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EXPERIMENTAL ASSESSMENT OF CENTRAL HYPERSENSITIVITY IN CHRONIC PAIN

Doctoral Thesis

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PUBLICATIONS AND STUDIES

This Ph.D. dissertation is based on one original paper (I) submitted for publishing in Pain, an international peer-reviewed journal and preliminary analysis and comments of two experimental studies on chronic pain (II and III).

I. AY Neziri, M. Curatolo, E. Nüesch, P. Scaramozzino, OK Andersen, L. Arendt-Nielsen, and P. Jüni
Factor analysis of pain response to thermal, electrical, and mechanical stimuli supports multi-dimensional pain assessment
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II. AY Neziri, OK Andersen, L. Arendt-Nielsen, M. Curatolo
Evidence of central hypersensitivity in patients with chronic low back pain
Ongoing study

III. AY Neziri, OK Andersen, L. Arendt-Nielsen, M. Curatolo
Evidence of central hypersensitivity in patients with chronic neck pain
Ongoing study

PREFACE

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CONTENTS

LIST OF COMMON ABBREVIATIONS AND DEFINITIONS

NWR	Nociceptive withdrawal reflex
RRF	Reflex receptive field
QST	Quantitative sensory tests
Pdt	Pain detection threshold
Ptt	Pain tolerance threshold
TA	Tibialis anterior muscle
VAS	Visual analogue scale
BDI	Beck depression inventory
STAI	State – Trait anxiety inventory
SF 36	Short-Form 36 questionnaire
AUC	Area under the curve

Central hypersensitivity	An increase in the excitability of neurons within the central nervous system, so that non-painful or low-intensity painful stimulation is able to induce pain or exaggerated pain, respectively
Pain	“Unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”
Psychophysical pain tests	Tests that are based on subjective verbal response to a painful stimulus
Electrophysiological pain tests	Tests that are based on electrophysiological responses to a painful stimulus
QST	Term that includes psychophysical and electrophysiological pain tests
Temporal summation	Increased pain perception during repeated stimulation at constant intensity
Reflex receptive field	Cutaneous area from which a nociceptive stimulus can evoke a reflex in a given muscle

1. INTRODUCTION

1.1. EXPERIMENTAL PAIN RESEARCH

Understanding mechanisms of pain is one of the most challenging tasks in clinical practice. Experimental pain research has given a very high contribution to the current understanding of pain mechanisms in humans.

The basic principle in human experimental pain research is to activate the nociceptive system by a well-defined stimulus and then record and quantify the evoked response. The general term that defines this methodology is quantitative sensory pain testing. The response is usually of verbal or electrophysiological character. Quantification of verbal responses to painful stimuli is also denoted as psychophysical pain research. Examples of electrophysiological responses include the nociceptive withdrawal reflex (NWR) and electroencephalographic recordings after nociceptive stimulation.

1.2. MULTI-MODAL APPROACH IN HUMAN PAIN RESEARCH

During the last decade, a multi-modal approach has been established in human pain research, assessing pain responses after applying various experimental pain modalities (Arendt-Nielsen, 1997). These different modalities are used to determine the efficacy of analgesics in clinical studies and to explore different aspects and mechanisms of nociception (Arendt-Nielsen, 2007). Central hypersensitivity, defined as an increased excitability of the central nervous system after pain stimulation, is deemed to be important in the generation and maintenance of chronic pain and is detected by various experimental pain tests (Sheather-Reid and Cohen, 1998; Sörensen, 1998; Koelbaek Johansen, 1999; Curatolo, 2001; Staud, 2001; Moog, 2002; Price, 2002.). The use of different experimental pain modalities is based on the assumption that different aspects of nociception are explored, resulting in a more differentiated assessment of the analgesic efficacy of interventions and more sensitive instruments of central hypersensitivity as compared with assessments of single pain modalities.

In a factor analysis of pain measures from 188 individuals who were subjected to different stimuli at threshold and supra-threshold level, Hastie et al concluded that responses to different experimental pain modalities represent distinct dimensions of pain perception (Hastie et al., 2005). Conversely, in a principal component analysis of 77 individuals, Neddermeyer et al recently concluded that differences in responses to pain stimuli were mainly related to variation between individuals rather than variation between responses to different pain stimuli, and that it is sufficient to distinguish between individuals who are generally stoical or are complaining about a painful stimulus irrespective of the experimental pain modality used (Neddermeyer et al., 2008). In a factor analysis of 300 individuals who underwent stimulation by a broad range of experimental pain modalities, we determined whether responses to different pain stimuli are distinct dimensions as suggested by Hastie et al (Hastie et al., 2005) or highly correlated as suggested by Neddermeyer et al (Neddermeyer et al., 2008)

1.3. PAIN AND CENTRAL HYPERSENSITIVITY

Prolonged afferent nociceptive input induces an increase in the excitability of central sensory neurons and plasticity changes that are responsible for a state of hyperexcitability of the central nervous system (central hypersensitivity) (Woolf and Salter, 2000). The hyperexcitable central nervous system amplifies the nociceptive signal, thereby producing an exaggerated pain response even in the presence of limited tissue damage.

There is evidence that localized tissue damage leads to a state of hyperexcitability that is not confined to the neural structures connected to the site of the lesion, but involves the whole spinal cord and the supraspinal centers (Samad et al., 2001; Suzuki et al., 2002). This phenomenon may be at least partially responsible for a widespread hypersensitivity to peripheral stimulation, with pain being experienced in response to stimulation of tissues that are distant from the site of injury.

1.4. ASSESSMENT OF CENTRAL HYPERSENSITIVITY IN PATIENTS

Central hypersensitivity can be investigated in humans by quantitative sensory tests (Klein et al., 2005; Curatolo et al., 2006). Using these methods, central hypersensitivity has been detected in different chronic musculoskeletal pain syndromes (Curatolo et al., 2006). For instance, patients with chronic low back pain display increased pain sensitivity and enlargement of the areas of referred pain after stimulation of tissues around and at distance from the site of pain (i.e. the leg or the thumb) (Giesecke et al., 2004; Laursen et al., 2005; O'Neill et al., 2007), suggesting that widespread central hypersensitivity is associated with this painful condition.

An investigation that evaluated patients after a whiplash injury in the acute phase and 6 months after injury found that those patients with persistent moderate or severe symptoms 6 months post-injury had displayed, soon after injury, widespread hypersensitivity (Sterling et al., 2003). Therefore, the presence of central hypersensitivity may be an indicator of negative prognosis. An acute peripheral lesion may induce plasticity changes leading to central hypersensitivity in a subset of individuals. Such hypersensitivity would facilitate the transition from acute to chronic pain and disability.

In human pain research a reflex withdrawal reaction can be elicited by transcutaneous electrical stimulation of a sensory peripheral nerve and the electromyographic response may be recorded from the flexor and extensor muscles. The elicited nociceptive withdrawal reflex (NWR) is a poly-synaptic spinal nociceptive reflex, and represents the mechanism of a response in both ipsilateral and contralateral muscle groups for withdrawing an extremity in order to avoid further tissue damage (Sherrington, 1910). The process is initiated by the nociceptive input, but elaboration takes place within the spinal cord. Additional afferent input, descending activity, and the excitability of the neurons in this pathway modulate the generation of the spinal nociceptive reflex.

The NWR and its modulation have been widely used in experimental (Hagbarth, 1960; Kugelberg et al., 1960; Willer and Bathien, 1977; Arendt-Nielsen et al., 2000; Andersen, 2007) and pharmacologic studies (Willer and Bathien, 1977; Willer, 1985; Arendt-Nielsen et al., 1990; Petersen-Felix et al., 1995; Curatolo et al., 1997; Petersen-Felix et al., 1998; Piguet et al., 1998; Escher et al., 2007) as a noninvasive neurophysiologic tool to objectively assess spinal nociceptive processing.

A phenomenon linked to hypersensitivity is reorganization at the spinal cord level that is manifested by changes in receptive field areas. The receptive field is the size of peripheral tissue that is innervated by a single spinal neuron. An expansion of the receptive fields of individual dorsal horn neurons following peripheral injury has been documented early (McMahon and Wall, 1984) and confirmed in muscle pain: an expansion of the cell population of the dorsal horn that could be excited by input from the inflamed muscle was observed (Hoheisel et al., 1994). The activation of silent synapses leads to the convergence of input from more than one source to the same neurons. These events are likely determinants of hyperalgesia at areas outside the injured region (secondary hyperalgesia) and enlargement of the pain areas, a clinically relevant phenomenon. So far no established method to assess nociceptive receptive fields in humans was available.

1.4.1. THE REFLEX RECEPTIVE FIELD (RRF) AS A QUANTITATIVE MEASURE OF CENTRAL HYPERSENSITIVITY IN HUMANS

Widely accepted experimental models of spinal central sensitisation in humans are all based on psychophysical measures of cutaneous allodynia, hyperalgesia or referred pain associated with experimental induction of pain in deep structures (Klein et al., 2005). In contrast, even robust noxious conditioning stimuli leading to accepted psychophysical signs of central sensitisation have very limited effects on the nociceptive withdrawal reflex. Topical capsaicin has been shown to produce enhanced reflexes, but only while the volunteers perceived ongoing pain from the treated skin site (Grönross and Pertovaara, 1993) or when concurrent pain was evoked from the skin sites with allodynia/hyperalgesia (Andersen et al., 1995). Deep pain evoked by i.m. injection of hypertonic saline had only marginal effects on withdrawal reflex sizes (Andersen et al., 2000). This lack of evidence for central manifestations might be related to minor changes in reflex gain associated with the human models despite the substantial changes in reflex excitability in animal models (Woolf, 1983;Xu et al., 1995;Tabo et al., 1998;Harris and Clarke, 2003). Alternatively, it could also be related to insufficient sensitivity of the reflex methods developed for human studies.

In chronic musculoskeletal pain patients, lower withdrawal reflex thresholds have been identified (Desmeules et al., 2003;Banic et al., 2004). Expansion of receptive field size is accepted as one of the most robust measures of central sensitisation in animal models (Cook et al., 1987;Hoheisel and Mense, 1989;Dubner, 1991). The encoding of the spinal reflex receptive fields is assumed to involve neurons located in deep laminae of the dorsal horn. Hence, wide dynamic range (WDR) neurons with receptive fields resembling the RRF for specific muscles have been identified (Schouenborg et al., 1995) which therefore are putative encoders of the RRF. These neurons do not have ascending collaterals indicating they are spinal reflex pathway interneurons. WDR neurons in the same part of the dorsal horn show prolonged firing following repetitive stimulation of C fibres (wind-up) (Schouenborg and Sjölund, 1983) and the firing is linked to gradual increases in withdrawal reflexes (You et al., 2003). Wind-up is closely associated with central sensitisation and hence assessment of RRF in humans could provide a unique and robust view of spinal nociceptive processing in human subjects. The participants tolerated the electrical stimulation well which was also the case in a similar study in chronic pain patients (Banic et al., 2004).

Intramuscular injection of capsaicin has been shown to produce signs of central sensitisation in human volunteers in the form of referred pain (Witting et al., 2000). The pain evoked by capsaicin lasted 38±5 minutes in the latter experiment for a dose of 100 µg in a volume of 1 ml injected into the brachioradial muscle. However, injection into the same foot muscle as in the present experiment (flexor digitorum brevis) did not modulate the RRF (Andersen, 2007) despite robust pain for ten minutes (average Visual Analogue Scale VAS rating above 3 on a 0-10 scale). This might be related to descending inhibition triggered by the capsaicin injection, and hence the pilot findings presented in this paper were obtained from a volunteer with complete spinal cord injury. Recordings from more subjects are clearly needed to decisively determine whether or not descending modulation is a key factor controlling the reflex pathway excitability in experimental chronic pain models. In animal models, the reflex excitability is substantially increased in spinal models compared to spinal intact animals (Carstens and Douglass, 1995;Gozariu et al., 1997;Clarke et al., 2002), in particular during central sensitisation (Harris and Clarke, 2003). The expansion of receptive fields of dorsal horn nociceptive neurons is further highly dependent on descending activity (Laird and Cervero, 1990;Yu and Mense, 1990;Schouenborg, 2002). The RRF in human spinal cord injured subjects is expanded compared to spinally intact subjects, indicating that descending control is essential for maintaining biomechanically functionally relevant RRF (Andersen et al., 2004).

