The riddle of low back pain:

An exploratory study of Central Sensitization features in primary care

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'Je kunt de wind niet veranderen:

Hoe de zeilen staan, bepaal jezelf voor de volle 100 procent'

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An exploratory study of Central Sensitization features in primary care

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Abbreviations

CFQ	Cognitive Fusion Questionnaire
CPM	Conditioned Pain Modulation
CS	Central Sensitization
CSI	Central Sensitization Inventory
HPT	Heat Pain Threshold
IEQ	Injustice Experience Questionnaire
LBP	Low Back Pain
NRS	Numeric Rating Scale
PCS	Pain Catastrophizing Scale
PIPS	Psychological Inflexibility in Pain Scale
PPT	Pressure Pain Threshold
QBPDS	Quebec Back Pain Disability Scale
QST	Quantitative Sensory Testing
RDQ	Roland Morris Disability Scale
SBT	Start Back screening Tool
TS	Temporal Summation
TSK	Tampa Scale for Kinesiophobia
VAS	Visual Analogue Scale

General introduction

General introduction

Low back pain (LBP) is the most common and biggest health problem in primary care physiotherapy practices in the Netherlands and is defined as "pain and discomfort, localized below the costal margin and above the inferior gluteal folds, with or without referred leg pain".(1, 2) According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".(3) LBP can be divided into three categories: specific spinal pathology, nerve root pain/radicular pain and non-specific LBP.(2, 4) The most common category is non-specific LBP which represents LBP that is not attributable to a known recognized specific pathology (like fracture, tumor, infections, osteoporosis, inflammatory disorders and structural deformity).(2, 4, 5) The incidence of LBP is 20% in the Dutch population.(4) Globally the prevalence of LBP is 540 million people who experience limitations in their daily activities.(6) Indeed, LBP entails high health and economic costs and personal burden.(5, 6) People may be restricted in their daily activities and their pain also affects their social participation. They worry about the social consequences of their (chronic) LBP, loss of jobs, lack of money and they experience family strain and disappointment with health care.(6) This may result in a reduced level of health satisfaction.(7) Most of the time LBP arises suddenly or starts slowly without any obvious apparent cause. People with LBP often recover within six weeks but there are people (42-75%) who still experience LBP after twelve months.(4, 8, 9)

According to the IASP, pain has a sensory and an emotional component, which makes (low back) pain complex.(3) The sensory component can be divided into three types of pain: nociceptive, neuropathic and central sensitization pain.(10) Nociceptive pain originates from activation of nociceptors. Pain arises, if there is actual or threatened tissue damage. If there are noxious chemical, thermal or mechanical stimuli, peripheral receptive terminals of primary afferents neurons will be activated, which may cause a pain sensation.(10) Neuropathic pain occurs when the somatosensory nervous system is involved in a primary lesion or disease such as radiculopathy.(10) Central sensitization (CS) pain is defined as "an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity".(11) Neurophysiological features of CS are: enhanced ascending nociceptive facilitation, dysfunctional endogenous analgesia and increased brain activity in a combination of brain regions known as the dynamic pain connectome.(12, 13) In clinical practice a single type of pain might be present, however sometimes there will be an overlap between different types of pain with one being predominantly present.(10) Pain can also be classified according to its duration: between 0 - <6 weeks it is called "acute pain", 6 - <12 weeks "subacute pain" and pain ≥ 12 weeks "chronic pain".(14)

Biopsychosocial components of low back pain

LBP is a multifactorial health problem involving a biological, psychological and social component.(13, 15, 16) The biopsychosocial model is useful to unravel the complexity of LBP (Figure 1). Let us suppose a person suffers from LBP caused by mechanical spinal loading related to (repeated) activities such as work, sports and daily activities. The person will exhibit appropriate behavior in order to avoid the pain; pain-related functional behavior (psychological component). This can have physical consequences such as hypertonia of trunk musculature, slower and stiffer spinal movements (biological component).(17) This pain-related functional behavior may be controlled from pain-related fear and/or distress (psychological component).(17) Evidence reveals that pain processes can be influenced by psychological factors such as emotional and cognitive factors.(6, 17) Emotional factors reflect the feeling of a person which arises from underlying pain cognitions. One example of such an emotional factor is fear. Fear could arise from beliefs regarding tissue damage. Fear has a negative

influence on pain in situations such as increased level of anger, frustration and perceived injustice.(17) Cognitive factors reflect the thoughts about a person's pain. This can also have negative influences on pain: pain catastrophizing or hypervigilance may be a consequence (psychological component).(17, 18) Social factors like historical and contextual social factors (e.g. socio-economic status, educational level or family history of disabling LBP) may affect the way people handle their LBP (social component).(17) In addition, sleep disturbance can develop if people experience high pain intensity. Smoking, sleep disturbance and/or sedentary behavior, summarized as 'lifestyle factors', also have negative influences on LBP (psychological component).(17, 19) These factors can result in symptoms such as generalized hypersensitivity (hyperalgesia and/or allodynia), widespread pain, higher pain intensity, lower quality of life, decreased pain thresholds and worse prognosis for recovery.(20, 21)

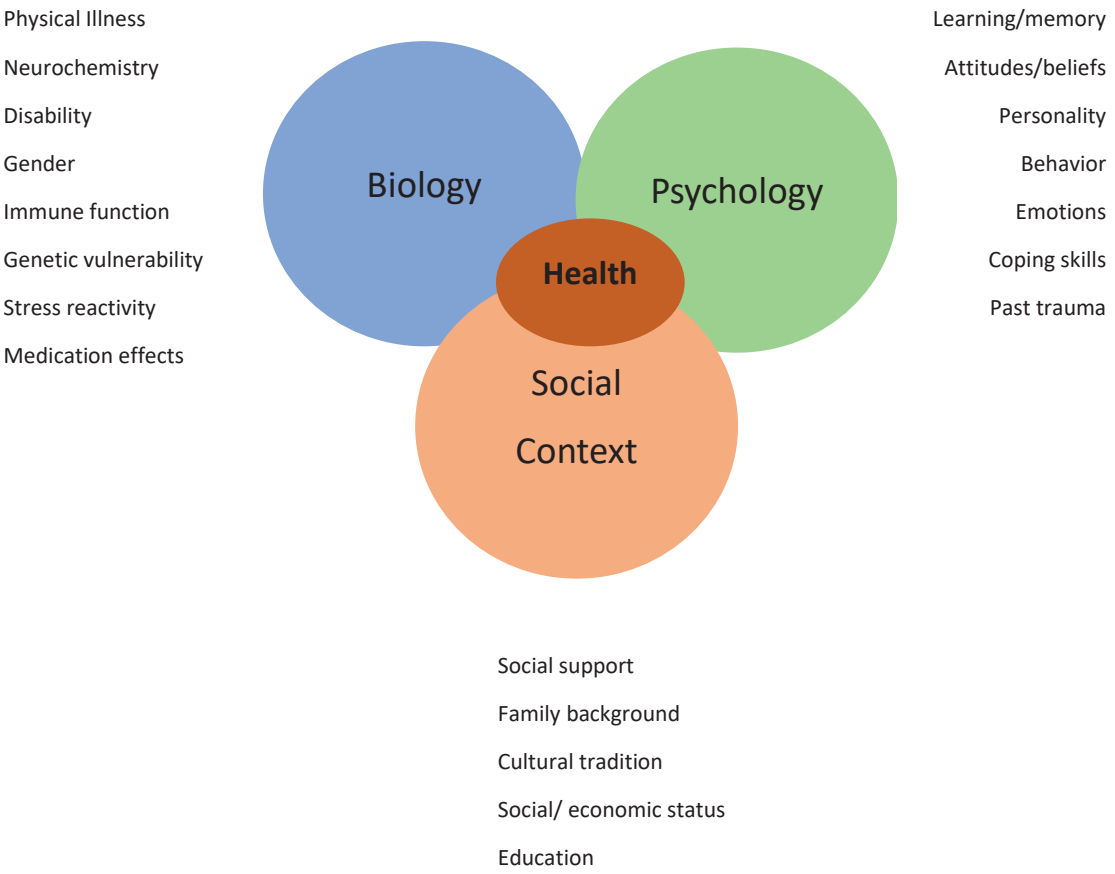

Figure 1: Biopsychosocial model

These signs and symptoms are characteristics of CS.(21) In recent years the term "Central Sensitization" was subjected to a process of development. This term was first used when increased spinal cord excitability was seen in rats due to peripheral nociceptive input from tissue damage or stimulation of C-fiber nociceptors.(22) Nowadays this term is commonly used although sometimes erroneously. It is applied by clinicians and scientists, the latter approaching the term

neurophysiologically.(23) Clinicians use the term CS to explain unexpected symptoms and signs such as increased pain sensitivity and widespread pain to themselves while Woolf used the term CS purely in a neurophysiological sense.(24) This has led to a certain friction between the scientists and the clinicians as to the meaning of the term CS. The definition of CS according to the IASP is "an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input".(3) From a clinical practice perspective there was a need to have a nomenclature for that group of people who had pain without nociception or neuropathy being responsible for the experienced pain (idiopathic pain or "pain of unknown origin").(25) This group of people experience chronic pain with regional and diffuse pain and is often combined with lack of sleep, fatigue, difficulties with mood and memories. They may also be sensitive to non-nociceptive stimuli such as sound and light.(26) Following various redefinitions and critical opinions a new term for CS pain in clinical practice has been proposed by the IASP: 'nociplastic pain'. According to the IASP nociplastic pain is defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain".(3) Kosek et al. (2021) emphasize that the term 'nociplastic pain' is not a synonym for the term CS. Nociplastic pain is intended for use by both clinicians and scientists by referring to people with pain and hypersensitivity who do not have neuropathy and have normal intact tissue. The neurophysiological CS is likely to be the dominant pain mechanism in nociplastic pain.(27)

People who experience chronic (LBP) pain often fight their pain which takes a lot of effort.(28) It includes emotions, images, memories, physical sensations and thoughts about their pain. This sometimes leads to avoiding other people and/or physical activity, engaging in excessive thoughts of pain, endlessly seeking information, and constantly checking for bodily sensations changes. This behavioural pattern is revealed to reduce physical and emotional discomfort and to seek relief and has been called "psychological inflexibility" or "destructive experiential avoidance".(28) It is natural to try to stop the pain, but in this way it is counterproductive and unsuccessful. Sometimes people live *with* or *in* their pain in such a way that they can no longer distinguish reality from imaginations. These people can no longer renounce their thoughts and become entangled in them. They will avoid situations that they feel are painful for them. They do not wonder how realistic these thoughts are. This is called 'cognitive fusion'.(28) For people with chronic (LBP) pain it is more important that they learn to pursue their own goals instead of reducing pain by avoiding several kinds of situations and activities.

