured before acute experimental LBP. As illustrated, the mean difference in PPT is close to zero, during and after experimental LBP. ($P > 0.05$ in both instances) (from study II).

to a low *local* lumbar PPT, a low *distant* PPT of the extremities or any combination thereof. The definition of a low pressure pain threshold as being in the lower 10% quantile was arbitrary – other arbitrary cut-off points (1%, 5% and 20%) did not affect the conclusion.

The findings where not due to a lack of mobility between LBP categories; of the 170 without LBP at baseline, 57 had developed LBP at 4-year follow-up. Similarly of the 94 participants with LBP at baseline, 32 had remitted at 4-year follow-up. "*A considerable number of participants changed LBP status during the 8-year follow-up period*", but having a low PPT at baseline did not increase the risk of developing LBP. See table 2 in study III on page 63.

Cross-sectional group comparison at baseline and at 8-year follow-up revealed a significant difference in both local L_4 PPT and distant PPT (average of the brachioradialis and tibialis anterior bilaterally) between participants with *no-or-remitted* LBP and *long-lasting* LBP ($0.003 \leqslant P \leqslant 0.024$), but no such difference between *no-or-remitted* LBP and *recent* LBP ($0.069 \leqslant P \leqslant 0.706$). See table 3 in study III on page 64.

4.5 SUMMARY OF STUDY IV

RESULTS The composite score of pain sensitivity was statistically significant between chronic LBP patients and controls ($P < 0.01$), but not between controls and acute LBP patients ($P = 0.11$). See figure 8.

The composite score of pain sensitivity was found to correlate weakly, but significantly with clinically relevant parameters such as disability, quality of life and clinical pain intensity. See figure 9.

A contingency with *improvement* in clinical pain was also found (dichotomized composite score of pain sensitivity) – participants with a high pain sensitivity being less likely to have experienced improvement in LBP since debut ($OR = 0.42$) or within the previous 2 weeks ($OR = 0.34$).

4.6 SUMMARY OF STUDY V

RESULTS The results of study V are summarized above in section 4.1 under paragraph *The Spring-Clamp*

4.7 TEMPORAL DEVELOPMENT OF GENERALIZED HYPERALGESIA IN LBP

The results of studies I-IV deal with the three hypothesis about the temporal association between generalized hyperalgesia and development of LBP, as illustrated in figure 2 on page 15:

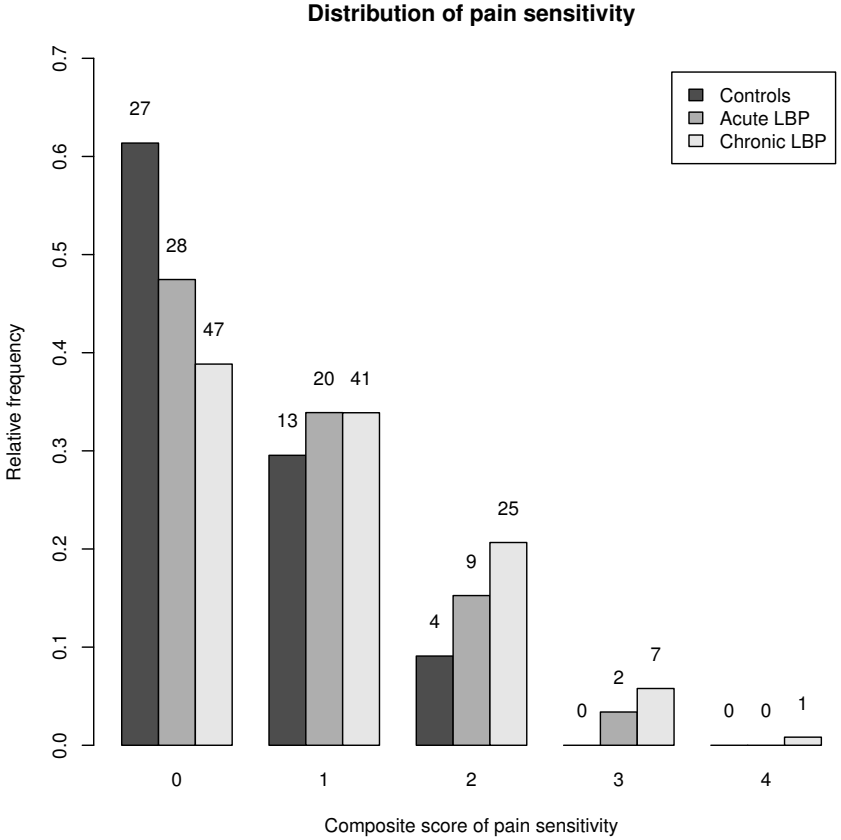

Figure 8: The relative frequency of the composite score of pain sensitivity (0-4) for pain free controls, acute LBP patients and chronic LBP patients (absolute number of observations above each bar). A significant difference was found between chronic LBP patients and controls ($P < 0.01$), but not between acute LBP patients and controls ($p > 0.05$) (from study IV).

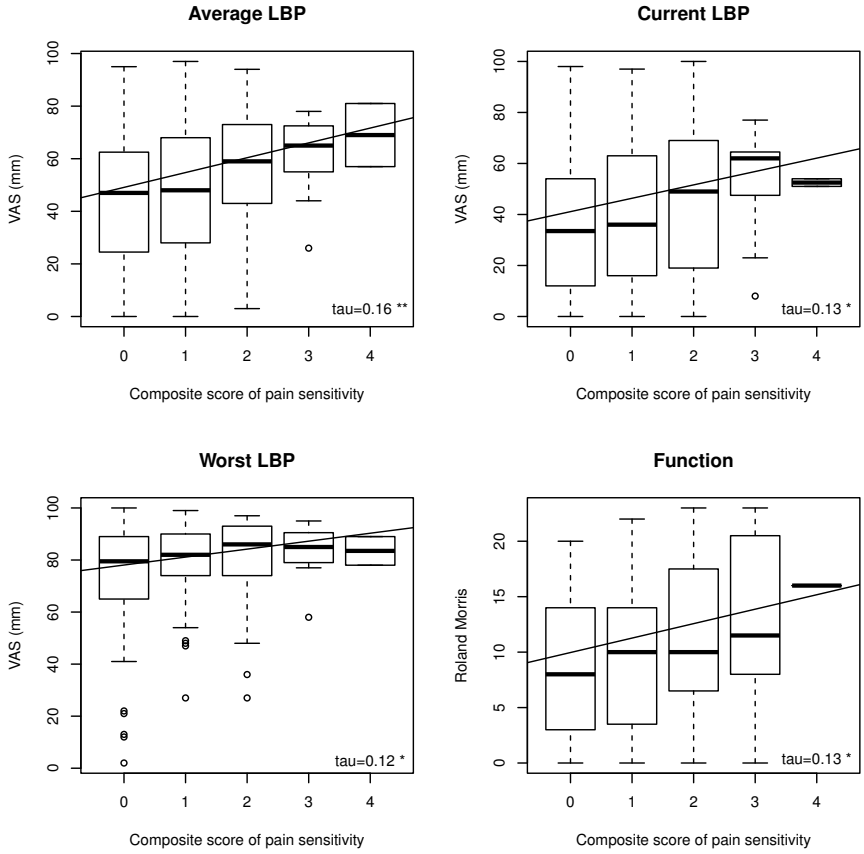

Figure 9: The composite score of pain sensitivity correlated with average ($P < 0.01$), current ($P < 0.05$) and worst LBP ($P < 0.05$) and the Roland Morris disability questionnaire ($P < 0.05$), as well as quality of life ($P < 0.01$) (not illustrated here) (from study IV).

4.7.1 *Hypothesis α — High pain sensitivity as a risk factor for future LBP in pain-free individuals*

Study III A low local or heterotopic pressure pain threshold did not constitutes a risk factor for the future development of LBP, in a LBP-free sample of the background population.

Study III *did not* support hypothesis α.