1.5. NOCICEPTIVE WITHDRAWAL REFLEX

Nociceptive withdrawal reflexes have been elicited by electrical stimulation in many human experimental pain studies (Hugon, 1973;Willer, 1977;Petersen-Felix et al., 1996;Andersen, 2007;France et al., 2007). This is a very efficient stimulus for evoking withdrawal reflexes even though it is non-natural. Heat stimulation has been attempted but the level needed for evoking spinal reflexes in an experimental setting is often associated with mild tissue damage (reddening) and large reflex variability (Andersen et al., 2006). Care must be taken with positioning of the stimulating electrodes in order to avoid stimulation of nerve trunks and ensure that very local sensations are evoked. Stimulation of nerve trunks activates axons innervating large areas and hence might cover both excitatory and inhibitory reflex receptive fields (Weng and Schouenborg, 1996;Sonnenborg et al., 2000) resulting in ambiguous assessments of the RRF. Habituation is often seen with electrical stimulation (Dimitrijevic et al., 1972) but by constantly changing the stimulation site the problem is minimised (Fuhrer, 1973;Carstens and Ansley, 1993). Blinding of the subjects as to position and timing of the next stimulation improves the quality of the recordings as the subject has less chance of modulating the withdrawal voluntarily.

A critical methodological aspect is detection of the pain thresholds as this is the method for ensuring even input to the spinal cord irrespective of stimulation site. Often subjects find that the quality of the sensations evoked at the different sites varies, which is probably related to skin thickness. Hence, stimulation at the heel is less sharp compared to stimulation in the arch of the foot, most likely due to larger spread of the current through thick epidermal layers. There is a strong correlation between electrode impedance and pain thresholds (Andersen et al., 2004). Furthermore, it is imperative to familiarise the volunteer before assessing the pain thresholds to avoid gradual adaptation to the electrical stimulations. Randomisation in the sequence the pain thresholds are detected is important and further direct comparisons between a ‘control’ site (site 5) helps to ensure that the intensity of the stimuli is comparable across stimulation sites. The lower VAS ratings at the heel could be explained by the less sharp quality of the electrical stimuli. Furthermore, the pain intensity stimulus-response curves might very well be less steep at skin sites with thick epidermal layers so multiplying the stimulus intensity at all sites with a fixed factor is not optimal. A future alternative could be to evoke the reflexes at stimulus intensities that produce similar pain intensity scores for all stimulation sites.

1.6. AIMS OF DOCTORAL THESIS

The aims of this doctoral thesis were:

1) To determine whether responses to different pain stimuli are distinct dimensions or highly correlated.
2) To test the hypothesis that patients with chronic pain develop central hypersensitivity, i.e. display lower pain thresholds to electrical, mechanical and thermal stimuli.
3) To test the hypothesis that patients with chronic pain display enlarged reflex receptive fields compared to pain-free subjects.

2. METHODS USED IN THE EXPERIMENTAL STUDIES

2.1. PAIN FREE SUBJECTS AND CHRONIC PAIN PATIENTS

To determine reference values of psychophysical and electrophysiological measures of nociception and to analyze the influence of demographic, psychological and health-related data on quantitative sensory tests (QST) and reflex parameters, 300 pain-free subjects (152 males and 148 females) participated in study I.

In study II, thirty seven patients with chronic low back pain (21 - 78 years, 21 males and 16 females) were investigated. Finally, in study III thirty patients with chronic neck pain (25 - 77 years, 16 males and 14 females) were analysed.

2.2. DEMOGRAPHIC DATA, PSYCHOLOGICAL AND HEALTH-RELATED VARIABLES

To measure the psychological and health related parameters, Beck Depression Inventory (BDI), State-Trait-Anxiety-Inventory (STAI), Catastrophizing Scale of the Coping Strategies Questionnaire (CSQ) and Short-Form 36 (SF-36) were used. Demographic data, i.e. gender, age, height, weight and body mass index (BMI) were recorded. These data were used for descriptive purposes of QST.

The BDI is a 21-item self-report measure assessing affective, cognitive and somatic symptoms of depression. Higher scores indicate higher levels of depressive symptoms (Beck et al., 1996).

The STAI is a 40-item self-report questionnaire designed to assess symptoms of anxiety. It consists of two independent scales: a state anxiety scale and a trait anxiety scale, each with 20 items, leading to a score between 20 and 80. Higher scores indicate greater levels of anxiety. The state and trait scales explore anxiety as a current emotional state and as a personality trait, respectively (Spielberger et al., 1979; Laux et al., 1981).

The 6-item catastrophizing scale of the CSQ was used to assess pain catastrophizing cognitions (Rosenstiel and Keefe, 1983). The subscale score is the mean of all 6 items, and higher scores indicate higher degrees of pain catastrophizing.

The SF-36 questionnaire is a self-administered, 36-item questionnaire that measures health-related functions in eight domains: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), vitality (VT), general health perceptions (GH), social functioning (SF), role limitations due to emotional problems (RE) and mental health (MH). These eight domains were grouped into two health dimension scales: physical (PF, RP, BP, VT) and mental (SF, GH, RE, MH) (Ware and Sherbourne, 1992). The total score was also calculated. Each scale ranges from 0 (lowest level of functioning) to 100 (highest level) (Ware et al., 1993).

2.3. PSYCHOPHYSICAL TESTS

2.3.1. GENERAL ASPECTS

Single electrical stimulation, repeated electrical stimulation (temporal summation), test for reflex receptive field, pressure stimulation, heat stimulation, cold stimulation and a cold pressor test were performed by a single investigator (AN), with the sequence of tests varied between patients. For pressure, heat and cold stimulation, pain detection and pain tolerance thresholds were assessed at three body regions as described below. During testing, the volunteers were lying in a bed, in a quiet room. A leg rest was placed under the knees to obtain a 30° semi-flexion during electrophysiological testing. Each subject underwent a training session in order to become familiar with the stimulation procedure before starting data collection. All tests were applied to the same body side within each subject, with the side selected by the investigator in a ratio of 1:1.

2.3.2. PRESSURE PAIN STIMULATION

Pain detection and tolerance thresholds were measured with an electronic pressure algometer (Somedic, Sweden) using a probe with 1 cm^2 surface. The pressure was increased from 0 at a rate of 30 kPa/s to a maximum pressure of 1000 kPa. Pain detection threshold was defined as the point at which the pressure sensation turned to pain. Pain tolerance threshold was defined as the point at which the subject felt the pain as intolerable. The subjects were instructed to press a button when these points were reached. The algometer displayed the pressure intensity at which the button was pressed. If the subjects did not press the button at 1000 kPa, this value was considered as threshold.

The test was performed at three locations on pain-free subjects and at the site of most severe pain on patients with chronic pain (fourth location), in a randomized order: 1) in the middle of a horizontal line drawn between the posterior border of the acromion and the spinous process of the 7th cervical vertebra (suprascapular) 2) in the middle of a horizontal line drawn between the upper border of the iliac crest and the corresponding spinous process (low back); 3) the center of the pulp of the ipsilateral 2nd toe (toe). 4) The site of most severe pain on the low back (low back group) or in the neck (neck group) was the fourth location which was tested.

2.3.3. THERMAL PAIN STIMULATION – HEAT AND COLD

Thermal stimulation is a natural modality to activate warm and cold receptors and nociceptors in the skin. Thermal polymodal nociceptors are innervated by both Aδ- and C-afferents (Meyer et al. 1994). In the present study (specifically study III) activation of the thermal nociceptors was achieved by contact thermodes. A contact peltier-based thermode of the dimensions 30x30 mm of thermo-sensory stimulator (Medoc TSA-II; Medoc Ltd, Ramat Yishai, Israel) was used in study III for estimating the heat and cold pain thresholds.

To estimate heat pain thresholds, the temperature of the thermode was continuously increased from 30 ºC to a maximum of 50.5 ºC at a rate of 1.5 ºC/s.

To estimate cold pain thresholds, the temperature of the thermode was continuously decreased from 30 ºC to a minimum of 0 ºC at a rate of 1.5 ºC/sec. Pain detection and tolerance threshold were defined as for pressure stimulation. Once the threshold was detected, the temperature of the probe returned to baseline.

The test was performed at three locations on pain-free subjects and at the site of most severe pain on patients with chronic pain (fourth location), in a randomized order: 1) in the middle of a horizontal line drawn between the posterior border of the acromion and the spinous process of the 7th cervical vertebra (suprascapular); 2) in the middle of a horizontal line drawn between the upper border of the iliac crest and the corresponding spinous process (low back); 3) the lateral aspect of the leg, midway between the knee and the lateral malleolus (leg). 4) The site of most severe pain on the low back (low back group) or in the neck (neck group) was the fourth location which was tested.

2.3.4. COLD PRESSOR TEST (ICE WATER STIMULATION)

The hand was immersed in ice saturated water (0.7±0.1 °C) for a maximum of 2 minutes. The subject was instructed to withdraw the hand when they felt the pain as intolerable and the time of hand immersion was recorded. If the hand was not withdrawn at 2 minutes, this time was recorded for data analyses. Perceived pain intensity was continuously rated with an electronic visual analogue scale (scaled from 0 – no pain to 100 mm – intolerable pain) and recorded by computer. The area under the pain intensity/time curve was determined. If the hand was withdrawn before the end of the 2 minutes, the pain intensity was considered to be maximal until the end of the period.

2.4. ELECTROPHYSIOLOGICAL TESTS

In studies II and III, the electrophysiological tests were the main outcomes. However, the studies evaluated also the subjective pain thresholds to the electrical stimuli applied (psychophysical responses). In order to simplify the description of the methodology, these psychophysical responses are described in this chapter.

2.4.1. SINGLE ELECTRICAL STIMULATION

Electrical stimulation was performed through surface electrodes placed caudal to the lateral malleolus, at the innervation area of the sural nerve (Banic et al., 2004). A 25 ms train-of-five square-wave impulses, each lasting 1 ms, was delivered by a computer-controlled constant current stimulator (University of Aalborg, Denmark). The stimulation train is perceived as a single stimulus. Electromyographic (EMG) reflex responses to electrical stimulation were recorded from the middle of the biceps femoris and the rectus femoris muscles (Ag/AgCl-electrodes).

The current intensity was increased from 1 mA in steps of 0.5 mA until: 1) a reflex with an amplitude exceeding 20 μV for at least 10 ms in the 70-150 ms post-stimulation interval was detected (single stimulus reflex threshold); and 2) a pain sensation was evoked (single stimulus pain threshold). The program delivered the impulses at random time intervals (between 8 and 12 s), so that the subject was not aware of when the stimulus was applied.

2.4.2. REPEATED ELECTRICAL STIMULATION (TEMPORAL SUMMATION)

The stimulus burst used for single stimulus was repeated five times with a frequency of 2 Hz, at constant intensity (Arendt-Nielsen et al., 1994). EMG recordings were similar as for single stimulation. The current intensity of the five constant stimuli was increased from 1 mA in steps of 0.5 mA until: 1) an increase in the amplitude of the last two or three reflexes above a fixed limit of 20 μV for at least 10 ms in the 70-150 ms post-stimulation interval was observed (temporal summation reflex threshold); and 2) the subjects felt pain during the last 2 to 3 of the 5 electrical bursts (temporal summation pain threshold).

2.4.3. REFLEX RECEPTIVE FIELDS (RRF)

To evaluate RRFs, a procedure, which is described in detail in a recent paper (Neziri et al., 2009), was employed. Ten surface electrodes (15 × 15 mm, type 700, Ambu A/S, Denmark) were mounted on the sole of the foot (see fig 1). A common anode (50 × 90 mm electrode, type Synapse, Ambu A/S, Denmark) was placed on the dorsum of the foot. A computer-controlled electrical relay delivered a stimulus to one of the 10 electrodes in a randomized sequence and double-blind manner. Each stimulus consisted of a constant current pulse train of five individual 1 ms pulses delivered at 200 Hz (Stimulator Noxitest IES 230, University of Aalborg, Denmark). This train of stimuli is felt as single stimulus.