Through Acceptance and Commitment Therapy (ACT) people learn to achieve their goals by increasing psychological flexibility.(28) Psychological flexibility is defined as "the capacity to persist or to change behaviour, including conscious and open contact with discomfort and other discouraging experiences, guided by goals and values".(28) For an increase of psychological flexibility the person must be able to change several psychological processes: behavior commitments/committed action, values, self as context, being present, cognitive defusion and acceptance.(29) With *committed action* the person is able to continuously adjust his behaviour to ultimately achieve an effective and flexible behaviour linked to his value.(29) *Values* are personal and lead to actions. The values provide direction, meaning and purpose to those actions. It is important for a person to pursue his values. This can be frightening, but clarifying the person's values can ultimately lead to that person being able to perform their action without avoiding the fear.(29) *Self as context* is based on self-evaluations: it is what we think we are. For example, a person labels himself as "depressed" in a particular situation and behaves accordingly. With self as context the idea is for a person to feel internal and external experiences separately and not label them together. If the person manages to do this, he will stay focused on himself and how he feels is not context dependent.(29) When a person is "*being present*" the focus is on the present rather

than on past or future events. A person can be “being present” if he focuses on internal and external events without any judgement. “Being present” helps the person to experience his world as it really is. Worrying is an example of a person not being in contact with the present, and instead being preoccupied with past or future events.(29) *Cognitive defusion* is the ability to distance yourself from thoughts. It is important to realize that thoughts can be good or bad counsellors which should not be automatically obeyed. Thoughts such as “I cannot, I do not deserve or I do not dare” do not help the people. They demotivate and are accusatory towards the person.(29) *Acceptance* is embracing emotions, impulses or thoughts instead of avoiding or repressing them. Acceptance is applied to internal emotions such as feelings that lead to avoidance. When these feelings have negative effects on someone’s functioning, an attempt will be made to allow these feelings in such a way that repression or avoidance is not necessary any more (acceptance).(29) The methods of treatment include mindfulness-related exercises, metaphor, paradox and exposure-based methods, together aiming at improved daily functioning.(28)

These kind of psychological components in combination with biological components involve many brain regions. Several studies show increased activation in these areas when nociceptors were stimulated.(12, 30) The nociceptive stimuli can be modulated by the different brain regions via ascending pathways from peripheral to central resulting in increased activity of nociceptive facilitatory pathways and/or decreased inhibitory mechanisms.(10) Research has shown that when nociceptors’ activity continue, this generates changes in the neuroplasticity of both central en peripheral sensory systems as well as in the emotional and motivational centers resulting in altered processing of (noxious) stimuli.(31) It is hypothesized that the emotional factors influence the various brain regions modulating the sensory system. A longitudinal study shows changes in both psychological factors measured by various questionnaires and by sensory measurements when patients with acute LBP transit into persistent LBP.(32)

Quantitative Sensory Testing

To investigate an increased responsiveness of nociceptive neurons in the central nervous system, related to symptoms of CS, Quantitative Sensory Testing (QST) is an appropriate tool. It is a psychophysical test method often used for examining the entire sensory system. (33, 34) QST has its origin in animal experiments and many studies have shown that QST can also be applied to humans.(35) This method is now commonly used in clinical neurological research.(33) There is also a shift in which study population QST-measurements are used. This method is also applied to people with musculoskeletal pain, as chronic pain and neuropathic pain have common characteristics.(36) The QST evaluates the thick myelinated Aβ-fibers, thin myelinated Aδ-fibers and unmyelinated C-fibers in their functioning (increase or decrease) and their pathways to the brain. The subjective perception thresholds are measured by means of calibrated stimuli.(33) The type of stimulus is dependent on the type of nerve fiber. For example, a heat stimulus stimulates the C and Aδ-fibers. Beside the thermal stimulus, QST involves several stimulus modalities such as mechanical and electrical stimuli.(35, 37) QST can be carried out in a static and in a dynamic way: applying a test stimulus only (static) or applying a test stimulus repeatedly (temporal summation (TS)) or in combination with a conditioning stimulus (conditioned pain modulation (CPM)) (dynamic). The first method is used to determine (pain, detection, tolerance) thresholds and provides information about (pain) sensitivity.(35, 38) A limitation of static QST-measurements is that it provides limited information about a complex neurophysiological process. To reduce this limitation, dynamic QST-measurements are performed. This second method tests central modulation and ascending and descending control.(36) The interpretation of the QST-measurements are based on comparisons between affected and unaffected body parts or

between patients and pain-free populations. They serve as “normative data” during experiments.(37) If the pain threshold is reduced in the affected area (local site) compared to the pain-free population, we may assume there is peripheral sensitization. If the pain threshold is reduced in the affected area together with a reduced pain threshold at another location, yet at the same segmental level, we may still assume there is peripheral sensitization. However, if the pain threshold is reduced in the affected area and at a body site which is not segmentally related (distant site), we may assume there is generalized sensitization; a characteristic of CS.(37) If the TS is enhanced, compared to pain-free populations, there is an increase of central gain of pain which is suggested as a feature of CS. If the conditioned pain modulation response is abnormal relative to the pain-free population, this is interpreted as dysfunctional endogenous analgesia, another characteristic of CS.(37) In order to provide appropriate treatment to the patient, it is important to objectify symptoms of CS. It is a challenge to objectify CS in the clinical practice. There are several questionnaires regarding pain (location, type and intensity) and a questionnaire that indicates whether the characteristics of CS is present: the Central Sensitization Inventory (CSI). Questionnaires are subjective and actually the phenomenon of pain is subjective: everyone experiences pain in their own way. To measure the functioning of the somatosensory system somewhat objectively, QST is the best we have. Interpreting the QST outcomes can be challenging in clinical practice due to the need to compare the results to norm values from a pain-free population. Therefore, interpretation of individual data is not yet possible. This could be further investigated. Another possibility is to further investigate associations between pain-related questionnaires and QST-measurements or associations between CSI and QST-measurements as Kregel et al. (2018) did.(39)

Central Sensitization Inventory

To provide information about CS-related symptoms the Central Sensitization Inventory (CSI) has been developed. This questionnaire measures somatic, cognitive and emotional symptoms and is used as screening tool; it alerts clinicians to any symptoms present that may be related to CS or indicate the presence of central sensitivity syndrome (CSS).(40) It can also inform the clinician to what extent the CS-related symptoms are present and thereby support the appropriate treatment for the patient. The use of this questionnaire aims to avoid unnecessary diagnostic procedures for people with long-term idiopathic pain.(40) In recent years different ways of interpreting this questionnaire have been developed. There is a cut-off score of ≥ 40/100 that represent an indication of the presence of CS/CSS-related symptoms.(41) Subsequently, a categorial rating scale was developed to assess the patient’s symptoms in a more nuanced way. This allowed more refined decisions to be made regarding the treatment.(42) A critical issue of the CSI is its content validity. Without international agreement on the definition of CS, and in absence of a gold standard for measuring CS, it remains difficult to study the content validity of the CSI in patients with chronic pain. Its content validity is likely to be restricted to the type of chronic pain patients on whom the content was developed (i.e. the selection of items/symptoms).(43) In addition, it remains questionable whether a self-reported measure can capture the complexity of a neurophysiological mechanism such as CS. This latter argument also questions the content and construct validity of the CSI.

Recently, three CSI “severity levels” have been developed in which the patient is categorized based on the outcome of the CSI symptom severity calculator after the patient had completed the CSI.(44) This questionnaire does not “diagnose” CS. The cut-off score of ≥ 40 is applied in an algorithm of Nijs et al. (2014) to support the clinician in classifying clinically between neuropathic pain, nociceptive pain and CS pain in people with LBP.(45) This algorithm arose at the time when people became more aware of the neurophysiological phenomenon “central sensitization” and was developed from Woolf’s

definition for CS. Just as the term of "central sensitization" has evolved, so has the algorithm. After the IASP introduced the term "nociplastic pain" a corresponding algorithm was developed. The origin of this algorithm is based on different sets of clinical criteria and relates to pain and hypersensitivity in body areas with normal tissue and not subject to neuropathic pain.(27) The clinical criteria for nociplastic pain are more comprehensive, better developed and more robust. Due to support from the IASP it holds more potential compared to the algorithm of Nijs et al. (2014).(46)

Subgroups in the Low Back Pain population

There are several guidelines for LBP that are based on the biopsychosocial model. The recommendations regarding best treatment consist of a combination of exercise, hands-on interventions and education.(47, 48) If LBP complaints are uncomplicated the management plan can be implemented in a monodisciplinary setting. For the more complicated LBP or for patients who do not recover in response to primary care, a multidisciplinary approach is more appropriate.(49) The complexity of LBP resides in the fact that LBP is a multidimensional phenomenon. It contains neurological, endocrine, immunological and psychological elements. Each time it is a the puzzle which element(s) is/are dominantly present.(50) It is then desirable that the interventions fits well with the dominant element(s). Although these interventions are successful and show good evidence, the effect size is small and many patients still experience LBP.(51) To increase the effects in treatment of LBP some suggest to tailor treatment to the specific underlying pain mechanism.(10, 52) Others divide the large group of patients with LBP in subgroups based on risk levels for poorer prognosis for recovery.(53) The latter is done by the questionnaire Start Back screening Tool (SBT). Based on an estimate of the development of persistent LBP, patients will be divided into a low, medium or high risk level. The outcome of the risk level indicates direction of the management plan.(53) Another questionnaire which divides patients with LBP into subgroups is the CSI. Based on the outcomes of the questionnaire the "Sensitization Inventory Symptom Severity Calculator" classifies the patients into one of the three subgroups: low, medium or high level of CS-related symptom severity.(44) The three subgroups have been developed to help clinicians with their clinical interpretation of the CSI score.(44) This is more nuanced in the interpretation of CS compared to the existing cut-off score of ≥ 40/100. Hence, this enables a better tailor-made treatment.