4.7.2 *Hypothesis β — Generalized hyperalgesia and acute/subacute LBP*

Study II Acute, experimental LBP did not induce generalized pressure pain hyperalgesia within a short timeframe (10 minutes).

Study III Participants with *recent* LBP did not exhibit local or generalized pressure pain hyperalgesia compared to those with *no-or-remitted* LBP

Study IV Generalized hyperalgesia assessed with a *composite score of pain sensitivity* was not evident in acute LBP compared to pain-free controls.

Studies II, III and IV did not support hypothesis β.

4.7.3 *Hypothesis δ — Generalized hyperalgesia and chronic LBP*

Study I Generalized hyperalgesia was demonstrated in chronic LBP patients with a specific pathoanatomical diagnosis, compared to pain-free controls

Study III Local and generalized pressure pain hyperalgesia was found in participants with *long-lasting* LBP compared to those with *no-or-remitted* LBP.

Study IV Generalized hyperalgesia assessed with a *composite score of pain sensitivity* was demonstrated in chronic LBP patients, compared to pain-free controls.

Studies I, III and IV did support hypothesis δ.

4.7.4 *Summary of overall results*

The results of study I-IV are summarized in table 1.

Generalized hyperalgesia and LBP

	Risk factor	Acute	Chronic
I			+
II		÷	
III	÷	÷	+
IV		÷	+

Table 1: Conclusions of study I-IV in relation to the three hypotheses investigated in the present thesis; that a high pain sensitivity constitutes a *risk factor* for the development of LBP in pain free participants, that generalized hyperalgesia is present in the *acute* phase of LBP and that generalized hyperalgesia develops in sync with *chronification* of LBP. A + signifies that the hypothesis is supported by the findings of the study, a ÷, that it is not.

5 DISCUSSION

5.1 NEW QST PROCEDURES

Study II required an experimental model of *acute LBP* and several models in common use, were considered. Intra-muscular, intra-articular and intra-discal injection of algogenic substances were considered less suitable, as pain intensity and duration are difficult to control and the procedures are inherently invasive and thus potentially harmful[18,20,57,61,62]. Mechanical and thermal stimulation were also considered, but are difficult to apply to deep structures, which is likely to be the common source of clinical LBP[8].

Electrical stimulation of lumbar facet joint structures offered the prospect of several benefits: the intensity and duration of electrical stimulation can be controlled easily, the stimulus can be applied to deep spinal structures and the procedure, albeit minimally invasive, was deemed safer than injection techniques.

As an experimental model of acute LBP, electrical stimulation of lumbar facet-joint structures proved useful, but also had several limitations and caveats. Deep insertion (approx. 5 cm) of two electrode needles does not allow for gross movement during examination and the study participants had to be positioned prone for close to half an hour. These are practical limitations, besides which, electrical stimulation is not a *natural* pain stimulus relying on transduction of an external stimuli, but rather stimulates neural tissues directly. In that sense, electrical stimulation will never be an accurate model of clinical pain conditions, such as LBP.

A further concern, is the accuracy of needle placement using ultrasonography, which is probably poorer than CT and videofluroscopy, although evidence suggests it is adequate[21,22,27,28,75]. An initial attempt was made to use MRI instead of ultrasound, but the poor resolution of MRI, combined with the small gauge (75x0.4 mm) of the electrode, meant it could not be visualized. Instead a series of trials were performed in which needle insertion was made on unembalmed cadavers using ultrasonography and follow-up CT was used to evaluate the procedure. Lessons learned from these trials suggested that mid-lumbar facet joints were more easily visialised and thus accuratly located than low lumbar facets, and that extensive facet degeneration in elderly individuals made it very difficult to visualize the joint space. For those reasons, the L_3-L_4 facet joint was targeted, and younger study participants were recuited (mean age 29).

Certain reservations are there for advisable: Periarticular stimulation with electrode needles inserted with the aid of ultrasonography is possible, indeed practicable, but caution must be exercised when stating exactly which tissues are being stimulated. But then again, the exact tissues and pathophysiological mechanisms responsible for clinical LBP are also most commonly uncertain and an argument can be made that other common experimental LBP models, such as *intra-articular* injection of an algogenic substance, is likely to sequester that substance from most of the pain sensitive tissues of a synovial joint complex.