The EMG was recorded with surface electrodes (type 720, Ambu A/S, Denmark) over the belly of the tibialis anterior muscle with an inter-electrode distance of 2 cm. The EMG signals were amplified (up to 50 000 times), filtered (5–500 Hz, 2nd order), sampled (2000 Hz), displayed on the computer screen, and stored on computer disk. The EMG signals were stored from 200 ms before stimulation until 1000 ms after stimulation onset.

First, the pain thresholds were determined for each of the 10 stimulation sites. Then a stimulus intensity equal to 1.5 times the individual pain threshold was delivered. The

EMG responses for each stimulation site were recorded from the tibialis anterior muscle. The perceived pain intensity was rated on a 10 cm electronic VAS (Aalborg University, Denmark), whereby 0 = no pain and 10 = the worst pain imaginable. Each electrical stimulus was scored by the subject and stored on the computer.

The area of the RRF was calculated using the procedure presented above in data analyses. It is expressed as the area of the foot from which a reflex from a given muscle can be elicited. The volume of the RRF was calculated by integration of the EMG activity in the identified RRF area by calibrating to a standard foot size of 25×10 cm and expressed as µV*mm².

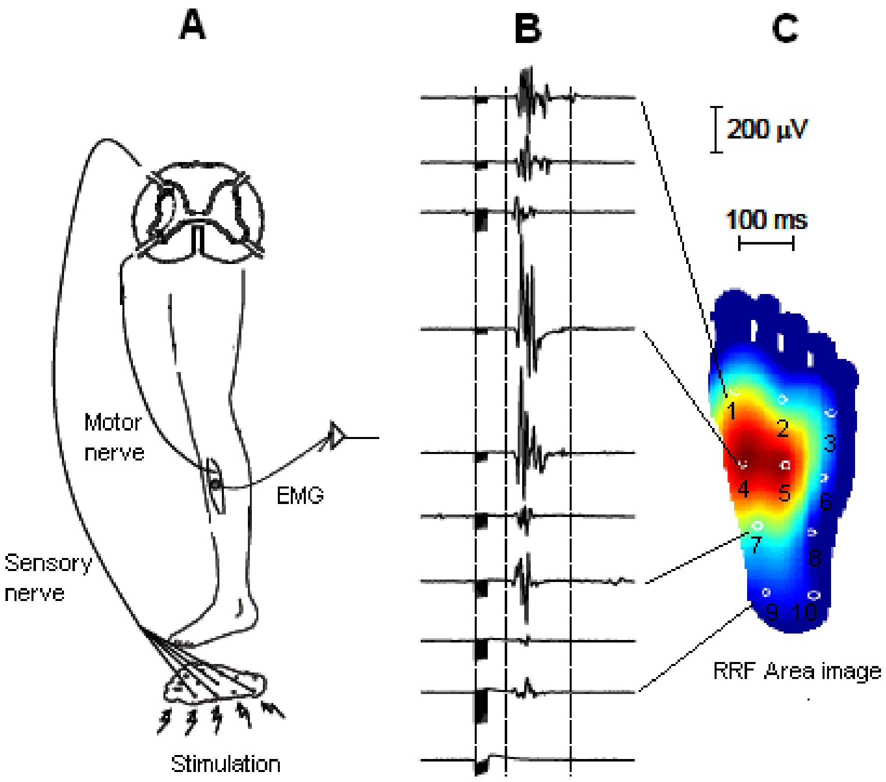


Figure 1. The general method for determining reflex receptive fields is depicted. A. Reflex responses were evoked by distributed electrical stimulation on the sole of the foot using surface electrodes. A common electrode was placed on the dorsum of the foot. The reflex responses were recorded by surface EMG. B. Four stimuli were delivered at all sites in randomized sequence, and the EMG signals were averaged for every stimulation site. The reflex size was quantified in the 60-180 ms time interval (indicated by the middle and right vertical lines). Stimulus onset is also indicated by the left vertical line. C. The two-dimensional interpolation map is then superimposed onto a map of the foot for depicting the reflex sensitivity in a particular muscle. The position of the electrodes is illustrated by white circles (Neziri et al., 2009)

2.4.4. EMG RECORDINGS

The electromyogram (EMG) was recorded with surface electrodes (type 720, Ambu A/S, Denmark) over the belly of the tibialis anterior (TA) muscle with an inter-electrode distance of 2 cm. Before attachment of the electrodes, the skin was lightly abraded and cleaned with isopropyl alcohol. The EMG signals were amplified (up to 50 000 times), filtered (5–500 Hz, 2nd order), sampled (2000 Hz), displayed on the computer screen, and stored on computer disk. The EMG signals were stored from 200 ms before stimulation until 1000 ms after stimulation onset.

2.5. DATA ANALYSIS

2.5.1. FACTOR ANALYSIS OF PAIN RESPONSES TO DIVERSE PAIN STIMULI (STUDY I)

A pre-specified stepwise approach was used to evaluate items (Streiner and Norman, 1995; Veenhof et al., 2006). We discarded items with >30% of truncated values. For example, in the case of heat pain tolerance in the leg, 39% of values were truncated at 50.5°, the maximum administered temperature. Therefore, the item was discarded. To identify potential redundancy between items the correlation between items was assessed. If Pearson's product-moment correlation between any two items was larger than 0.80, we discarded one of the items based on clinical judgment. Principal factor analysis with subsequent varimax rotation was used to derive factors. The maximum number of factors to be retained was not restricted. A factor was retained if its Eigenvalue was >1 and a factor loading of at least 0.50 was required to indicate a salient variable-factor relationship (Manly, 1994). Finally, we scattered the retained factors against each other and determined their correlation using Pearson's product-moment correlation. All analyses were performed in the overall set of 300 individuals and stratified according to gender and age, with the cut-off for age of 44 years pre-specified according to the upper age limit observed in the study by Neddermeyer et al (Neddermeyer et al., 2008). Analyses were performed in Stata 10.1 (STATA Institute Inc, College Station, TX, USA).

2.5.2. METHOD TO DETERMINE REFLEX RECEPTIVE FIELD PARAMETERS (STUDIES II-III)

To analyse data in studies II and III, the size of the reflexes were quantified by the root mean square (RMS) amplitude of the individual reflexes. The reflex sizes for each stimulation position were averaged. The RMS was calculated in the 80-180 ms post-stimulus window (Andersen, 2007). In order to illustrate the reflex receptive field, two-dimensional interpolation was calculated of the grand mean reflex size (mean of all subjects and all stimuli) for all stimulation sites using a custom made Matlab program. To be able to perform statistical analysis on the measured RRF, a number of features were extracted but only from the interpolated image (see Figure 2) to avoid basing the findings on extrapolated values. The interpolated image is the part of the image encompassed by the electrodes whereas the extrapolated values refer to the fringe of the image, i.e. the edges of the foot not covered by the electrodes. The features were designed to quantify the size and location of the RRF. The area of the RRF was assessed in a two step procedure. First, the fraction of the interpolated image with a Z-score higher than 2.58 (corresponding to a α-level of 0.01) based on the pre-stimulus EMG activity was determined. The Z-score is calculated for each pixel in the image by subtracting mean pre-stimulus EMG activity and subsequently dividing by the standard deviation of the pre-stimulus activity. The distribution of the pre-stimulus activity (mean and standard deviation) was determined from all sweeps. This threshold corresponds to likelihood for significant EMG activity of 99%. However, often an increase in the EMG tone is seen in response to the stimulus which is not equal to a significant reflex activity. Hence, the standard deviation of the identified map with Z-scores above 2.58 was calculated. The RRF area was subsequently defined as that fraction of the sole of the foot with EMG activity higher than peak EMG minus 2 times the calculated standard deviation as illustrated in Figure 2.

The volume (RRF area × reflex size) of the RRF was calculated by integration of the EMG activity in the identified RRF area by calibrating to a standard foot size of 25×10 cm (Andersen et al., 2001). The location of the peak of the interpolated EMG was identified and marked in the interpolated image, see Figure 3. In addition the Center of Gravity (CoG) was calculated for the identified RRF and indicated on the RRF. The CoG was included in case the distribution of the RRF is skewed and hence the peak is not located near the center of the RRF. The CoG is calculated as the cumulative sum of the reflex size (pixel value) multiplied by the distance and subsequently divided by the cumulative reflex size. Both peak and CoG were calculated with reference to the top left corner of the image (arbitrary). The location of these values is expressed as percentage of the width/length of the image relative to the top left corner (Figure 3).

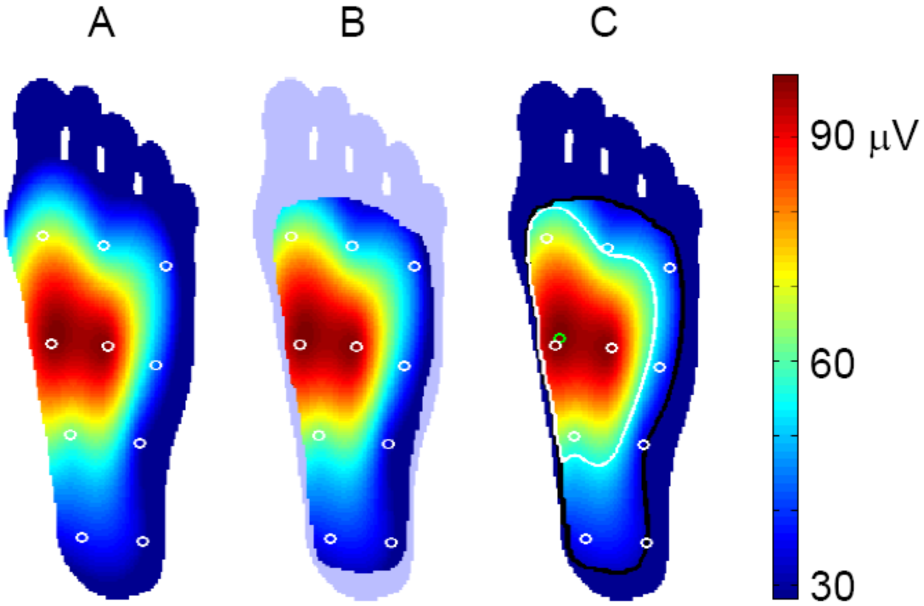


Figure 2. A. Illustration of the mean reflex receptive field of 30 healthy volunteers. This RRF includes both interpolated and extrapolated values. In particular the extrapolated values must be treated with caution. The determination of the RRF size in every individual volunteer was therefore only based on the interpolated values (illustrated in B). C. The border of the RRF is outlined by the white line (see methods section for details). The black line illustrates the part of the RRF with EMG level higher than the pre-stimulus EMG level ($P<0.001$) (Andersen et al., 2001).

Onset latency was detected using the same method as used in (Andersen et al., 2001). In short, the onset latencies were determined by the first signal component 5 times larger than the background noise for a period of more than 7 ms with the constraint that no component earlier than 60 ms was detected. The background noise was calculated by the RMS of the pre-stimulus.

2.5.3. COMPARING RRF OF CHRONIC PAIN PATIENTS AND PAIN-FREE SUBJECTS (STUDIES II-III)

Studies II and III are not yet completed, therefore the analysis should be considered as preliminary. The main outcome according to the study hypothesis was the assessment of reflex receptive fields. Secondary outcomes were subjective pain thresholds and parameters of spinal cord nociceptive excitability (nociceptive withdrawal reflexes to single and repeated electrical stimulation), and pain thresholds to mechanical and thermal pain stimuli.

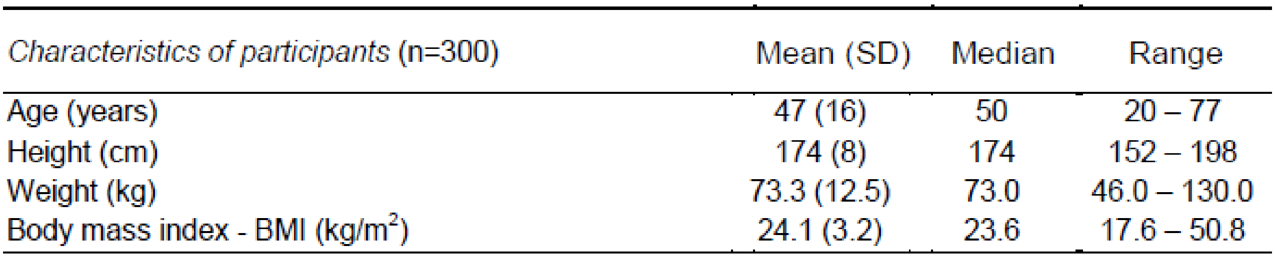
RRF areas between groups were compared using the unpaired t test (for normally distributed data). Pain and reflex thresholds to single and repeated electrical stimulation and pain thresholds to mechanical and thermal stimuli, were compared between groups by the Mann-Whitney rank sum test (for non-normally distributed data). P-values < 0.05 were considered as significant.