In recent years several studies have been conducted to create subgroups in the large group of patients with LBP. One study created subgroups based on "the 2011 FM Criteria and Severity Scales". (54) Another study created subgroups based on QST-measurements.(55) These studies were conducted to enhance the knowledge and understanding about LBP and its neurophysiology, the relation between psychological and the neurophysiological, and from a broader view, the biopsychosocial components belonging to LBP. They investigated to what extent an interaction between these components exists within the LBP population, and how it manifests. Unraveling the riddle of LBP remains important to improve tailor-made treatment to the individual patient.

Low back pain in primary care

In 2019 LBP was the most common health problem (6.6%) in primary care.(1) The assumption is that in patients with LBP, who attend the primary care, the biomedical factors are more present in relation to the psychosocial factors; they indicate less high pain intensity and are less limited in their work/ daily activities compared to people with LBP in secondary or tertiary care.(49) Morso et al. (2013) investigated the differences in characteristics of people with LBP between primary and secondary care

in Denmark.(56) The people with LBP in primary care: more were employed, had a shorter duration of LBP, had a higher pain intensity in their lower back and less leg pain intensity compared to people in secondary care.(56) The level of activity limitations were nearly the same for both populations with LBP. Not significant, but conspicuous the 'medium risk level' of the SBT was slightly higher in people with LBP in primary care compared to those with LBP in secondary care. Also remarkable, a high proportion of 'low risk levels' of the SBT was present in the people with LBP in secondary care.(56)

In primary care, it was notable that many patients with LBP consulted the practice. This raised the question of how to better understand the health problem associated with LBP in primary care. It is more than just pain: a personal world of (for example) thoughts, emotions, behavior with LBP is hidden behind the phenomenon of pain. Although much has been published about LBP, curiosity was stimulated and the desire was to further unravel the phenomenon of CS in patients with LBP seen in primary care. Beside the question whether CS occurs in people with LBP, the question arose to what extent CS is present in people with LBP in primary care specifically. Furthermore, in this dissertation we wanted to obtain knowledge about CS in relation to the other components of the biopsychosocial model. This dissertation mainly focuses on the biological and psychological components of this model.

While taking the entire physiotherapeutic process into account, this dissertation will focus on the physiotherapeutic diagnostic process for patients with LBP seen in primary care. For a clinician in primary care it would be helpful if there were characteristics that increase the suspicion or even likelihood of the presence of CS in people with LBP. By recognizing these characteristics, after intake and physical examination, the treatment can be adjusted accordingly. When clinicians utilize the SBT or the CSI in primary care patients with LBP, it is useful to have information about the extent to which psychological factors play a role in the relevant risk level. In addition, it is also useful to know to what extent pain sensitivity plays a role in the risk levels of patients with LBP seen in primary care. The treatment can be specifically applied to these outcomes. Hopefully, this will provide each patient with LBP with the required treatment that is tailor-made and will increase the effect of the treatment. The treatment options are not included in the scope of this dissertation.

During this PhD period, the understanding of CS in patients with LBP, has evolved. The included studies have used the concept of CS as it was customary at the time of initiating the PhD. The descriptions of the chapters below indicate, if necessary, how this is interpreted regarding the current understanding and vision. At the end of this dissertation a critical reflection will take place, in which the concept of CS will be identified and interpreted with today's vision.

Based on the biopsychosocial model the biological component is discussed first. It is important to know whether CS occurs in people with LBP. Roussel et al. (2013) wrote a narrative review about this topic, indicating that CS is present in 25% of people with LBP.(57) There was no systematic review on QST-measurements in people with LBP compared to healthy controls. This knowledge gap is clarified in **chapter 2.** A systematic review with meta-analysis is included in which studies were investigated for the presence of CS in people with LBP compared to healthy controls by means of extensive QST measurements. In this chapter the term "CS" refers to the neurophysiological phenomenon. With the current knowledge, this is used correctly.

Many studies show a positive association between symptoms of CS and previously mentioned psychological factors in patients with LBP.(16, 42, 58) Somatosensory changes and the development of symptoms of CS can be caused by several psychological factors like fear, stress, catastrophizing, inadequate illness perception and depression.(15) Based on the biopsychosocial model, the psychological component is discussed next. Attitude/beliefs and behaviors are factors included within the psychological component of the biopsychosocial model. Avoidance behavior towards people or activities in order to reduce physical and emotional discomfort is called "psychological inflexibility".(28) ACT attempts to increase psychological flexibility, whereby several psychological processes have to change.(28) It is assumed that the avoidance behavior based on psychological inflexibility and cognitive fusion are involved in the development of symptoms of CS. However, studies supporting or refuting this assumption are unavailable and as such are therefore a research priority. In addition, people are sometimes preoccupied with an intense event in the past, which leads to a sense of perceived injustice. They worry a lot, have many negative beliefs and they do not really connect with the present. So they do not experience the world as it is. This is the opposite of "being present" what ACT aims to achieve. It is also assumed that perceived injustice can influence the development of CS. Until recently no studies had been performed to examine these three possible associations (psychological inflexibility, cognitive fusion and perceived injustice) in patients with LBP seen in primary care. Psychological inflexibility and cognitive fusion are a derivative of the first generation of the cognitive behavioral therapy. Perceived injustice is not directly linked to cognitive behavioral therapy, but can be regarded as 'not being able to connect with the present moment'. **Chapter 3** reports an innovative explorative study examining the associations between the inflexibility pattern of behavior, cognitive fusion and perceived injustice with symptoms of CS in people with LBP in primary care. It was also investigated whether there is a difference in widespread pain, intensity of pain, functional disability, kinesiophobia, pain catastrophizing, inflexibility pattern of behavior, perceived injustice and cognitive fusion between people with LBP with symptoms of CS and those without symptoms of CS in primary care. In this chapter, the concept of CS is referred to as "symptoms of CS". With current knowledge, the term "nociplastic pain" would be more appropriate to consider, yet only symptoms of CS were studied, and according to the IASP clinical criteria for nociplastic pain, symptoms of CS do not suffice to establish nociplastic pain.(59) In addition, the content validity of the CSI, used to study symptoms of CS, remains an issue.(43)

Several studies have reported significant differences in QST-measurements between people with LBP and healthy controls in secondary and/or tertiary setting. Based on the biological component of the biopsychosocial model, it was still unknown whether CS occurs at all in primary care and whether there was a difference in QST-measurements between people with LBP with CS and those without CS in primary care. In this chapter CS refers to the neurophysiological phenomenon and has been correctly used according to the current insights. In **chapter 4** an observational case-control study was performed. Patients with acute and chronic LBP who were being treated in primary care were recruited. These people with acute and chronic LBP formed a new study population and are different as the included population as described in chapter 3. Extensive QST-measurements and a few questionnaires were conducted. The outcomes of the QST-measurements of the people with acute and chronic LBP and healthy controls were compared. This clearly indicated that CS occurs in patients with acute and chronic LBP in primary care. In addition, the results of the QST-measurements of the people with LBP with symptoms of CS were compared to the results of the QST-measurements of those without CS in primary care.

Some recent studies subgroup people with LBP based on the cut-off score of the CSI (≥40/100) or severity levels of the same questionnaire according to Neblett et al. (2017).(60) The risk levels of the SBT indicate that as the level increases, psychological factors play a more dominant role in persistent

LBP.(53) As the severity level of the CSI increases, the patient will experience the CS-related symptoms more intensely (somatic, cognitive and emotional symptoms).(44) Based on the biological and psychological components of the biopsychosocial model, we were curious to know to what extent both the sensory and psychological variables change with increasing the risk/ severity levels based on the SBT and CSI. Until now no research has done this. Investigating the changes in the psychological factors is not new in itself, however investigating these changes in combination with the sensory changes is innovative. In **chapter 5** an innovative cross-sectional study was performed. It investigated whether differences exist in the sensory system and various psychological and disability factors between the risk levels based on the SBT and based on the CSI in people with acute and chronic LBP in primary care. These participants are the same people described in chapter 4. This is a first tentative attempt to investigate characteristics of subgroups, based on the SBT and CSI, in people with acute and chronic LBP in primary care. This chapter discusses CS which is related to neurophysiological changes of the somatosensory system. The term "nociplastic pain" is already used further on in this chapter, but we cannot assert that the clinical criteria for nociplastic pain(59) apply to (part of) the patients studied here. At the time of preparing the study and collecting the data, the clinical criteria for nociplastic pain(59) were not yet available.

The last chapter is the general discussion.