The application of a spring-clamp in study III was employed to induce painful mechanical pressure on the thumb, and was also found to be useful. The procedure is undoubtedly easier to use than the '*rubber probe [. . .] attached to a hydraulic piston, a combination of valves [. . .] and a scale [with] calibrated weights*' used by Giesecke et al.[23]. It is certainly also more affordable than an electronic pressure algometer.

As an added benefit, the spring-clamp looks *innocuous* and is unlikely to instill the kind of apprehension in patients, that a syringe with hypertonic saline, or simply mentioning electrical stimulation can. Conversely, the spring-clamp has obvious drawbacks, as mentioned in study V: it can only be used to apply a fixed and constant mechanical pressure and only to tissues which will fit inside the jaws of the opened clamp.

The study by Egloff et al.[17], which was published during data collection in study IV and V, employed a clothes peg in an experimental setup much like the one in the current studies. The current findings with a spring-clamp echo those of Egloff et al.[17] very closely.

The spring-clamp was chosen, partly because mechanical pressure of the thumb has been used in previous studies on pain sensitivity in chronic LBP[13,23], partly to test the clamp, with the intention of using it as a QST pain stimuli in future multi-site, cohorte studies of primary care patients.

All in all, the two novel models of experimental pain stimuli, served their purpose and appear to be useful experimental pain stimuli.

5.2 ASSESSING GENERALIZED HYPERALGESIA

The current findings support the presence of generalized hyperalgesia in chronic LBP, but as mentioned in section 2.7, previous research on hyperalgesia in LBP has been somewhat discordant. An important factor, which may influence the conclusions reached in different studies, is the coice of QST procedures. Hastie et al.[31], Greenspan et al.[26] and Neziri et al.[59] employed principle component analysis and factor analysis to demonstrate that a large number of different measures of pain sensitivity reflected 4 or 5 underlying components. Conversely Neddermeyer et al.[58], also employing principle component analysis,

concluded that 8 different QST measures, reflected a single underlying component, which explained half the variance and carried heavy loading from all 8 QST measures – however, Neddermeyer et al. made use of threshold measures only, whereas Hastie et al., Greenspan et al. and Neziri et al. employed both threshold, response measures, after sensation and temporal summation.

In the present thesis, threshold measures were used in study I with ambiguous results; a significant group difference was found in tibialis anterior PPT, but not in infraspinatus PPT. In study II, PPT was used exclusively as a measure of change in heterotopic pain sensitivity and no change was found. In study III, two different PPT setups were used at baseline and 8-year follow-up and demonstrated group differences at both points in time. In study IV, PPT and CPT tolerance thresholds were used, with a significant group difference demonstrated in CPT tolerance, but not in PPT.

When future studies are to be undertaken, consideration should be given to standardizing a set of QST procedures which are feasible to employ in large study populations, and which give an adequate picture of pain sensitivity (and modulation). *Adequate* is likely to require several QST measures from different pain *domains*, such as threshold, tolerance, response, spatial distribution and others. A composite score of pain sensitivity, such as employed in study IV, may be a candidate for such an assessment.

However, mechanical pressure pain threshold measurement with an algometer appears to be the most commonly used QST pain stimuli and is to our experience, the only QST pain stimulus which has found some, albeit limited clinical application in musculoskeletal pain conditions. The spring-clamp was used in studies IV and V, in part to test its feasability as just one pain stimulus in a set of QST procedures, in future cohorte studies of primary care LBP patients.

5.3 "DIAGNOSING" GENERALIZED HYPERALGESIA

The definition of generalized hyperalgesia as an *increased* respons to a painful stimulus, suggests that the *normal* response is known, which is rarely the case. The usual approach in published research has been to compare groups of patients with pain-free control groups, and as noted, this commonly results in significant group differences. Recently, efforts have been made to establish population based reference values for experimental pain responses, such as the study by Neziri et al.[59] and the Tromsoe Pain population based cohorte study in Norway[60]. As variability is quite large, it may prove difficult to establish clinically meaningful reference value, which can be used to diagnose generalized hyperalgesia.