3. RESULTS

3.1. FACTOR ANALYSIS OF PAIN RESPONSES (STUDY I)

3.1.1. CHARACTERISTICS OF INCLUDED PAIN-FREE PARTICIPANTS

Between March 2006 and December 2007, 300 consecutive healthy volunteers were included in the study and examined. The characteristics of the 300 participants are presented in Table 1. 148 were women and 152 men, the mean age was 47 in women (SD 16) and 48 in men (SD 16), and the body mass index was 23.3 (SD 3.8) and 24.9 (SD 2.2), respectively. All participants were of Caucasian origin.



Characteristics of participants (n=300)	Mean (SD)	Median	Range
Age (years)	47 (16)	50	20 – 77
Height (cm)	174 (8)	174	152 – 198
Weight (kg)	73.3 (12.5)	73.0	46.0 – 130.0
Body mass index - BMI (kg/m^2)	24.1 (3.2)	23.6	17.6 – 50.8

Table 1. Characteristics of participants

3.1.2. CHARACTERISTICS OF INCLUDED PAIN TESTS

Table 2 presents the characteristics of the 18 retained quantitative sensory testings (pain detection and tolerance thresholds) and the 4 nociceptive withdrawal reflex analyses. Four sensory testings were discarded because there were more than 30% truncated values: heat pain tolerance on the leg (39% truncated values), cold pain tolerance on the leg (96% truncated values), cold pain tolerance on the low back (96% truncated values) and cold pain tolerance on the suprascapular region (90% truncated values).

N=300	Mean (SD)	Median	Range
Quantitative sensory tests			
Pressure pain detection toe (kPa)	214 (95)	200	83 - 686
Pressure pain tolerance toe (kPa)	483 (177)	463	120 - 1000
Pressure pain detection low back (kPa)	352 (131)	339	80 - 1000
Pressure pain tolerance low back (kPa)	729 (200)	722	206 – 1000
Pressure pain detection suprascapular (kPa)	301 (103)	297	107 – 801
Pressure pain tolerance suprascapular (kPa)	625 (181)	611	253 – 1000
Heat pain detection leg (°C)	43.0 (2.7)	42.9	36.2 – 50.5
Heat pain detection low back (°C)	40.6 (2.2)	40.4	34.0 – 50.5
Heat pain tolerance low back (°C)	47.9 (1.8)	47.8	39.3 – 50.5
Heat pain detection suprascapular (°C)	40.3 (2.1)	39.9	34.8 – 49.9
Heat pain tolerance suprascapular (°C)	47.6 (1.6)	47.4	39.0 – 50.5
Cold pain detection leg (°C)	2.2 (6.0)	0.0	0.0 – 26.2
Cold pain detection low back (°C)	3.3 (6.5)	0.0	0.0 – 28.2
Cold pain detection suprascapular (°C)	4.3 (6.7)	0.0	0.0 – 25.8
Cold pressor test: hand withdrawal time (s)	37 (22)	31	7 - 120
Cold pressor test: area under the curve (cm*s)	1003 (97)	1025	556 - 1156
Electrical single stimulation pain detection (mA)	11 (3)	11	5 - 26
Electrical repeated stimulation pain detection (mA)	9 (2)	8	4 - 21
Nociceptive withdrawal reflex analyses			
Electrical single stimulation reflex threshold (mA)	16 (4)	16	5 - 31
Electrical repeated stimulation reflex threshold (mA)	9 (2)	8	4 - 21
Reflex receptive field area tibialis anterior (proportion)	0.33 (0.17)	0.30	0.04 – 0.77
Reflex receptive field volume tibialis anterior (µV*mm^2)	0.26 (0.31)	0.12	0.00 – 1.62

Table 2. Characteristics of pain tests

3.1.3. INTER-ITEM CORRELATIONS BETWEEN ITEMS OF PAIN TESTS

Table 3 presents the inter-item correlations of the 22 items grouped according to type of stimulus. Correlations were typically high within the same type of stimulus, but low between different types. The median correlation between items within the same type of stimulus was 0.51 for pressure (range 0.09 to 0.75), 0.51 for heat (0.36 to 0.73), 0.68 for cold (0.59 to 0.73), 0.61 for electrical stimuli (0.60 to 1.00) and 0.79 for the two measures on reflex receptive fields. The median inter-item correlation between items of different types of stimulus was 0.03 (-0.40 to 0.37).

	Pressure pain detection toe	Pressure pain tolerance toe	Pressure pain detection low back	Pressure pain tolerance low back	Pressure pain detection suprasc.	Pressure pain tolerance suprasc.	Heat pain detection leg	Heat pain detection low back	Heat pain tolerance low back	Heat pain detection suprasc.	Heat pain tolerance suprasc.	Cold pain detection leg	Cold pain detection low back	Cold pain detection suprasc.	El. single stimulation pain det.	El. single stimulation reflex th.	El. repeated stimulation pain det.	El. repeated stimulation reflex th.	Reflex receptive field area TA	Reflex receptive field volume TA	Cold pressor: hand withdrawal t.	Cold pressor: area under the cu.
Pressure pain detection toe	1.00																					
Pressure pain tolerance toe	0.74	1.00																				
Pressure pain detection low back	0.49	0.29	1.00																			
Pressure pain tolerance low back	0.48	0.55	0.68	1.00																		
Pressure pain detection suprascapular	0.28	0.09	0.73	0.51	1.00																	
Pressure pain tolerance suprascapular	0.30	0.33	0.52	0.75	0.68	1.00																
Heat pain detection leg	0.32	0.25	0.29	0.26	0.14	0.17	1.00															
Heat pain detection low back	0.22	0.18	0.22	0.14	0.20	0.16	0.51	1.00														
Heat pain tolerance low back	0.09	0.22	0.11	0.31	0.03	0.28	0.37	0.50	1.00													
Heat pain detection suprascapular	0.26	0.22	0.19	0.16	0.16	0.16	0.54	0.73	0.39	1.00												
Heat pain tolerance suprascapular	0.17	0.26	0.06	0.25	0.01	0.27	0.36	0.42	0.67	0.55	1.00											
Cold pain detection leg	-0.03	0.00	-0.14	-0.09	-0.35	-0.22	-0.13	-0.26	-0.19	-0.14	-0.04	1.00										
Cold pain detection low back	-0.07	0.02	-0.18	-0.11	-0.30	-0.15	-0.15	-0.27	-0.13	-0.22	-0.09	0.59	1.00									
Cold pain detection suprascapular	0.07	0.13	-0.11	-0.07	-0.40	-0.23	-0.01	-0.19	-0.07	-0.15	-0.02	0.68	0.73	1.00								
Electrical single stimulation pain detection	-0.02	-0.06	0.09	0.06	0.21	0.12	-0.11	0.05	0.05	-0.06	-0.09	-0.19	-0.19	-0.23	1.00							
Electrical single stimulation reflex threshold	0.10	0.06	0.06	0.10	0.07	0.10	-0.01	0.05	0.16	-0.04	0.03	-0.02	-0.09	-0.06	0.68	1.00						
Electrical repeated stimulation pain detection	0.07	0.05	-0.01	0.03	-0.01	0.01	0.01	0.12	0.11	0.10	0.11	0.03	-0.01	-0.02	0.61	0.60	1.00					
Electrical repeated stimulation reflex threshold	0.07	0.06	-0.01	0.03	-0.01	0.01	0.02	0.12	0.11	0.10	0.12	0.03	-0.01	-0.02	0.61	0.60	1.00	1.00				
Reflex receptive field area tibialis anterior	0.11	0.14	-0.11	-0.04	-0.20	-0.12	0.15	0.09	0.13	0.18	0.16	0.01	0.11	0.19	-0.17	-0.17	-0.07	-0.07	1.00			
Reflex receptive field volume tibialis anterior	0.01	0.08	-0.16	-0.12	-0.23	-0.20	0.06	0.08	0.04	0.13	0.10	0.03	0.07	0.17	-0.21	-0.26	-0.08	-0.08	0.79	1.00		
Cold pressor test: hand withdrawal time	-0.17	-0.21	-0.21	-0.32	-0.21	-0.36	-0.16	-0.12	-0.25	-0.17	-0.23	0.06	0.02	-0.03	-0.11	-0.12	-0.17	-0.17	-0.08	-0.07	1.00	
Cold pressor test: area under the curve	0.19	0.25	0.19	0.32	0.16	0.37	0.14	0.12	0.28	0.17	0.27	-0.01	0.06	0.13	0.07	0.11	0.22	0.22	0.05	0.04	-0.93	1.00

Table 3. Inter-item correlation of items of used pain modalities (22 items retained, N=300)

3.1.4. FACTOR ANALYSIS

In the factor analysis, five factors emerged with Eigenvalues from 1.05 to 4.46 before varimax rotation. Results from factor analysis after varimax rotation are shown in Table 4. Factor loadings indicated that factor 1, explaining 23% of the total variance, related to pressure: the median load on factor 1 was 0.71 for pressure items (range 0.60 to 0.85), and 0.05 for remaining items (-0.15 to 0.31). Factor 2 related to heat (21% of variance), with a median factor loading of 0.72 for heat items (0.55 to 0.75). Factor 3 related to cold (18% of variance, median loading 0.74 [0.73 to 0.86]), factor 4 to electrical stimulation (15% of variance, median loading 0.78 [0.75 to 0.79]), and factor 5 related to reflex receptive fields (12% of variance, median loading 0.81). The 5 factors cumulatively explained 89% of the variance.

Table 5 presents results of factor analysis stratified by age, Table 6 shows results stratified by gender. Results were much the same.

Item	*Factor 1: Pressure*	*Factor 2: Heat*	*Factor 3: Cold*	*Factor 4: Electrical stimulation*	*Factor 5: Reflex receptive fields*
Pressure pain detection toe	**0.67**	0.15	0.11	0.08	0.25
Pressure pain tolerance toe	**0.60**	0.21	0.23	0.07	0.28
Pressure pain detection low back	**0.79**	0.05	-0.16	-0.23	-0.10
Pressure pain tolerance low back	**0.85**	0.16	0.01	0.04	-0.06
Pressure pain detection suprascapular	**0.67**	-0.03	-0.45	0.01	-0.22
Pressure pain tolerance suprascapular	**0.74**	0.16	-0.16	0.03	-0.20
Heat pain detection leg	0.24	**0.55**	-0.06	-0.08	0.11
Heat pain detection low back	0.11	**0.72**	-0.24	0.04	0.08
Heat pain tolerance low back	0.13	**0.71**	-0.02	0.12	0.01
Heat pain detection suprascapular	0.13	**0.75**	-0.15	-0.05	0.14
Heat pain tolerance suprascapular	0.12	**0.74**	0.07	0.02	0.05
Cold pain detection leg	-0.10	-0.11	**0.73**	-0.04	-0.04
Cold pain detection low back	-0.08	-0.15	**0.74**	-0.07	0.01
Cold pain suprascapular	-0.04	-0.04	**0.86**	-0.07	0.12
Electrical single stimulation pain detection	0.04	-0.08	-0.22	**0.79**	-0.11
Electrical single stimulation reflex threshold	0.07	0.04	0.00	**0.78**	-0.14
Electrical repeated stimulation reflex threshold	-0.15	0.12	0.05	**0.75**	-0.01
Reflex receptive field area tibialis anterior	-0.05	0.13	0.08	-0.09	**0.81**
Reflex receptive field volume tibialis anterior	-0.13	0.06	0.04	-0.14	**0.81**
Cold pressor test: hand withdrawal time	0.31	0.24	0.15	0.17	0.03
Eigenvalue	4.46	2.64	2.04	1.78	1.05
% of variance	22.81	20.98	17.95	15.02	11.74
Cumulative % of variance	22.81	43.79	61.74	76.76	88.50

Table 4. Results from factor analysis of the Varimax rotation, with the five factors corresponding to pressure, heat, cold, electrical stimulation and reflex receptive fields, as observed in 300 pain free subjects.