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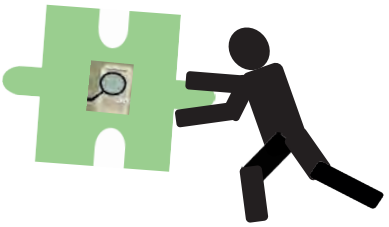
Chapter two



Pain Mechanisms in Low Back Pain: a Systematic Review and Meta-analysis of Mechanical Quantitative Sensory Testing Outcomes in People with Non-Specific Low Back Pain

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Abstract

Background: Mechanical quantitative sensory testing (QST) assesses sensory functioning and detects functional changes in (central) nociceptive processing. It has been hypothesized that these functional changes might be apparent in people with nonspecific low back pain (LBP), although the results are mixed.

Objective: The aim of this systematic review was to examine whether sensory function, measured with QST, was altered in people with nonspecific LBP.

Methods: This systematic review was conducted according to PRISMA guidelines. Six databases were searched for relevant literature. Studies comparing mechanical QST measures involving people with subacute and chronic low back pain and HC were included if 1) pressure pain thresholds (PPTs), 2) temporal summation, or 3) conditioned pain modulation were reported. Risk of bias was assessed using the Newcastle-Ottawa scale. When possible, the results from different studies were pooled.

Results: Twenty-four studies were included. Scores on the Newcastle-Ottawa scale varied between 1 and 6 points. People with nonspecific LBP, compared to healthy controls, had significantly lower PPTs at remote sites and increased temporal summation at the lower back. The PPTs measured at the scapula were significantly lower in patients with nonspecific LBP than in healthy controls (pooled mean difference, 119.2 kPa; 95% confidence interval: 91.8, 146.6kPa; P<0.00001.

Conclusion: The PPT measurements at remote body parts were significantly lower in people with nonspecific LBP compared with healthy controls. Temporal summation and conditioned pain modulation measurements had mixed outcomes.

Level of evidence: Therapy, level 3a. J Orthop Sports Phys Ther 2019;49(10):698-715. Epub 23 Aug 2019. doi:10.2519/jospt.2019.8876

Keywords: central sensitization, conditioned pain modulation, low back pain, pressure pain threshold, temporal summation

Introduction

Nonspecific low back pain (LBP) is one of the most common health problems and places an enormous burden on individuals, their families and society.(1) Nonspecific LBP is pain felt at the lower back, between the lower rib and gluteal fold, for which no specific pathophysiological process can be designated.(2)

Current guidelines for nonspecific LBP suggest biopsychosocial approaches and individually tailored interventions, consisting of combinations of education, exercise, and hands-on interventions.(3) In cases where monodisciplinary approaches fall short of success, multidisciplinary biopsychosocial rehabilitation is indicated.(2) Although the success of these interventions is well demonstrated, effect sizes are still generally small and recurrence rates are high.(3, 4) There is a clear need for improvements in the management of nonspecific LBP. One suggestion is to better align treatments for LBP with the underlying biological processes.(5, 6)

Changes in the neurophysiological processing of nociceptive information may play an important role in nonspecific LBP.(5, 7) Amplification of peripheral nociceptive information at the height of the dorsal horn, enhanced processing of nociceptive information within several brain nuclei and their interrelated connections that together form a 'dynamic pain connectome' are taken as important biological processes that should be considered in nonspecific LBP.(8) Enhanced processing of nociceptive information is currently summarized as 'central sensitization (CS)'(5, 9) "an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity".(10)

From a clinical perspective, it is valuable to know whether central sensitization is part of the nonspecific LBP problem. Central sensitization is associated with higher pain intensity, widespread pain, worse prognosis and lower quality of life.(11, 12) Central sensitization is a neurophysiological concept, and the underlying processes cannot be directly measured in clinical practice. Quantitative sensory testing (QST) is used to study altered sensory processing, as a derivative of signs of central sensitization.(7, 13)

Central sensitization is suggested to be the dominant pain mechanism in about 25% of the population with nonspecific LBP.(14) A previous narrative review reported on differences between people with chronic LBP and healthy controls in several QST measures. Lower pain thresholds at remote body parts, enhanced temporal summation and abnormal conditioned pain modulation were interpreted as signs of central sensitization.(15-20) A narrative review does not systematically screen the available literature, may not be comprehensive, does not take methodological quality of included studies into account, and does not pool data statistically to generate firm conclusions.

We performed a systematic review to examine whether sensory function, measured with QST, was altered in people with nonspecific LBP compared with healthy controls. We aimed to critically appraise current literature comparing remote pressure pain thresholds (PPTs), local and remote temporal summation, and conditioned pain modulation in people with nonspecific LBP and healthy controls to examine whether sensory functioning, measured with QST, is altered in people with nonspecific LBP.

Methods

Protocol and registration

The review protocol was registered a priori at the International Prospective Register of Systematic Reviews (registration number: CRD42017055599). This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (www.prisma-statement.org).

Eligibility criteria

Studies were included if the following criteria were met: (1) studies involved adults (18 years of age or older) with nonspecific LBP (subacute and chronic) and healthy controls; (2) sensory functioning was determined by using PPT, mechanical temporal summation, and/or conditioned pain modulation measures; and (3) studies were written in Dutch, English or German. Subacute nonspecific LBP is defined as pain that has been present between 6 and 12 weeks.(21) Chronic nonspecific LBP is defined as pain that persists for at least 12 weeks.(2) Various QST procedures are described in the literature. The PPT is defined as the minimum amount of pressure that elicits a painful sensation.(22) Temporal summation is the increased pain response after a series of identical stimuli.(20) Conditioned pain modulation is the increase in PPT after a painful stimulus on a remote body part.(13) To enable meta-analysis, only studies using mechanical procedures were chosen. Central sensitization can be a normal physiological phenomenon during the acute LBP phase, but will resolve in most cases.(23) Studies involving patients with subacute and/or chronic LBP were included in the meta-analysis, as the difference between these 2 groups cannot clearly be delineated from a pain physiological perspective, but rather stems from epidemiological convention. Central sensitization can be apparent in both groups. Studies involving people with sciatica, pelvic problems, pregnancy, whiplash associated disorders, nonspecific neck pain, fibromyalgia, low back surgery, or any other medical condition besides nonspecific LBP were excluded.

Information sources and search strategy

Literature was searched up to January 7, 2019 in Medline, the Cochrane Library, Google Scholar, Web of Science, CINAHL and EMBASE. An information specialist from the medical library of the Erasmus University Medical Centre (Rotterdam, the Netherlands) constructed search strategies for the different databases. Main keywords were *central sensitization, pain threshold, hyperalgesia, hypoalgesia, quantitative sensory testing, wind-up, conditioned pain modulation, low back pain, inhibition and facilitation and synonyms.* The search string for Medline is displayed in Appendix 1.

Study selection

After removal of duplicates, the titles and abstracts of retrieved articles were screened for relevance by 2 independent investigators (H.d.B. and W.P.). Full text versions of relevant articles were obtained and assessed for eligibility by the same 2 investigators. If there was uncertainty about whether an article fit the criteria a third investigator (L.V.) was consulted and made the final decision. Corresponding authors of original studies were contacted in an attempt to obtain extra information when necessary.

Risk of bias in individual studies

Risk of bias was assessed independently by H.d.B. and W.P. The Newcastle-Ottawa quality assessment scale (NOS) for nonrandomized studies, including case-control studies and cohort studies was used.(24) The NOS has a 'star rating system' in which a study is assessed on 3 aspects: selection of the

study groups, the comparability of the groups and ascertainment of the exposure or outcome of interest.(24) Each aspect contains several items that can be scored with 1 star (except 'comparability', which can score up to 2 stars) (see Appendix 2). This process leads to a score between 0 and 9 stars.(25) Investigators assessed the included studies independently. Inter-rater agreement was calculated (Kappa and 95% Confidence Interval (CI)) using SPSS Version 24(IBM Corporation, Armonk, NY). Disagreements were solved through discussion. When necessary, the third investigator (L.V.) determined the final score.

Data extraction and data items

The following data were extracted from the included articles: authors and year of publication; number of participants; definition of nonspecific LBP; study design; QST measures; location of QST-stimuli and temporal summation protocol; PPT-, temporal summation,- and conditioned pain modulation results; and study conclusions. Data were extracted by both investigators independently. In case of missing data, authors were contacted and requested to provide required information.

Data management and meta-analysis

In most articles, results of PPTs, temporal summation, and conditioned pain modulation were reported as mean, 95% CI, standard deviation and *P* values. All data of PPT outcomes from individual articles were recorded or converted to the unit kilopascals. Studies were grouped based on the applied QST protocol (remote PPT, temporal summation, conditioned pain modulation, or local temporal summation) and further clustered according to the remote body location (scapula, arm, hand, gluteal, lower leg and lumbar). If a cluster contained at least 2 studies reporting means and standard deviations for patients with nonspecific LBP and healthy controls, a meta-analysis was performed for PPT and temporal summation outcomes using a binary random-effects meta-analysis model. Meta-analyses were performed using Review Manager software (Version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark). Meta-analyses for temporal summation were pooled based on identical remote body locations, temporal summation protocols, and outcome unit. Heterogeneity was assessed using I^2 statistic. For the interpretation of the I^2 values, the following classification was used: 0% to 40%, no heterogeneity; 30% to 60%, moderate; 50% to 90%, substantial; and 75% to 100%, considerable heterogeneity.(26) If heterogeneity was higher than 60% (predetermined) and a subgroup contained at least 3 articles, then studies were pooled according to their NOS score and divided into below average and average or above average scores.(27, 28) If the *P* value of 'the overall effect' of the meta- analysis was smaller than .05 (predetermined), then the effect was considered significant. Studies not included in the meta-analysis were described separately. Funnel plots were created and inspected for publication bias (asymmetrical figure). A meta-analysis was not performed for conditioned pain modulation because of differences in measurement protocols. Some studies used cold or hot water, while other studies used a thermode, as a noxious stimuli. In some studies, the participants had to immerse their foot, leg or hand in a bucket of ice water.[4, 22, 25, 32] In another study the participants had to immerse their hand in a bucket of hot water.(29) In one study the noxious stimulus was applied with a thermode on the dorsal part of the hand.(30) The temporal summation measurements were more uniform across studies. Most of the temporal summation protocols referred to the German Research Network on Neuropathic Pain, and the remaining used temporal summation protocols similar to that of the German Research Network on Neuropathic Pain.(31)

Results

Study selection

The search yielded 6801 articles. The flow chart of inclusion is shown in Figure 1. After removing duplicates (n= 4198), the remaining 2603 articles were screened by title and abstract. Full texts of 62 articles were read. Finally, 24 articles were included in this review.(13, 15-19, 29, 30, 32-47) The corresponding authors of 2 publications were contacted with the request to provide the required details for meta-analysis. Both authors responded and delivered the required information.