The large population variability in pain responses, could be overcome by comparing the potentially *increased* pain response to an individual

reference value, measured before the presumed onset of generalized hyperalgesia. This would be a difficult task, if the individual reference had to be measured before onset of pain. However, the finding that generalized hyperalgesia appears to develop in the course of chronification of LBP rather than in the acute phase, suggests that it may be possible to determine personal reference values for patients early in the course of LBP.

5.4 INTERACTION OF GENERALIZED HYPERALGESIA AND CHRONIC PAIN

To elucidate the temporal relationship of generalized hyperalgesia and LBP, a longitudinal cohorte study of a sufficiently large sample of the background population would have been ideal. Study III initially offered the prospect of such a study, but proved impossible due to unavoidable differences in QST procedure at baseline and follow-up.

The current studies however, support a temporality in the association of generalized hyperalgesia and LBP, which is one of the necessary requirements if causality is to be implied. A causal relationship between development of chronic LBP and generalized hyperalgesia, if such exists, is difficult to demonstrate conclusively in human research, but the *Bradford Hill* criteria for causality[36] requires evidence of association, consistency, specificity, temporality, biological gradiant, coherence, reversibility and mechanistic/biological plausability.

The relatively large number of studies on many different chronic pain conditions, provides evidence of a *consistent association* between chronic pain and generalized hyperalgesia, although there are of course exceptions, such as the paper by Peters et al.[63]. *Reversibility* has also been demonstrated, albeit in only a few studies[32,79,83], whereas the *mechanistic/biological plausability* is supported by large body of evidence in animal studies (see Sandkühler[70] for a recent review). The *temporality* of the association of chronic pain and generalized hyperalgesia has been demonstrated in at least one previous study (on chronic headache)[10]. Taken as a whole, these findings suggests a close, possibly causal relationship between chronic pain and generalized hyperalgesia.

Interestingly, despite the repeated association of generalized hyperalgesia and chronic LBP, no correlation was found between the composite score of pain sensitivity and duration of LBP in study IV. A high number of outliers in LBP duration (21 between 1798 and 13421 days) were not the cause, as correlation was calculated non-parametrically. In addition, pain sensitivity was (weakly) correlated with such important clinical parameters as disability, quality of life, intensity of clinical pain and recent improvement in clinical pain, which LBP duration was not[1]. Conversely, duration of LBP was correlated to 3 of 8 questions in

1 LBP duration correlated weakly with one of three measures of clinical pain

the psychological profile (coping, risk of persisten pain and depression) (post-hoc analysis, data not presented).

It seems pain sensitivity, at least in a sub-group of LBP patients, changes during the progression towards chronicity, and is related to important clinical parameters such as disability, clinical improvement and others. It stands to reason, that implementing a manageable *'package'* of QST in a primary care setting as part of the standard clinical assessment of first-time LBP episode, may have prognostic value in so far as particular QST profiles with increased risk of chronicity can be identified earlier in the course of LBP.

6

CONCLUSION

The current studies support the following conclusions:

- Generalized hyperalgesia does not pre-date the onset of LBP
- Generalized hyperalgesia is not present in acute LBP
- Generalized hyperalgesia is present in chronic LBP
- Although generalized hyperalgesia is observed in *chronic* LBP only, it is not a simple correlate of LBP duration
- Generalized hyperalgesia correlates with important aspects of the clinical presentation of LBP, such as disability, clinical pain and quality of life
- It is possible to develop simple and reliable pain stimuli, which can be used to assess pain sensitivity in a clinical setting

These conclusions in turn indicate, that a window of opportunity may exist in the early, acute phase of LBP, in which an individual heterotopic baseline pain sensitivity can be assessed with an approriate set of QST procedures: QST may potentially add important information to the clinical management of LBP, but is currently not part of the standard clinical examination in LBP.

Due to copyright Appendix II, Publications (pp. 43–98) has been
removed from this publication.

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