Age 20 – 44 years (n=132)	*Factor 1: Pressure*	*Factor 2: Heat*	*Factor 3: Cold*	*Factor 4: Electrical stimulation*	*Factor 5: Reflex receptive fields*
Pressure pain detection toe	**0.75**	0.07	-0.12	-0.04	-0.12
Pressure pain tolerance toe	**0.72**	0.14	0.11	0.00	0.00
Pressure pain detection low back	**0.78**	0.01	-0.13	-0.06	-0.18
Pressure pain tolerance low back	**0.84**	0.22	0.00	0.06	-0.03
Pressure pain detection suprascapular	**0.74**	0.11	-0.33	0.05	-0.10
Pressure pain tolerance suprascapular	**0.76**	0.31	-0.01	0.13	0.06
Heat pain detection leg	0.33	**0.55**	-0.15	-0.02	0.02
Heat pain detection low back	0.10	**0.69**	-0.38	-0.01	-0.03
Heat pain tolerance low back	0.22	**0.75**	-0.06	0.20	0.06
Heat pain detection suprascapular	0.10	**0.73**	-0.28	-0.08	0.03
Heat pain tolerance suprascapular	0.20	**0.80**	0.06	0.03	0.05
Cold pain detection leg	-0.21	-0.28	**0.60**	-0.15	-0.18
Cold pain detection low back	-0.20	-0.20	**0.63**	-0.17	-0.11
Cold pain suprascapular	-0.09	-0.15	**0.79**	-0.12	0.00
Electrical single stimulation pain detection	0.04	-0.03	-0.19	**0.75**	-0.19
Electrical single stimulation reflex threshold	0.04	0.06	-0.04	**0.73**	-0.30
Electrical repeated stimulation reflex threshold	-0.01	0.08	-0.05	**0.71**	-0.12
Reflex receptive field area tibialis anterior	-0.08	0.11	-0.06	-0.19	**0.82**
Reflex receptive field volume tibialis anterior	-0.13	-0.02	-0.03	-0.21	**0.82**
Cold pressor test: hand withdrawal time	0.28	0.30	0.41	0.27	0.15
Age 45 – 78 years (n=168)					
Pressure pain detection toe	**0.68**	0.09	0.06	0.10	0.29
Pressure pain tolerance toe	**0.55**	0.16	0.13	0.08	0.35
Pressure pain detection low back	**0.80**	0.17	-0.13	-0.02	-0.09
Pressure pain tolerance low back	**0.84**	0.08	0.25	0.01	0.08
Pressure pain detection suprascapular	**0.72**	-0.02	-0.38	0.00	-0.23
Pressure pain tolerance suprascapular	**0.77**	0.09	0.07	0.01	-0.10
Heat pain detection leg	0.18	**0.54**	-0.04	-0.17	0.05
Heat pain detection low back	0.17	**0.76**	-0.26	0.06	-0.01
Heat pain tolerance low back	-0.04	**0.65**	0.28	0.05	0.21
Heat pain detection suprascapular	0.20	**0.77**	-0.18	-0.05	0.07
Heat pain tolerance suprascapular	0.03	**0.66**	0.15	0.03	0.17
Cold pain detection leg	0.01	0.09	**0.75**	0.02	-0.07
Cold pain detection low back	0.03	-0.14	**0.87**	0.00	0.09
Cold pain suprascapular	0.03	-0.03	**0.93**	-0.01	0.03
Electrical single stimulation pain detection	0.01	-0.10	-0.12	**0.85**	0.02
Electrical single stimulation reflex threshold	0.07	-0.03	0.04	**0.79**	0.01
Electrical repeated stimulation reflex threshold	-0.02	0.15	0.10	**0.80**	-0.02
Reflex receptive field area tibialis anterior	0.02	0.08	0.09	0.00	**0.80**
Reflex receptive field volume tibialis anterior	-0.07	0.12	-0.02	0.00	**0.80**
Cold pressor test: hand withdrawal time	0.37	0.30	0.16	0.21	0.18

Table 5. Results from factor analysis of the Varimax rotation, with the five factors corresponding to pressure, heat, cold, electrical stimulation and reflex receptive fields, as observed in 300 pain free subjects stratified by age

Males (n=152)	*Factor 1: Pressure*	*Factor 2: Heat*	*Factor 3: Cold*	*Factor 4: Electrical stimulation*	*Factor 5: Reflex receptive fields*
Pressure pain detection toe	**0.67**	0.11	-0.04	0.04	0.27
Pressure pain tolerance toe	**0.57**	0.23	0.22	-0.03	0.21
Pressure pain detection low back	**0.77**	0.08	-0.19	0.00	0.13
Pressure pain tolerance low back	**0.83**	0.24	0.15	0.03	-0.07
Pressure pain detection suprascapular	**0.67**	0.01	-0.44	0.06	-0.11
Pressure pain tolerance suprascapular	**0.72**	0.22	-0.03	-0.06	-0.24
Heat pain detection leg	0.27	0.41	-0.08	-0.13	0.34
Heat pain detection low back	0.20	**0.73**	-0.27	0.06	0.17
Heat pain tolerance low back	0.13	**0.73**	0.06	0.13	-0.07
Heat pain detection suprascapular	0.18	**0.68**	-0.14	0.02	0.26
Heat pain tolerance suprascapular	0.15	**0.81**	0.22	0.00	0.02
Cold pain detection leg	-0.05	-0.11	**0.62**	0.08	0.15
Cold pain detection low back	-0.08	-0.03	**0.71**	-0.05	0.03
Cold pain suprascapular	-0.01	0.05	**0.84**	-0.06	0.20
Electrical single stimulation pain detection	-0.01	-0.04	-0.18	**0.83**	-0.09
Electrical single stimulation reflex threshold	0.05	0.05	0.00	**0.78**	-0.03
Electrical repeated stimulation reflex threshold	-0.01	0.15	0.14	**0.76**	-0.01
Reflex receptive field area tibialis anterior	0.32	0.14	0.16	-0.10	**0.79**
Reflex receptive field volume tibialis anterior	-0.06	0.05	0.17	-0.04	**0.79**
Cold pressor test: hand withdrawal time	0.24	0.23	0.30	0.03	0.03
Females (n=148)					
Pressure pain detection toe	**0.65**	0.16	0.25	0.14	0.28
Pressure pain tolerance toe	**0.62**	0.18	0.24	0.15	0.32
Pressure pain detection low back	**0.71**	-0.04	-0.18	-0.06	-0.32
Pressure pain tolerance low back	**0.86**	0.09	-0.08	0.01	-0.10
Pressure pain detection suprascapular	**0.57**	-0.13	-0.50	-0.05	-0.37
Pressure pain tolerance suprascapular	**0.74**	0.09	-0.25	0.07	-0.22
Heat pain detection leg	0.14	**0.67**	-0.05	0.00	0.00
Heat pain detection low back	-0.05	**0.73**	-0.24	0.02	0.03
Heat pain tolerance low back	0.15	**0.71**	-0.09	0.07	0.04
Heat pain detection suprascapular	0.05	**0.80**	-0.17	-0.70	0.11
Heat pain tolerance suprascapular	0.11	**0.69**	-0.05	0.01	0.10
Cold pain detection leg	-0.08	-0.12	**0.80**	-0.08	-0.10
Cold pain detection low back	-0.05	-0.24	**0.75**	-0.10	0.00
Cold pain suprascapular	-0.05	-0.12	**0.87**	-0.07	0.06
Electrical single stimulation pain detection	0.06	-0.14	-0.27	**0.76**	-0.12
Electrical single stimulation reflex threshold	0.09	0.03	-0.02	**0.81**	-0.21
Electrical repeated stimulation reflex threshold	-0.05	0.10	0.00	**0.74**	-0.02
Reflex receptive field area tibialis anterior	-0.10	0.10	0.02	-0.11	**0.80**
Reflex receptive field volume tibialis anterior	-0.16	0.06	-0.04	-0.26	**0.79**
Cold pressor test: hand withdrawal time	0.38	0.26	0.10	0.28	0.05

Table 6. Results from factor analysis of the Varimax rotation, with the five factors corresponding to pressure, heat, cold, electrical stimulation and reflex receptive fields, as observed in 300 pain free subjects stratified by gender

Figure 3 presents scatter plots and corresponding Pearson's correlation coefficients between the five factors. Graphical inspection of plots did not suggest any correlation between the five factors and corresponding correlations were near null (median 0.02, range -0.04 to 0.05).

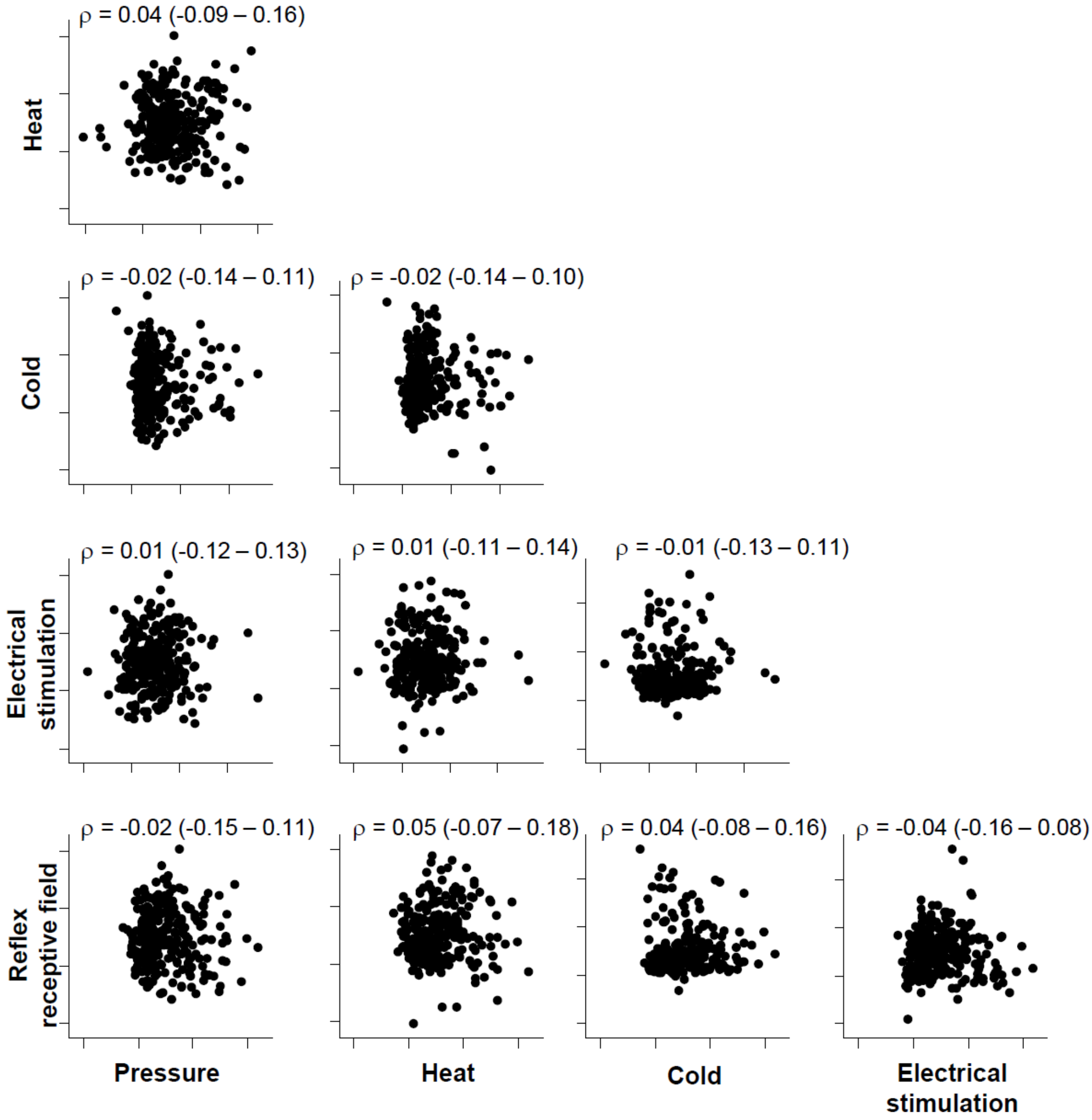


Figure 3. Correlation between different factors, i.e. pain modalities (Pearson's ρ with 95% confidence Interval)

Figure 4 presents scatter plots stratified according to age (left) and gender (right). Again, correlations between factors were near null in younger (median 0.01, range -0.06 to 0.16) and older subjects (median -0.02, range -0.21 to 0.08), in men (median -0.03, range -0.21 to 006) and women (median 0.04, range -0.02 to 0.17).