Study characteristics

Study characteristics are shown in Table 1. In all studies, different measurements were taken at the same moment. All studies used PPT as outcome measure, except the study by Meints et al.(47) Seven studies involved temporal summation (13, 18, 29, 34, 38, 41, 45) and 6 studies involved conditioned pain modulation.(15, 29, 30, 43, 45, 46) Eight studies conducted PPT measurements and temporal summation measurements.(13, 18, 29, 34, 38, 41, 45, 46) In about half of the studies (n=13), patients and controls were appropriately matched for age and sex.(15, 16, 18, 29, 30, 36-38, 40, 41, 43, 45, 46) In 21 studies, PPTs were taken at both the lower back and a remote body site (eg, forehead, thenar eminence, wrist, hand, infraspinatus, triceps brachii, gluteus maximus or second toe). In one study, only the lumbar area was tested using conditioned pain modulation.(30) In another study, only the remote hand was tested using temporal summation.(47)

Risk of bias

Results of risk-of-bias assessment are shown in Table 2. Agreement between the 2 reviewers (K=0.69; 95%CI:0.61, 0.77), was 'substantial'.(48) Each article could have a maximum score of 9 points on the NOS. None of the 24 articles had a score above 6 points, and the average score was 4. Only 2 articles (33, 41) had an adequate case definition. All articles, except those of Blumenstiel et al., Farasyn and Meeusen as well as Farasyn and Lassat, used the "same method of ascertainment for cases and controls".(13, 33, 44) None of the articles reported "nonresponse rate". The third independent researcher was not required for making final decisions.

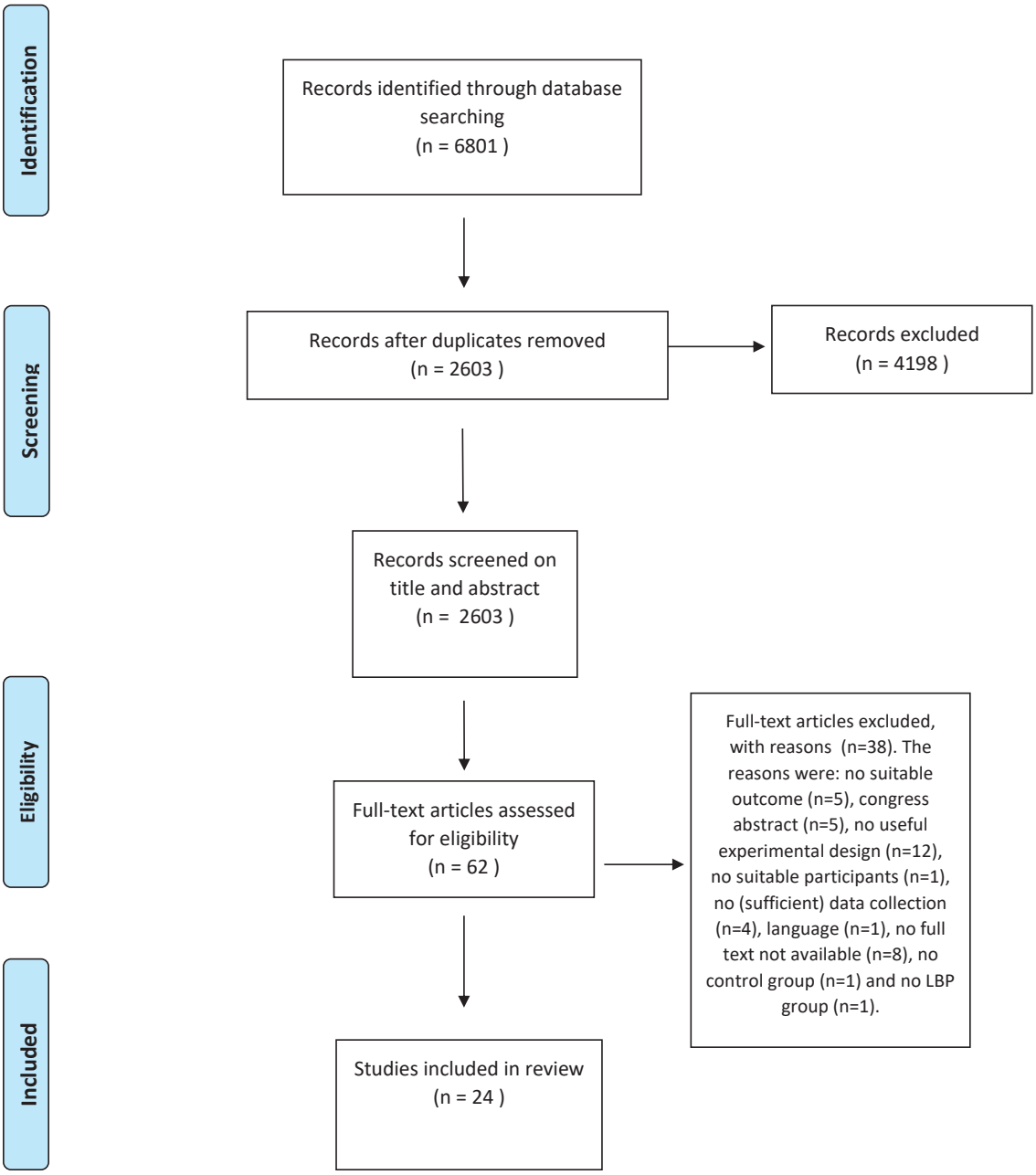

FIGURE 1. Flowchart of study inclusion into the systematic literature review and subsequent meta-analysis.

Table 1. Characteristics of included studies (n=24)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
Blumenstiel et al. 2011	N= 23 with CBP (all female), mean age: 43.4 (SD: 8.6) and N=20 healthy controls (female/men ratio not mentioned), mean age: 38.3 (SD: 7.6)	The presence of back pain for at least 45 days within the last 3 months	Cross sectional study	PPT and TS	Paraspinal muscles and dorsum of the hand. CBP: on the most painful area in the back and on the hand dorsum of the same side of the body as HC site. TS protocol: the ratings of single pin-prick stimulation were compared with those of a series of 10 repeated pin-prick stimuli of the same force (256mN) over the same area. TS was calculated by dividing the mean ratings of series by the mean pain ratings of single stimuli	**PPT local (the back):** CBP versus HC (mean kPa/95% CI): 239.3/200-287 versus 352/286-432 (P<0.01) **TS local (the back):** CBP versus HC (mean /95% CI): 2.36 /1.74-3.21 versus 3.61 /2.56-5.11, n.s. **PPT remote (hand):** CBP versus HC (mean kPa/95% CI): 345/ 301-394 versus 318 273/370, n.s. **TS remote (hand):** CBP versus HC (mean /95% CI): 3.57 /2.74-4.67 versus 2.81 /2.07-3.82, n.s.
Corrêa et al. 2015	N= 30 with LBP (18 females and 12 men), mean age: 51 (SD: 8.7) and N= 30 healthy controls (18 females and 12 men), mean age: 47 (SD: 7.7)	Classified as having chronic nonspecific low back pain using the diagnostic triage as recommended by the European Guidelines as well as by the American Physical Therapy Association Guidelines	Case-control study	PPT and CPM	Bilateral 5 cm lateral to the L3 spinous process and 5 cm lateral to the L5 spinous process and m. tibialis anterior of the right leg 5 cm from tibial tuberosity	**PPT local (lumbar):** LBP versus HC (mean kPa (SD)/95%CI): 253.0 (96.5) versus 342.5 (127.7)/ 40.9-131.1, p=0.001 **PPT remote (m. Tibialis anterior)**: LBP versus HC (mean kPa (SD)/95%CI): 262.4 (93.1) versus 321.8 (84.5)/ 13.5-105.4, p=0.012 **CPM:** LBP versus HC (mean (SD)/95%CI): -47.17 (73.3) versus 71.4 (83.8)/ 77.9-159.2, p<0.001