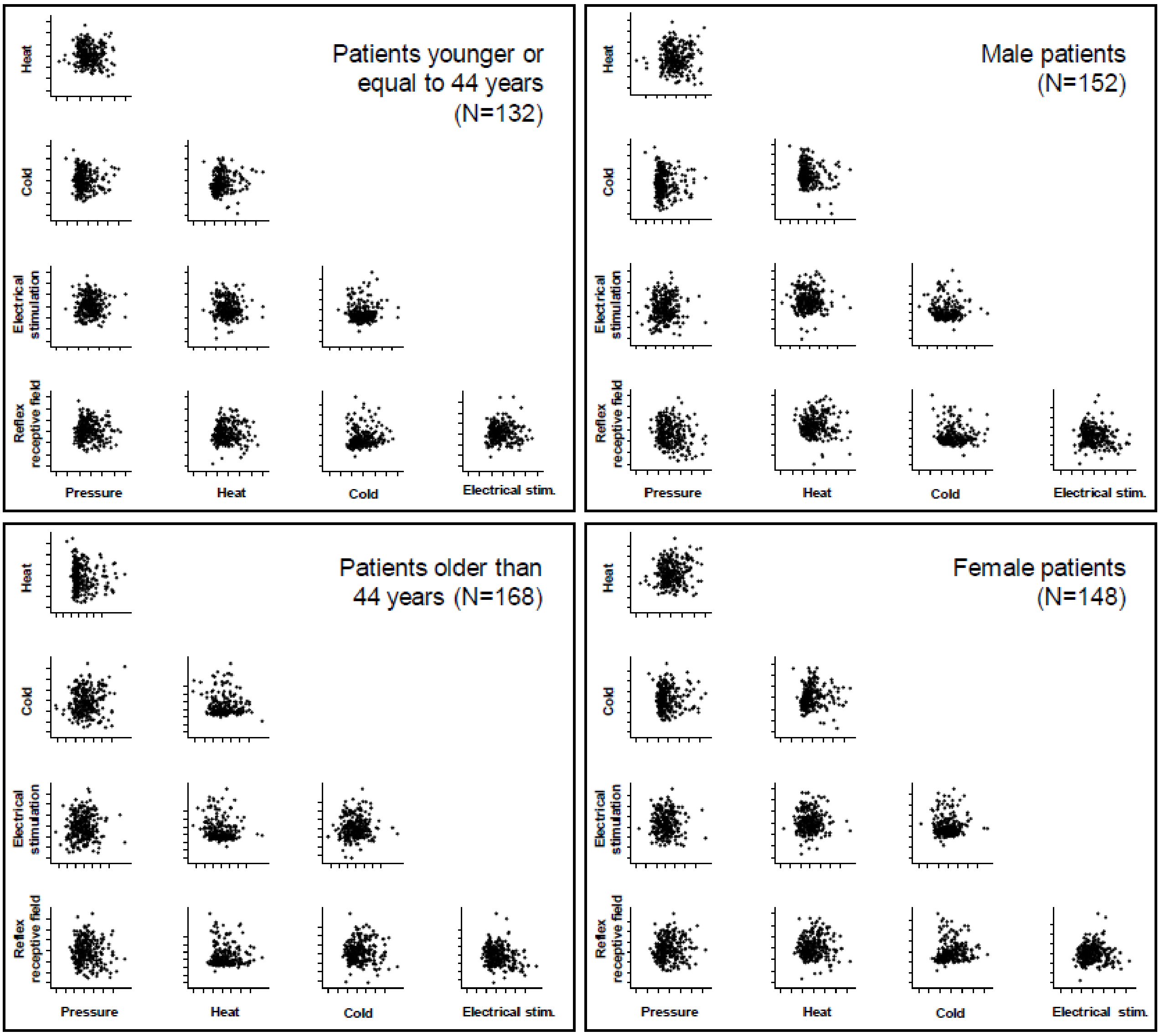
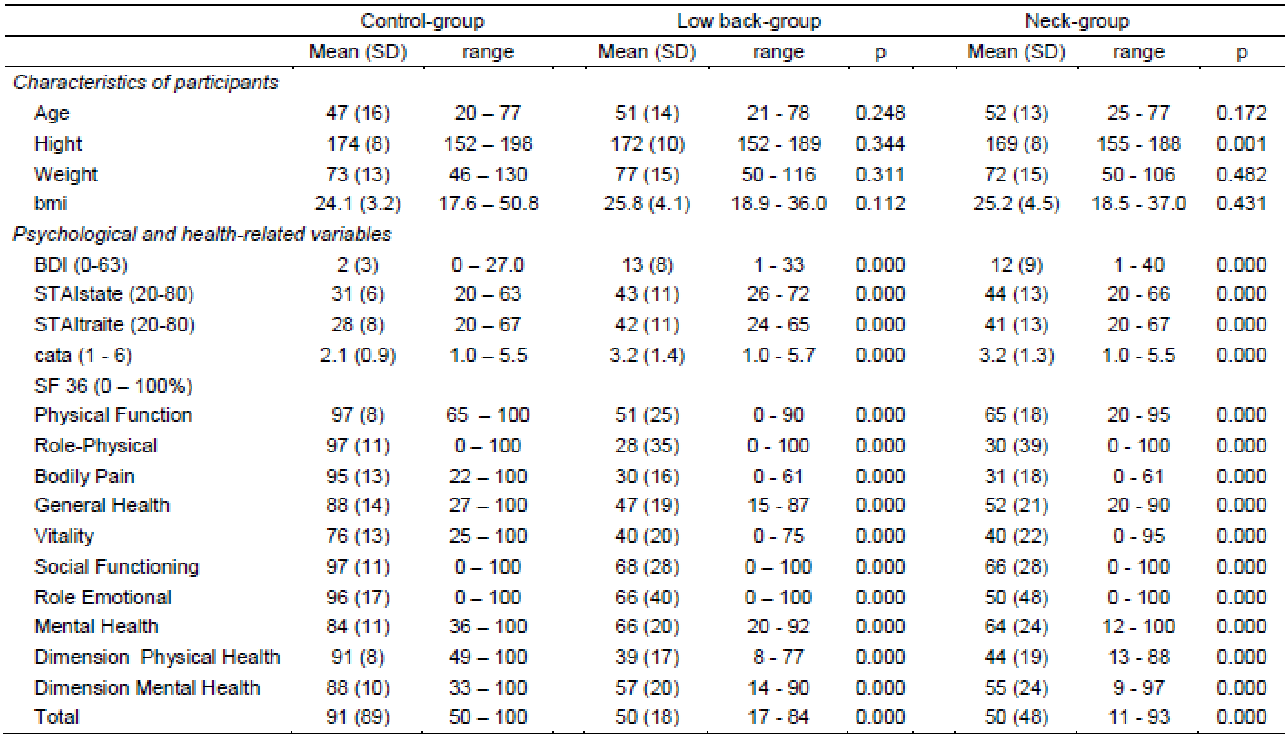


Figure 4. Correlation between different factors, i.e. pain modalities stratified by age and gender.

3.2. EVIDENCE OF CENTRAL HYPERSENSITIVITY IN CHRONIC PAIN PATIENTS (STUDIES II - III)

3.2.1. CHARACTERISTICS OF INCLUDED PARTICIPANTS, PSYCHOLOGICAL AND HEALTH-RELATED VARIABLES

The descriptive variables in the two groups of patients and controls are presented in Table 7. Compared with the pain-free subjects, the groups of patients displayed higher scores for depression, anxiety and catastrophizing, as well as lower scores of SF-36 parameters. This was expected and is consistent with findings of previous studies on chronic pain patients (Banic et al., 2004; Herren-Gerber et al., 2004; Laursen et al., 2005). The two groups were comparable for all the other descriptive variables.



	Control-group		Low back-group			Neck-group		
	Mean (SD)	range	Mean (SD)	range	p	Mean (SD)	range	p
Characteristics of participants								
Age	47 (16)	20 – 77	51 (14)	21 - 78	0.248	52 (13)	25 - 77	0.172
Hight	174 (8)	152 – 198	172 (10)	152 - 189	0.344	169 (8)	155 - 188	0.001
Weight	73 (13)	46 – 130	77 (15)	50 - 116	0.311	72 (15)	50 - 106	0.482
bmi	24.1 (3.2)	17.6 – 50.8	25.8 (4.1)	18.9 - 36.0	0.112	25.2 (4.5)	18.5 - 37.0	0.431
Psychological and health-related variables								
BDI (0-63)	2 (3)	0 – 27.0	13 (8)	1 - 33	0.000	12 (9)	1 - 40	0.000
STAIstate (20-80)	31 (6)	20 – 63	43 (11)	26 - 72	0.000	44 (13)	20 - 66	0.000
STAItraite (20-80)	28 (8)	20 – 67	42 (11)	24 - 65	0.000	41 (13)	20 - 67	0.000
cata (1 - 6)	2.1 (0.9)	1.0 – 5.5	3.2 (1.4)	1.0 - 5.7	0.000	3.2 (1.3)	1.0 - 5.5	0.000
SF 36 (0 – 100%)								
Physical Function	97 (8)	65 – 100	51 (25)	0 - 90	0.000	65 (18)	20 - 95	0.000
Role-Physical	97 (11)	0 – 100	28 (35)	0 - 100	0.000	30 (39)	0 - 100	0.000
Bodily Pain	95 (13)	22 – 100	30 (16)	0 - 61	0.000	31 (18)	0 - 61	0.000
General Health	88 (14)	27 – 100	47 (19)	15 - 87	0.000	52 (21)	20 - 90	0.000
Vitality	76 (13)	25 – 100	40 (20)	0 - 75	0.000	40 (22)	0 - 95	0.000
Social Functioning	97 (11)	0 – 100	68 (28)	0 – 100	0.000	66 (28)	0 - 100	0.000
Role Emotional	96 (17)	0 – 100	66 (40)	0 – 100	0.000	50 (48)	0 - 100	0.000
Mental Health	84 (11)	36 – 100	66 (20)	20 - 92	0.000	64 (24)	12 - 100	0.000
Dimension Physical Health	91 (8)	49 – 100	39 (17)	8 - 77	0.000	44 (19)	13 - 88	0.000
Dimension Mental Health	88 (10)	33 – 100	57 (20)	14 - 90	0.000	55 (24)	9 - 97	0.000
Total	91 (89)	50 – 100	50 (18)	17 - 84	0.000	50 (48)	11 - 93	0.000

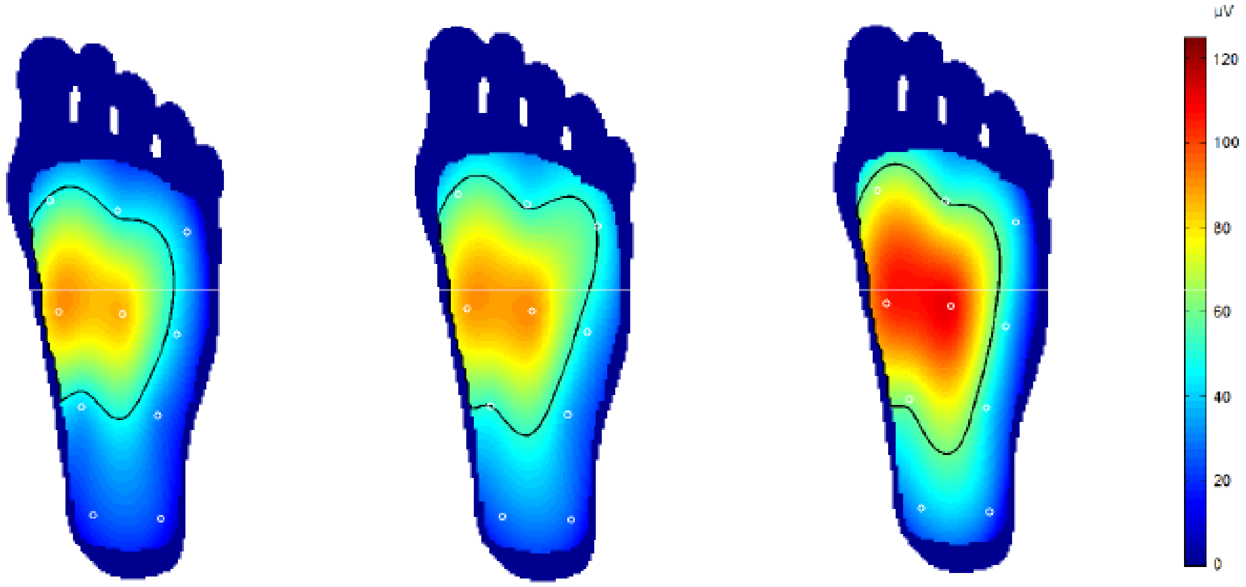
Table 7. Demographical, psychological and health-related variables. BMI: body-mass index. BDI: Beck Depression Inventory. STAI: State Trait Anxiety Inventory. CSQ: Coping Strategies Questionnaire. SF: short-form.