Table 1. (continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
Farasyn & Meeusen 2005	N= 87 with nLBP (39 females and 48 men), mean age: 43 (SD: 13) and N= 64 healthy controls (40 females and 24 men), mean age: 40 (SD: 11)	Subacute low back pain as defined by the Dutch guideline for physiotherapy	Cross sectional study	PPT	Paravertebral musculature (5 cm lateral) T6, T10, L1, L3, 4 cm lateral of L5. 3 cm lateral of the iliac crest of the M. Gluteus max, m. Gluteus med, m. Tensor fasciae latae, mid point of the left m. Triceps brachii.	**PPT local (L3):** nLBP versus HC (mean kg/cm^2 (SD)): 5.1(1.3) versus 7.7(1.7), p<0.001 **PPT local (L5):** nLBP versus HC (mean kg/cm^2 (SD)): 7.2(1.6) versus 9.5(1.2, p<0.001 **PPT remote (m. Triceps brachii):** nLBP versus HC (mean kg/cm^2 (SD)): 6.7(1.8) versus 7.1 (1.7), p=0.119 **PPT remote (m. Tensor Fasciae Latae):** nLBP versus HC (mean kg/cm^2 (SD)): 6.3(1.5) versus 7.1(1.4), p<0.001
Farasyn & Meeusen 2007	N=58 with LBP (25 females and 23 men), mean age: 45 (SD: 13) and N= 64 healthy controls (38 females and 26 men), mean: 40 (SD: 11)	Nonspecific low back pain is defined as pain for which no disorder in the anatomical structure can be found to sufficiently accounts for the patient's complaints	Clinical trial	PPT	Mid point of the left m. Triceps brachii, paravertebral musculature (erector spinae, ES) 5 cm from L1, L3, and 4 cm from L5, 3 cm below iliac crest from proximal part of the gluteus maximus. (back pain related site)	**PPT local (L5):** LBP versus HC (mean(SD)): 7.3 (1.7) versus 9.5 (1.2), p<0.001 **PPT remote (m. Triceps brachii):** LBP versus HC (mean(SD)): 6.9 (1.5) versus 7.1 (1.7), p=0.457 **PPT remote (m. Gluteus maximus):** LBP versus HC (mean(SD)): 6.4 (1.6) versus 8.0 (1.5), p<0.001
Farasyn & Lassat 2016	N=30 CLBP (? females and ? men), mean age: 47 (SD: 13), N=30 healthy controls	'Simple backache' is defined as a LBP that is not attributed to any	Cross sectional design	PPT	m. erector trunci: T8, T10, L1, L3, 3 cm distally of the iliac crest from the proximal part of the Gluteus maximus	**PPT local (L1):** CLBP versus HC (mean kg/cm^2(SD)): 3.71(1.20) versus 8.69(1.66), p≤0.001

Table 1. (continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
	(? females and ? men), mean age: 41, (SD: 11)	recognizable pathology like nerve root pain and serious spinal pathologies such as an infection, tumor, osteoporosis, rheumatoid arthritis, fracture, or inflammation			(GLUT SUP), Trochanter major of the Femur (GLUT INF)	**PPT local (L3):** CLBP versus HC (mean kg/cm^2 (SD)): 5.29(1.27)) versus 9.86(1.41), p≤0.001 **PPT remote (T8):** CLBP versus HC (mean kg/cm^2 (SD)): 3.96(1.30) versus 7.03(1.50), p≤0.001 **PPT remote (T10):** CLBP versus HC (mean kg/cm^2 (SD)): 3.73(1.10) versus 7.77(1.31), p≤0.001 **PPT remote (gluteus maximus, pars superior):** CLBP versus HC (mean kg/cm^2 (SD)): 3.73(1.17) versus 9.10(1.83), p≤ 0.001 **PPT remote (gluteus maximus, pars inferior):** CLBP versus HC (mean kg/cm^2 (SD)): 3.84(0.94) versus 8.81(2.01), p≤0.001
Gerhardt et al. 2015	N= 77 with CBP, divided in CLP= 48 (24 females and 24 men), mean age: 59.7 (SD: 11.8) and CWP= 29 (17 females and 12 men), mean age: 55.2 (SD: 8.3), N= 40 healthy controls (17 females and 23 men), mean: 61.6 (SD: 12.0)	CWP= according to ACR: chronic back pain plus contra-lateral limb pain (upper + lower and left + right side of the body. CLP: is defined as CWP criteria not fulfilled	Cross sectional study	PPT and TS	Paraspinal muscles L1 to L5 of the painful low back area, dorsum pain-free ipsilateral hand. PPT at the hand that was tested at the thenar TS protocol: ratings of single pinprick stimulation were compared with a series of ten repeated pinprick stimuli of the same force (256 mN) over the same area. The mean ratings of series divided by the mean pain ratings of single stimuli was calculated as the TS	**PPT local (lumbar):** CLP versus HC (mean kg/cm^2 (SD)): 0.72 (0.22) versus 0.81(0.15), p=0.000 **PPT local (lumbar):** CWP versus HC (mean kg/cm^2 (SD)): 0.74 (0.19) versus 0.81(0.15), n.s. **TS local (lumbar):** CLP versus HC (mean (SD)): 0.38(0.26) versus 0.30(0.22), n.s. **TS local (lumbar):** CWP versus HC (mean (SD)): 0.42 (0.20) versus 0.30 (0.22), p=0.000 **PPT remote (hand dorsum):** CLP versus HC (mean kg/cm^2 (SD)): 0.64(0.15) versus 0.68 (0.12), n.s.

Table 1. (continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
						PPT remote (hand dorsum): CWP versus HC (mean kg/cm^2 (SD)): 0.62 (0.11) versus 0.68 (0.12), n.s. **TS remote (hand dorsum):** CLP versus HC (mean (SD)): 0.32 (0.31) versus 0.30 (0.24), n.s. **TS remote (hand dorsum):** CWP versus HC (mean (SD)): 0.34 (0.18) versus 0.30 (0.24), n.s.
Giesbrecht & Battié 2005	N=30 with CLBP (30 females and 0 men),mean age: 41.6 (SD=9.7), N= 30 healthy controls (30 females and 0 men), mean age: 42.2 (SD=9.5)	No description	Cross sectional design	PPT	Test sites were measured bilaterally: paraspinal muscles C5, L3, L5, wrist extensor muscle, middle phalanx of the second finger, calf muscle.	**PPT local (L3 and L5):** CLBP versus HC (mean lb/cm^2 (SD)): 5.9(3.0) versus 8.0(2.9), p=0.0083 **PPT remote (wrist extensor and 2nd finger):** CLBP versus HC (mean lb/cm^2 (SD)): 5.1(1.6) versus 6.1(1.6), p=0.0163 **PPT global (L3,L5, wrist extensor, 2nd finger, calf muscle, C5):** CLBP versus HC (mean lb/cm^2 (SD)): 5.6(2.1) versus 6.9(2.1), p=0.0175
Goubert, et al. 2017	N=16 CLBP (8 females and 8 men), mean age: 46 (SD: 14, median:50, IQR:28), N=21 healthy controls (12 females and 9 men), mean age: 38(SD:13, median:40, IQR:29)	No description	Cross sectional design	PPT, TS and CPM	m. erector spinae at 5 cm lateral of proc spin vertebrae L3, quadriceps muscle at the middle between SIAS and basis patella, trapezius muscle at the middle between acromion and proc spinosus C7, and the web between index finger and thumb dorsal side hand.	**PPT local (lower back):** CLBP versus HC (mean kPa(SD)): 623.70(340.29) versus 715.89(433.45) **TS local (lower back):** CLBP versus HC (mean (SD)): 12.46(5.57) versus 11.13 (6.38)

Table 1. (continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
					TS protocol: the previous determined mean PPT intensity was applied 10 repetitive times at each assessment site and was maintained one second before being released. Pressure was increased, during one second, until the previously determined mean PPT intensity was reached, followed by one second of rest. After the first, fifth, and tenth stimulus, a numeric rating scale score (NRS) of the pressure induced pain sensation was recorded. Area under the curve of pain sensation during pulse 1, 5, 10 when mean PPT was applied 10 repetitive times.	**PPT remote (trapezius):** CLBP versus HC (mean kPa(SD)):396.19(167.69) versus 511.91(368.73) **PPT remote (hand):** CLBP versus HC (mean kPa(SD)): 447.18(223.59) versus 567.81(407.96) **PPT remote (quadriceps):** CLBP versus HC (mean kPa(SD)): 612.92(248.11) versus 733.54(458.95) **TS remote (trapezius):** CLBP versus HC (mean (SD)): 12.79 (5.58) versus 11.35 (5.10) **TS remote (hand):** CLBP versus HC (mean (SD)): 12.29 (6.88) versus 11.98(5.38) **TS remote (quadriceps):** CLBP versus HC (mean (SD)): 12.5 (5.48) versus 11.30(6.17) **CPM (no CS):** CLBP versus HC (mean vas score(SD): 0.58(0.93) versus 1.11(1.61) **CPM (no CS minus CS):** CLBP versus HC (mean vas score(SD)): 0.01(0.35) versus 0.32(0.72)
Laursen et al. 2005	N=10 with CLBP(10 females and 0 men), mediaan age: 45,(range 28-58), N=41 healthy controls (41 females and 0 men) mediaan age: 42, (range 25-61).	No description	Cross sectional study	PPT	Midline of abdomen, midline of low back, lateral surface of upper arm, pulpa of forefinger, first joint dorsal side forefinger, midpoint of the lower extremity, medial border of scapula	**PPT local (midline low back):** CLBP versus HC (median kPa): 269 versus 520, p<0.001 **PPT remote (medial scapula):** CLBP versus HC (median kPa): 295 versus 620, p<0.001 **PPT remote (1st joint forefinger):** CLBP versus HC (median kPa): 340 versus 850, p< 0.001 **PPT remote (pulpa forefinger):** CLBP versus HC (median kPa): 408 versus 860, p<0.001 **PPT remote (below umbilicus):** CLBP versus HC (median kPa): 238 versus 388, p<0.001