3.2.2. Results of electrical, mechanical and thermal pain thresholds and Reflex receptive fields in chronic pain patients

Patients with chronic low back pain and chronic neck pain were characterized by larger RRF areas than pain-free subjects. This is reflected by the enlargement of the area of the foot sole from which a nociceptive reflex in the tibialis anterior muscle can be elicited (black line of Figure 5). Furthermore, the reflex amplitude was higher in patients than in pain-free subjects, as shown in the colour map of Figure 5.

The subjective pain threshold and the threshold to evoke a nociceptive reflex after a single electrical stimulus were lower in patients, compared to the pain-free subjects (Table 8). The same was observed with repeated electrical stimulation evoking temporal summation: both the threshold to induce the subjective feeling of increasing pain sensation and the threshold that evokes a nociceptive reflex during repeated stimulation were lower in patients, compared to the pain-free subjects (Table 8).

Furthermore, patients were characterized by lower pressure pain detection and tolerance thresholds, and with lower heat pain detection thresholds than pain-free subjects.



Pain-free
Mean (SD) 0.33 (0.17)

Chronic low back pain
Mean (SD) 0.39 (0.21)
P=0.042

Chronic neck pain
Mean (SD) 0.42 (0.16)
P=0.004

Figure 5. Mean reflex receptive fields (RRF) for controls (left), chronic low back pain (middle) and chronic neck pain patients (right). The white dots indicate the stimulation sites. The black line represents the contour of the RRF area. The colours indicate the reflex amplitude.

	Control-group		Low back-group			Neck-group		
	Mean (SD)	range	Mean (SD)	range	p	Mean (SD)	range	p
Pressure pain stimulation (kPa)								
Pressure pain detection - toe	214 (95)	83 - 686	159 (94)	41 - 465	0.001	200 (86)	69 - 407	0.451
Pressure pain tolerance - toe	483 (177)	120 - 1000	415 (174)	157 - 823	0.029	469 (183)	119 - 879	0.690
Pressure pain detection - site of most severe pain	---	---	176 (124)	18 - 673	0.000	107 (111)	0 - 525	0.000
Pressure pain tolerance - site of most severe pain	---	---	475 (265)	102 - 1000	0.000	314 (281)	4 - 1000	0.000
Pressure pain detection - low back	352(131)	80 - 1000	253 (128)	71 - 595	0.000	324 (158)	111 - 739	0.302
Pressure pain tolerance - low back	729 (200)	206 - 1000	587 (259)	227 - 1000	0.000	654 (247)	226 - 1000	0.066
Pressure pain detection - suprascapular	302 (103)	107 - 801	188 (105)	65 - 418	0.000	210 (119)	46 - 540	0.000
Pressure pain tolerance - suprascapular	790 (112)	253 - 1000	554 (258)	200 - 1000	0.038	503 (267)	138 - 1000	0.001
Heat pain stimulation (°C)								
Heat pain detection – leg	43.0 (2.6)	36.2 - 50.5	44.0 (3.6)	36.8 - 50.0	0.033	44.3 (3.3)	36.9 - 50.1	0.013
Heat pain tolerance – leg	49.4 (1.2)	44.7 - 50.5	49.4 (3.7)	28.0 - 50.5	0.895	49.8 (1.3)	44.3 - 50.5	0.071
Heat pain detection - site of most severe pain	---	---	39.6 (3.0)	33.0 - 45.9	0.011	40.9 (3.5)	34.0 - 49.0	0.186
Heat pain tolerance - site of most severe pain	---	---	47.5 (2.7)	40.2 - 50.5	0.286	47.8 (2.4)	42.7 - 50.5	0.507
Heat pain detection - low back	40.7 (2.2)	34.0 - 50.5	39.8 (2.8)	34.7 - 46.7	0.047	40.8 (3.5)	35.5 - 49.3	0.740
Heat pain tolerance - low back	47.9 (1.8)	39.3 - 50.5	47.7 (2.4)	41.6 - 50.5	0.582	47.8 (2.0)	42.7 - 50.5	0.808
Heat pain detection - suprascapular	40.3 (2.1)	34.8 - 49.9	41.0 (3.1)	36.4 - 47.5	0.120	41.4 (3.6)	35.5 - 49.5	0.020
Heat pain tolerance - suprascapular	47.6 (1.6)	39.0 - 50.5	48.3 (2.5)	40.0 - 50.5	0.024	48.7 (1.7)	44.3 - 50.5	0.001
Cold pain stimulation (°C)								
Cold pain detection – leg	2.2 (6.0)	0.0 - 26.2	5.0 (8.4)	0.0 - 25.6	0.014	10.5 (10.9)	0.0 - 28.0	0.000
Cold pain detection - site of most severe pain	---	---	10.3 (9.8)	0.0 - 25.4	0.000	12.2 - 10.7	0.0 - 28.3	0.000
Cold pain detection - low back	3.3 (6.5)	0.0 - 28.2	10.6 (10.9)	0.0 - 26.3	0.000	9.9 (10.7)	0.0 - 28.2	0.000
Cold pain detection - suprascapular	4.3 (6.7)	0.0 - 25.8	10.3 (10.0)	0.0 - 27.2	0.000	11.9 (27.5)	0.0 - 27.6	0.000
Cold water test - pressor test								
Hand withdrawal time (seconds)	37 (22)	7 - 120	50 (35)	8 - 120	0.03	45 (37)	7 - 120	0.023
Electrical stimulation and withdrawal nociceptive reflex								
Single stimulation pain detection (mA)	10.8 (2.5)	5.0 - 26.0	7.2 (2.6)	3.0 - 14.0	0.000	7.2 (2.3)	5.0 - 15.0	0.000
Single stimulation reflex threshold (mA)	16.2 (3.7)	5.3 - 31.3	11.0 (4.3)	3.7 - 21.0	0.000	10.4 (3.4)	5.3 - 19.0	0.000
Repeated stimulation pain detection (mA)	8.5 (2.2)	4.0 - 20.7	6.2 (2.2)	3.0 - 14.0	0.000	5.6 (2.0)	2.0 - 11.3	0.000
Repeated stimulation reflex threshold (mA)	8.5 (2.2)	4.0 - 20.8	7.1 (2.5)	3.0 - 14.3	0.000	6.2 (2.3)	2.3 - 11.0	0.000
RRF area (proportion)	0.33 (0.17)	0.04 - 0.77	0.39 (0.21)	0.03 - 0.81	0.042	0.42 (0.16)	0.10 - 0.81	0.004
RRF volume (μV*mm²)	0.26 (0.31)	0.00 - 1.62	0.27 (0.25)	0.02 - 1.00	0.864	0.36 (0.33)	0.01 - 1.17	0.097

Table 8. Pressure pain, thermal pain (heat and cold), area and volume of RRF and thresholds after single and repeated (temporal summation) electrical stimulation.

4. DISCUSSION

4.1. FACTOR ANALYSIS SUPPORTS MULTIMODAL APPROACH OF PAIN ASSESSMENT (STUDY I)

In this analysis of 300 consecutive healthy volunteers, we found five clearly distinct dimensions of responses to five distinct experimental pain modalities. Each of the dimensions explained approximately 10 to 20% of the observed variance, and the five factors cumulatively explained about 90% of the variance. The correlation between the five dimensions was essentially null, with 95% confidence intervals for the pairwise correlation between two dimensions excluding any relevant correlation. Taken together, this indicates that attempts to simplify current multi-modal approaches of pain assessment are unjustified.

To my knowledge, this is the largest study addressing the interrelation between responses to different experimental pain stimuli. It was performed in unselected, consecutive healthy volunteers by a single assessor according to a standardised protocol. Different accepted experimental pain modalities were employed in view of their potential usefulness in future observational studies and clinical trials. In addition to these strengths, the study has also some limitations. Even though the study is based on recruitment of consecutive volunteers, the recruitment strategy will not result in a population-based sample. Therefore, results may not be fully generalisable to the general population. Located in Switzerland, the study only included individuals of Caucasian origin and cannot be generalised to individuals of other ethnicity. Furthermore, it is unclear whether these results on pain-free subjects apply to patients with pain.

Neddermeyer et al recently suggested that responses to different experimental pain modalities were correlated and that the variance was attributable more to the difference in subjects than to the difference in responses to different pain stimuli. They concluded that characterizing a person as being generally stoical or complaining about any painful stimulus appears to be justified (Neddermeyer et al., 2008). Our results are essentially in opposition to those of Neddermeyer et al., but fully concordant with several other studies (Lautenbacher and Rollman, 1993; Janal et al., 1994; Lautenbacher et al., 1994; Hastie et al., 2005). Albeit smaller than ours, these studies all suggested the multi-modal approaches used in contemporary pain research to be useful. Why are results of Neddermeyer et al at odds with ours and earlier studies? Explanations may include chance or bias. A partial explanation, however, which deserves attention is that the principal component analysis used by Neddermeyer et al (Neddermeyer et al., 2008) is bound to assign most of explained variance to the first factor identified in the analysis. We avoided this by using varimax rotation after the initial principal factor analysis and unsurprisingly found the percentage of explained variance to be rather equally distributed between the five identified factors.

When determining the correlation between the five different factors identified in our analysis, we found correlations near null, which suggested that the five factors represent five distinct dimensions of pain perception, which are directed orthogonally to each other. From a mechanistic point of view, this may be sensible. The response to pressure, for example, is mainly mediated by C-fibers (Cline et al., 1989; Culp et al., 1989; Koltzenburg et al., 1992; Liu et al., 1995; Kiso et al., 2001), whereas pain as a response to electrical stimuli is mediated also by Aδ fibers (Schady et al., 1983; LaMotte et al., 1991; McAllister et al., 1995; Ziegler et al., 1999). Heat evokes pain through a stimulation of vanilloid receptor-1 (TRPV1) (Caterina et al., 1997; Davis et al., 2000), whereas cold induced pain is associated with a stimulation of the transient receptor potential cation-channels TRPM8 (McKemy et al., 2002; Peier et al., 2002; Colburn et al., 2007) or TRPA1 (Story et al., 2003). The mechanisms that underlie the different responses to different pain modalities remain only partially understood.

4.1.1. CONCLUSIONS (STUDY I)

Our current understanding of the different dimensions of pain assessment is still incomplete. Our study indicates that any attempt to characterise a person as generally stoical or complaining as recently suggested (Neddermeyer et al., 2008) is an undue simplification. Responses to different experimental pain modalities represent different pathways and should be assessed in combination in future clinical and pharmacological studies. This will further increase our understanding of the complexity of mechanisms leading to chronic or acute pain and its modification in experimental settings and clinical practice.