Table 1. (continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
						PPT remote (upper arm): CLBP versus HC (median kPa): 196 versus 649, p<0.001 **PPT remote (lower extremity):** CLBP versus HC (median kPa): 392 versus 739, p<0.01
Lewis et al. 2010	N=15 with CLBP (9 females and 6 men), mean age: 40.9 (SD: 11.3), N=15 healthy controls (6 females and 9 men), mean age: 38.7 (SD: 12.3)	LBP was defined as per the International Association for the Study of Pain	Cross-sectional design	PPT	PL4 (lateral to spinous process or in immedite adjacent paraspinal musculature), LPL5 (between PSIS and PIIS), Deltoid site	**PPT local (PL4):** LBP versus HC (mean kPa(95% CI)): 462.1(371.1-553.1) versus 634.4(534.5-734.3), n.s. **PPT remote(LPL5):** LBP versus HC (mean kPa(95% CI)): 380.9(299.8-462) versus 535.9(441.9-629.9), n.s. **PPT remote (deltiod site):** CLBP versus HC, M(95%CI): 296.2(227.4-365) versus 401.9(283.7-685.6). n.s.
Marcuzzi et al. 2018	N=7 with persistent LBP (3 females and 4 men), mean age: 30.6(SD:11.9) and N=43 healthy controls (25 females and 23 men), mean age: 30.0 (SD:9.8)	NRS ≥ 2 at 4 months post inclusion with acute LBP (pain and discomfort localised below the costal margin and above the inferior gluteal folds with or without leg pain lasting more than 24 hours but less than 3 weeks preceded by a	Cohort study	PPT, TS and CPM	Bilaterally at the back, dorsum of the left hand (except for PPT, was tested at the thenar eminence) TS protocol: the perceived magnitude of pain from a single pinprick stimulus (256 mN) on a 101-point numeric rating scale was compared with that of a series of 10 pinprick stimuli of the same force to measure TS. The repeated stimuli were delivered at a rate of 1/s within an area of 1 cm^2. TS was calculated as the mean pain rating from the 5 series of 10 repeated stimuli, divided by the mean pain rating from the 5 single stimuli.	**PPT local (Back):** LBP versus HC (mean kPa(SE)): 374(66) versus 457(26) **TS local (Back):** LBP versus HC (mean (SE)): 3.9(0.7) versus 2.1(0.3), p=0.671 **PPT remote (hand):** LBP versus HC (mean kPa(SE)):345(57) versus 384(22) **TS remote (hand):** LBP versus HC (mean (SE)): 4.2(1.6) versus 1.9(0.1), p=0.072 **CPM:** LBP versus HC (mean (SE)): -14.2(5.8) versus -13.4(2.3), p=0.348

Table 1.(continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
		pain-free period of at least 1 month.				
Meints et al. 2018	N=167 with CLBP (97 females and 70 men), mean age: 40.77(12.29) and N=33 healthy controls (18 females and 15 men), mean age: 43.35 (10.84)	No description	Based line data from longitudinal treatment study	TS	Dorsum of the right middle finger (middle phalanx) TS protocol: mechanical punctate pain was assessed using weighted pinprick stimulators. Participants used a 0 (no pain) to 100 (worst pain imaginable) numeric rating scale to rate the sensation of pain produced by 64mN, 128 mN and 256 mN stimulators. The lowest-force stimulator that produced a painful sensation was then used to apply a train of 10 stimuli to the skin at a rate of 1 pinprick per second. Participants provided pain ratings for the first, fifth, and tenth stimulus. To calculate TS the pain intensity rating after the first stimulus was substracted from the rating after the tenth stimulus.	**TS remote (hand):** LBP versus HC (mean(SD)): 15.97(17.57) versus 14.64(16.73), d=0.08
Mlekusch et al. 2016	N=34 CLBP (17 females and 17 men), mean age:50.8 (SD:14), N= 30 healthy controls (16 females and 14 men), mean age: 37.4(SD: 10.9)	No description	Case control design	PPTT and CPM	2nd toe	**PPT remote (2nd toe):** CLBP versus HC (mean kPa(SD)): 407.8(178.6) versus 548.8(183.6), p<0.001 **CPM:** CLBP versus HC (mean kPa(SD)): 568.5(238.3) versus 681.0(190.6), p=0.025

Table 1.(continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
O'Neill et al. 2007	N=12 CLBP (6 females and 6 men), mean age: 46.4, N=12 healthy controls (age and sex-matched), mean age: 47.1	No description	Cross sectional design	PPT	m. tibialis anterior (TA) and m. Infraspinatus (IS)	**PPT remote (IS):** CLBP versus HC (median kg (95%BI)): 4.65(3.50-6.77) versus 6.40(5.09-10.00), n.s. **PPT remote (TA):** CLBP versus HC (median kg (95%BI)): 5.45(4.07-8.89) versus 8.05(5.55-10.00), p<0.05
Neziri et al. 2012	N=40 CLBP (19 females and 21 men), mean age: 50.5 (SD: 13,2), N=300 healthy controls (148 females and 152 men), mean age: 47.1 (SD: 15,6)	No description	Case-control study	PPT	Suprascapular, pulp of 2nd toe, severe most pain site (SMP) low back, non-painful site (NPS) low back, middle of upper border of iliac crest and corresponding spinous process at low back (controls only)	**PPT local (SMP LB):** CLBP versus HC (mean kPa (SD)): 168(113) versus 352(131). OR(95%CI): 0.13(0.07-0.24), p<0.001 **PPT local (NPS LB):** CLBP versus HC (mean kPa (SD)): 249(132) versus (352(131). OR(95%CI): 0.37(0.24-0.57), p<0.001 **PPT remote (suprascapular):** CLBP versus HC (mean kPa (SD)): 185(103) versus 302(103). OR(95%CI): 0.25(0.15-0.40), p<0.001 After full adjustment for: age, gender, BMI,STAI Trait and Catastrophizing **PPT local (SMP LB):** OR(95%CI): 0.10(0.04-0.18), p<0.001 **PPT local (NPS LB):** OR(95%CI): 0.38(0.22-0.68), p<0.001 **PPT remote (suprascapular):** OR(95%CI): 0.27(0.15-0.51), p<0.001

Table 1.(continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
O'Sullivan et al. 2014	N=19 LBP (15 females and 4 men), mean age:41.9 (SD: 13.9), N=19 healthy controls (females 11 and 8 men), mean age:42.6 (SD: 14.9)	MP group : LBP associated with reports of specific and consistent mechanical aggravating and easing factors. NMP group: LBP was more widespread and ill defined, LBP being more constant, non-remitting, spontaneous and where minor mechanical loading factors resulted in exaggerated or prolonged pain responses	Cross-sectional design	PPT	Dorsal of the wrist joint line, L5/S1 interspinous space, lateral calcaneus	**PPT local (lumbar) MP:** MP versus HC (median kPa(IQR)): 288.7 (289.0) versus 352.7 (222.3) **PPT remote (wrist) MP:** MP versus HC (median kPa(IQR)): 302.0 (177.3) versus 301.3 (141.7) **PPT remote (heel) MP:** MP versus HC (median kPa(IQR)): 315.0 (159.0) versus 309.3 (151.0) **PPT local (lumbar) NMP:** NMP versus HC (median kPa(IQR): 183.0 (115.3) versus 352.7 (222.3)) **PPT remote (wrist) NMP:** NMP versus HC (median kPa(IQR)): 239.7 (167.7) versus 301.3 (141.7) **PPT remote (heel) NMP:** NMP versus HC (median kPa(IQR)): 270.3 (109.3) versus 309.3 (151.0)

Table 1.(continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
Owens et al. 2016	N=25 CLBP (14 females and 11 men), mean age: 57.64(SD: 10.84), N=25 healthy controls (14 females and 11 men), mean age: 55.16(SD: 7.86)	No description	Observational study design	PPT, TS (mechanical) and CPM	TS mechanical pain: back of the nondominant hand and ipsilateral trapezius bilaterally. TS heat pain: the volar surface of the forearm. CPM: with PPT the dominant dorsal forearm and ipsilateral trapezius TS protocol: was assessed using a nylon monofilament. To assess TS participants were instructed to provide a verbal 0-100 rating of pain following a single contact of the monofilament. Then, participants were instructed to provide another 0-100 rating of their greatest pain intensity experienced following a series of 10 contacts, which were provided at a rate of one contact per second. This procedure was repeated twice at each anatomical location. Pain ratings for the single and multiple contacts performed at each anatomical location were averaged across the two trials	**PPT remote (forearm):** CLBP versus HC (mean kPa(SD)): 369.70(217.94) versus 393.16(180.87) **PPT remote (trapezius):** CLBP versus HC (mean kPa(SD)): 340.80(196.27) versus 412.98(212.67) **TS mechanical remote (hand):** CLBP versus HC (mean vas score(SD)) 1 contact:9.96(16.07) versus 4.32(5.13) **TS mechanical remote (hand):** CLBP versus HC (mean vas score(SD)) 10 contacts: 25.68(24.63 versus 10.80(10.92) **TS mechanical remote (trapezius):** CLBP versus HC (mean vas score(SD)) 1 contact: 9.02(13.88) versus 4.12(3.77) **TS mechanical remote (trapezius):** CLBP versus HC (mean vas score(SD)) 10 contacts: 31.24(29.92) versus 14.38(15.09) **CPM (forearm):** CLBP versus HC (mean kPa(SD)): 402.97(209.65) versus 449.88(213.29) **CPM (trapezius):** CLBP versus HC (mean kPa(SD)): 398.40(230.01) versus 525.40(246.71)