4.2 INCREASED PAIN SENSITIVITY TO MECHANICAL AND THERMAL PAIN STIMULI IN CHRONIC PAIN PATIENTS (STUDIES II-III)

Patients with chronic low back pain and chronic neck pain were characterized by lower pressure pain detection and tolerance thresholds, and with lower heat and cold pain detection thresholds than pain-free subjects (Table 8), demonstrating exaggerated pain responses following sensory stimulation of healthy tissues, in accordance with previous studies on chronic pain patients (Sheather-Reid and Cohen, 1998; Sorensen et al., 1998; Koelbaek Johansen et al., 1999; Curatolo et al., 2001; Staud et al., 2001; Moog et al., 2002; Price et al., 2002; Maquet et al., 2004; Rolke et al., 2006; Farasyn et al., 2008). However, the analyses of psychological parameters should be seen under the consideration that the studies are not yet completed, and the results may change to some degree after recruiting all subjects needed to reach statistical power of the study.

4.3 EXPANSION OF REFLEX RECEPTIVE FIELDS IN CHRONIC PAIN PATIENTS (STUDIES II-III)

Previous animal and human studies using the withdrawal reflex paradigm indicated that the reflex is organized in a modular fashion: each muscle or synergistic muscle group has a well-defined cutanous receptive field, the reflex receptive field (RRF) (Schouenborg and Kalliomaki, 1990; Andersen et al., 1999). Nociceptive input applied to that area evokes a withdrawal reflex in the muscle, while stimulation outside the area has no effect (Sonnenborg et al., 2000). The reflex receptive field is probably encoded by wide-dynamic range (WDR) neurons located in the deep dorsal horn (Schouenborg et al., 1995). Receptive field expansion has been demonstrated in WDR projection neurons in this part of the dorsal horn (Dubner, 1991). The present investigation provides evidence that a chronic human pain condition is associated with expansion of nociceptive reflex receptive fields.

4.3.1 NWR AND PAIN THRESHOLDS

The reflex threshold after application of a single electrical stimulus was lower in patients than in controls (see Table 8). Because the site of stimulation is outside the area of pain, this finding indicates that patients display generalized spinal cord hypersensitivity. Accordingly, the reflex threshold after application of repeated electrical stimulation was lower in patients than in controls (see Table 8), indicating generalized facilitated temporal summation. Temporal summation probably reflects neuronal integration processes that can lead to neuronal hyperexcitability (Price, 1972; Arendt-Nielsen et al., 1994). The results on single and repeated electrical stimulation are consistent with observations in chronic neck pain and fibromyalgia patients (Desmeules et al., 2003; Banic et al., 2004).

4.3.2 ENLARGED AREAS OF RRF IN CHRONIC PAIN

The enlarged area of RRF observed (Table 8, Figures 5-6) indicates that such a generalized spinal cord hyperexcitability is associated with an expansion of the nociceptive receptive fields in the spinal cord. This suggests that the modular organization of the pathways responsible for the nociceptive withdrawal reflex may undergo reorganization under pathological conditions.

Expansion of receptive fields following tissue damage has been observed in several animal investigations. For instance, appearance of new receptive fields of spinal cord neurons could be induced by intramuscular injection of bradykinin in rats, suggesting that silent synaptic connections within the spinal cord are activated (Hoheisel et al., 1993). However, this phenomenon has been investigated in regions of the spinal cord that correspond to the site of tissue damage. In contrast, finding in studies II and III demonstrated that expansion of receptive fields occurs at an area far distant from the site of expected tissue damage. To date, animal research provides only indirect support to explain this finding. An early investigation found that blocking descending pathways by cooling the thoracic spinal cord of cats produced expansion of receptive fields at L7 level, suggesting that such widespread expansion of receptive fields may result from changes in descending modulation (Zieglgansberger and Herz, 1971). Later investigations showed that peripheral inflammation can lead to widespread spinal cord hyperexcitability via activation of descending facilitatory pathways that involve the spinal 5-HT3 receptor (Suzuki et al., 2002). Tissue damage has been shown to produce generalized expression of COX-2 in the spinal cord, mediated by the humoral release of inflammatory mediators from the damaged tissue (Samad et al., 2001).

The above data from animal experiments suggest that humoral factors and/or changes in descending modulatory influences may play a role in the widespread expansion of receptive fields observed in the present study. However, the results of human studies on descending modulation are not unequivocal. In a study on healthy volunteers, rapid and slow distension of the rectum induced facilitation and inhibition of the nociceptive reflex, respectively (Bouhassira et al., 1998). The former finding would support the hypothesis that clinical pain arising from visceral structures, in our case from the pelvis, can lead to widespread spinal cord hypersensitivity. On the other hand, inhibition of the nociceptive reflex by slow distension of the rectum indicates that spinal hyperexcitability can undergo heterotopic inhibition via descending modulation.

A well-known method to study endogenous modulation in humans is the assessment of diffuse noxious inhibitory control: under normal conditions, pain after application of a test nociceptive stimulus is attenuated by the application of an additional "conditioning" noxious stimulus to a remote body region, reflecting diffuse endogenous inhibition (Chitour et al., 1982; Ge et al., 2004). A study that applied this model to neuropathic pain patients revealed a complex picture: the effect of conditioning stimuli on spinal nociception depended on the type of stimulus applied and the pathophysiological mechanisms underlying the pain condition (Bouhassira et al., 2003). A study investigating the efficacy of coping skill training in patients with arthritis of the knee found an increase in nociceptive reflex threshold, suggesting that spinal nociceptive reflexes may be influenced by descending modulation (Emery et al., 2006). On the other hand, techniques to induce expectancy-mediated analgesia reduced subjective pain, but not nociceptive reflex thresholds in patients with fibromyalgia (Goffaux et al., 2009).

Noteworthy, the few available human studies have used different methods of assessing descending modulation and have been conducted on patients with different types of pain conditions. This renders the interpretation of the data difficult. Based on the available literature, spinal cord hypersensitivity that leads to generalized expansion of nociceptive receptive fields may be the result of multiple factors, including tissue damage via neural and humoral mediators, as well as influences from higher centres mediated by descending pathways. The present investigation will hopefully stimulate further research on the determinants of this phenomenon in pain patients.

4.3.3 CONCLUSIONS (STUDIES II - III)

Studies on chronic low back pain and chronic neck pain, i.e. studies II and III provided evidence for widespread expansion of spinal nociceptive receptive fields and increased sensitivity to mechanical and thermal stimuli in a human chronic pain condition. This finding contributes to the elucidation of the mechanisms that underlie central hypersensitivity in human chronic pain conditions and may become a target for the development of future therapeutic interventions.

5. SUMMARY

The aims of this doctoral thesis were: 1) to determine whether responses to different pain stimuli are distinct dimensions or highly correlated; 2) to test the hypothesis that patients with chronic pain develop central hypersensitivity, i.e. display lower pain thresholds to electrical, mechanical and thermal stimuli, and 3) to test the hypothesis that patients with chronic pain display enlarged reflex receptive fields compared to pain-free subjects.

In study I, five clearly distinct factors were found representing responses to five distinct experimental pain modalities: pressure, heat, cold, electrical stimulation and reflex receptive fields. Each of the dimensions explained approximately 10 to 20% of the observed variance, and the five factors cumulatively explained about 90% of the variance. The correlation between the five dimensions was essentially null, with 95% confidence intervals for the pairwise correlation between two dimensions excluding any relevant correlation. Correlations were typically high within the same type of stimulus, but low between different types. Taken together, this indicates that attempts to simplify current multi-modal approaches of pain assessment are unjustified. Responses to different experimental pain modalities represent different dimensions and should be assessed in combination in future pharmacological and clinical studies to represent the complexity of nociception and pain experience.

In studies II and III, patients with chronic low back pain displayed a larger area of reflex receptive field, compared with pain-free subjects. This is reflected by the enlargement of the area of the foot sole from which a nociceptive reflex in the tibialis anterior muscle can be elicited. Furthermore, the reflex amplitude was higher in patients than in pain-free subjects. The subjective pain threshold and the threshold to evoke a nociceptive reflex after a single electrical stimulus were lower in patients, compared to the pain-free subjects. The same was observed with repeated electrical stimulation evoking temporal summation: both the threshold to induce the subjective feeling of increasing pain sensation and the threshold that evokes a nociceptive reflex during repeated stimulation were lower in patients, compared to pain-free subjects. Furthermore, patients were characterized by lower pressure pain detection and tolerance thresholds, and by lower heat pain detection thresholds than pain-free subjects.

Studies on chronic low back pain and chronic neck pain, i.e. studies II and III provided evidence for widespread expansion of spinal nociceptive receptive fields and increased sensitivity to mechanical and thermal stimuli in a human chronic pain condition. This finding contributes to the elucidation of the mechanisms that underlie central hypersensitivity in human chronic pain conditions and may become a target for the development of future therapeutic interventions.

6. ZUSAMMENFASSUNG AUF DEUTSCH

Die Ziele dieser Dissertation waren: 1) festzustellen, ob Reaktionen auf verschiedene Schmerzreize verschiedene Dimensionen zeigen oder hoch korreliert sind, 2) die Hypothese zu prüfen, dass Patienten mit chronischen Schmerzen zentrale Überempfindlichkeit entwickeln, d.h. niedrigere Schmerzschwellen auf elektrische, mechanische und thermische Reize zeigen, und 3) die Hypothese zu prüfen, dass Patienten mit chronischen Schmerzen erweiterte Reflex-rezeptive Felder im Vergleich zu schmerzfreien Probanden zeigen.

In der Studie I wurden fünf deutlich unterschiedliche Dimensionen in den Reaktionen auf fünf verschiedene experimentelle Schmerz-Modalitäten gefunden: Druck, Hitze, Kälte, elektrische Stimulation und Reflex-rezeptive Felder. Jede der Dimensionen erklärte etwa 10 bis 20% der beobachteten Varianz, und die fünf Faktoren erklärten zusammen etwa 90% der Varianz. Die Korrelation zwischen den fünf Dimensionen war im Wesentlichen null, mit 95% Vertrauensintervallen für die paarweisen Korrelationen zwischen zwei Dimensionen, die jede relevante Korrelation ausschließen. Die Korrelationen innerhalb der gleichen Reizarten waren typisch hoch, aber niedrig zwischen verschiedenen Arten. Zusammen genommen ergibt sich, dass Versuche, aktuelle multimodale Ansätze der Schmerzbewertung zu vereinfachen, unberechtigt sind. Reaktionen auf verschiedene experimentelle Schmerzmodalitäten stellen verschiedene Dimensionen dar und sollten in zukünftigen pharmakologischen und klinischen Studien kombiniert bewertet werden, um die Komplexität von Nozizeption und Schmerzerfahrung abzubilden.

In den Studien II und III zeigten Patienten mit chronischen Rückenschmerzen vergrößerte Reflex-rezeptive Felder als schmerzfreie Probanden. Dies manifestiert sich in einer Erweiterung des Bereichs der Fußsohle, aus dem ein nozizeptiver Reflex im Musculus tibialis anterior ausgelöst werden kann. Außerdem war die Reflex-Amplitude bei den Patienten höher als bei den schmerzfreien Probanden. Die subjektive Schmerzschwelle und die Schwelle für einen nozizeptiven Reflex nach einem einzigen elektrischen Reiz waren bei Patienten niedriger als bei schmerzfreien Probanden. Derselbe Befund wurde bei wiederholter elektrischer Stimulation erhoben, die temporale Summation verursacht: sowohl die Schwelle, die das subjektive Gefühl einer zunehmenden Schmerzempfindung verursacht, als auch die Schwelle, die einen nozizeptiven Reflex während der wiederholten Stimulation hervorruft, waren niedriger bei Patienten als bei schmerzfreien Probanden. Außerdem halten Patienten niedrigere Druckschmerzwahrnehmungsschwellen und Toleranzschwellen sowie niedrigere Hitzeschmerzwahrnehmungsschwellen als schmerzfreie Probanden.

Die Studien zu chronischen Rückenschmerzen und chronischen Nackenschmerzen, d.h. Studien II und III, haben eine Erweiterung der spinalen nozizeptiven rezeptiven Felder und eine erhöhte Empfindlichkeit auf mechanische und thermische Reize bei einem chronischen Schmerzzustand nachgewiesen. Dieser Befund trägt zur Erklärung der Mechanismen bei, die der zentralen Überempfindlichkeit bei chronischen Schmerzzuständen zugrunde liegen, und könnte die Entwicklung von zukünftigen therapeutischen Strategien fördern.

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