Table 1.(continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
Özdolap et al. 2014	N=70 CLBP (44 females and 26men), mean age 37.6 (SD: 10.1), N= 62 healthy controls (33 females and 29 men), mean age: 34.6 (SD: 9.6)	No description	Cross sectional design	PPT	18 tender points defined by the American College of Rheumatology for fibromyalgia syndrome, 12 points for the sciatic valleix (bilateral middle point of glut max, middle point of the gluteal sulcus, middle and posterior point of thigh, popliteal fossa, middle and posterior point of cruris, middle point of Achilles tendon) and 4 lumbar paravertebral points (bilateral 2 cm lateral to the L2 and L4 spinous process)	**PPT local (4 lumbar points):** CLBP versus HC (mean kg/cm^2): 18.8 versus 28.7, p<0.001 **PPT remote (12 sciatic valleix points):** CLBP versus HC (mean kg/cm^2(SD)): 78.5(25.8) versus 93.4(26.1), P=0.001 **PPT remote (fibromyalgia tender points):** CLBP versus HC (mean kg/cm^2(SD)): 87.2(29.5) versus 105.0(31.6), p=0.001
Puta et al. 2013	N=18 LBP(18 females and 0 men), mean age: 51.2 (SD:4.2),N=16 healthy controls (16 females and 0 men), mean age: 51.1(SD: 5.5)	No description	Cross sectional design	PPT and TS	Painful body site paraspinal Th12 to L5 and non-painful body site hand (palmar) TS protocol: was assessed by trains of ten punctate stimuli. To determine the TS, the ratio of the mean pain rating of trains divided by the mean pain rating to a single stimulus was calculated	**PPT local (back):** CLBP versus HC (log_{10} mean kPa(SD)):152(2.182(0.278)) versus 197(2.294(0.188)), p=0.19 **TS local (back):** CLBP versus HC (log_{10} mean (SD)):2.48(0.394(0.205)) versus 3.30(0.519(0.326)), p=0.20 **PPT remote (hand):** CLBP versus HC (log_{10} mean kPa(SD)):238(2.376(0.222)) versus 209(2.321(0.146)), p=0.41 **TS remote (hand):** CLBP versus HC (log_{10} mean (SD)):2.14(0.331(0.245)) versus 2.62(0.419(0.289)), p=0.35
Rabey et al. 2015	N=64 CLBP(35 females and 29 men), mean age: 34.6 (SD: 10.6), N=64 healthy controls (35 females and 29 men), mean age: 33.5 (SD: 11.0)	No description	Case-controlled trial	PPT and CPM (heat noxious stimuli)	CLBP: most painful lumbar region. In HC over paraspinal muscles adjacent to the L5 spinous process	**NRS with concurrent CS**: CLBP (mean/ SD (95%CI): 7.3/1.4(6.9-7.6), p=<0.001 **NRS with concurrent HC:** HC (mean/ SD (95%CI): 5.8/1.3(5.5-6.2), p=0.35

Table 1.(continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
Schenk et al. 2007	N=38 CLBP (38 females and 0 men), mean age nurses: 51.9 (SD: 4.5), mean age: secretaries 52.7(SD: 4.8), N=68 healthy controls (68 females and 0 men), mean age nurses: 51.8(SD: 4.8) mean age secretaries: 52.9 (SD 5.1)	No description	Cross sectional design	PPT	paravertebral muscles, m. quadratus lumborum, os ilium, iliolumbar ligament, m. piriformis, greater trochanter, middle of forehead	**PPT local (back):** CLBP versus HC (median kp/s(IQR)), p=0.68 **PPT remote (forehead):** CLBP versus HC (median kp/s(IQR)),p=0.049
Simmond & Claveau 1997	N=23 CLBP(12 females and 11 men), mean age: 43.2 (SD: 12.9), N=23 healthy controls (12 females and 11 men), mean age: 43.0 (SD: 12.4)	No description	Cross sectional design	PPT (dolorimeter)	L3-L4 interspinous space and on the ulnar border of the forearm	**PPT local (back) dolorimeter:** CLBP versus HC (mean kg/cm^2 (SD)): 4.74(2.24) versus 5.24(1.76), n.s. **PPT remote (arm) dolorimeter:** CLBP versus HC (mean kg/cm^2 (SD)): 5.18(3.38) versus 5.52(1.98), n.s.
Tesarz et al. 2015	N=93 CLBP(61 females and 32 men), mean age:58.2 (95%CI 26,3-60,2), N=31 healthy controls (18 females and 13 men), mean age: 60.1 (95%CI 55,7-64,5)	No description	Cross sectional design	PPT and TS	Paraspinal muscles at the height of lumbar segments L1 to L5 of the low back area, and on the dorsum of the ipsilateral hand. TS protocol: the train of pinprick stimuli was given within a small area of 1 cm^2 and the subject was asked to give a pain rating representing the pain at the end of the train using a numeric rating scale. The mean ratings of series divided by the mean	**PPT local (back):** nsCLBP-W-TE versus HC (mean kg/cm^2 (95%CI)): 0.69 (0.65-0.73) versus 0.77(0.72;0.83), p=0.001 **TS local (back):** nsCLBP-W-TE versus HC (mean(95%CI)): 0.46(0.40-0.51) versus 0.29(0.20-0.38), p=0.010 **PPT remote (hand):** nsCLBP-W-TE versus HC (mean kg/cm^2 (95%CI)): 0.61(0.58-0.64) versus 0.65(0.60-0.69), p=0.006 **TS remote (hand):** nsCLBP-W-TE versus HC (mean(95%CI)): 0.39(0.33-0.45) versus 0.31(0.22-0.41), p=0.320

Table 1.(continued)

Authors	Participants	Definition NSLBP	Study design	Stimulus	Locations and TS protocol	Results
					pain ratings of single stimuli was calculated as TS	
Yildiz et al. 2017	N=121 CLBP (81 females and 40 men), mean age:36.8(SD:9.9), N= 91 healthy controls (65 females and 26 men), mean age:34.1(SD:10.2)	No description	Case-control design	PPT	middle point of the dorsum of the forearm, the middle point of the upper trapezius muscle, paravertebral muscles al L1, L3 and L5 were examined bilaterally	**PPT local (L1):** CLBP versus HC (mean kg/cm^2 (SD)): 6.9(2.3) versus 8.1(2.1), p<0.001 **PPT local (L3):** CLBP versus HC (mean kg/cm^2 (SD)): 6.9(2.3) versus 8.0(2.2), p<0.001 **PPT local (L5):** CLBP versus HC (mean kg/cm^2 (SD)):6.9(2.4) versus 8.0(2.1), p<0.001 **PPT remote (forearm):** CLBP versus HC (mean kg/cm^2 (SD)):7.2(2.1) versus 7.7(2.1), p=0.089 **PPT remote (trapezius):** CLBP versus HC (mean kg/cm^2 (SD)): 5.6(2.2) versus 7.0(2.4), p<0.001

ACR: American College of Rheumatology, [c:] statistical test for group differences is analysis of variance test, CLP: chronic localized pain, CWP: chronic widespread pain , IS: infraspinatus, MP: mechanical pain, NMP: non mechanical pain, NPS LB: nonpainful site at low back, n.s.= no significant , nsCLBP-W-TE: nonspecific chronic low back pain without trauma exposure, OR: odds ratio, SMP LB: site of most severe pain at low back, TA: tibialis anterior

Table 2: Results of Risk of Bias Assessment of the selected studies (n= 24)

Studies	Selection				Comparability		Exposure			Score/stars
	1	2	3	4	1a	1b	1	2	3	
Blumenstiel et al. 2011	-	-	*	-	*	-	-	-	-	2
Corrêa et al. 2015	-	-	-	*	*	*	-	*	-	4
Farasyn & Meeusen 2005	-	-	-	*	-	-	-	*	-	2
Farasyn & Meeusen 2007	*	-	-	*	*	-	-	-	-	3
Farasyn &Lassat 2016	-	-	*	*	-	-	-	-	-	2
Gerhardt et al. 2015	-	*	-	*	-	-	*	*	-	4
Giesbrecht & Battié 2005	-	-	*	*	*	*	*	*	-	6
Goubert et al. 2017	-	-	*	*	*	*	-	*	-	5
Laursen et al. 2005	-	-	*	*	-	-	-	*	-	3
Lewis et al. 2010	-	-	-	*	-	-	-	*	-	2
Marcuzzi et al. 2018	-	*	*	-	-	*	*	*	-	5
Meints et al. 2018	-	-	*	-	-	-	-	*	-	2
Mlekusch et al. 2016	-	*	*	*	*	*	-	*	-	6
O'Neill et al. 2007	-	*	-	*	*	*	-	*	-	5
Neziri et al. 2012	-	*	*	*	*	*	-	*	-	6
O'Sullivan et al. 2014	-	*	-	*	*	*	-	*	-	5
Owens et al. 2016	-	-	*	*	*	*	-	*	-	5
Özdolap et al. 2015	-	-	-	*	-	-	*	*	-	3
Puta et al. 2013	-	-	-	-	*	*	-	*	-	3
Rabey et al. 2015	-	-	*	-	*	*	-	*	-	4
Schenk et al. 2007	-	-	*	*	-	-	*	*	-	4
Simmonds & Claveau 1997	-	-	-	-	*	*	-	*	-	3
Tesarz et al. 2015	*	-	-	*	*	*	*	*	-	6
Yildiz et al. 2017	-	-	-	-	-	-	-	*	-	1

Selection: 1) the case definition being adequate, 2) representativeness of the cases, 3) selection of controls, 4) definition of controls. Comparability: 1a) study controls of age and/or gender, 1b) questionnaire. Exposure: 1) ascertainment of exposure, 2) same method of ascertainment for cases and controls, 3) non-response rate.

Pressure Pain Threshold

The results of the meta-analysis are shown in figures 2 through 6. Funnel plots were symmetrical, and no sign of publication bias was noted. The PPT, measured at the scapula (figure 2), was significantly lower in patients with nonspecific LBP than in healthy controls (pooled mean difference, 119.2 kPa; 95%CI: 91.8, 146.6 kPa; *P*<.001). (18, 29, 35, 36, 42, 45) The PPT measured at the arm (figure 3), was significantly lower in patients with nonspecific LBP than in healthy controls (mean difference: 36.32 kPa; 95%CI: 2.27,70.37 kPa; *P*=.04).(32, 33, 40, 42, 45) For PPTs, measured at the hand (figure 4), heterogeneity was high, I^2= 97%.(13, 16, 29, 34, 37, 38, 41, 46) Subgroup analysis revealed that I^2 values dropped to 6% and 0% when taking into account studies with NOS scores at or above 4 or below 4, respectively. Pooled PPT values of studies with NOS score of 4 or greater were significantly lower in the group with nonspecific LBP compared to healthy controls (mean difference, 5.20 kPa; 95%CI: 1.32, 9.07 kPa; *P*=.009). Pooled PPT values of studies with NOS score less than 4 were significantly higher in the group with nonspecific LBP compared to healthy controls (mean difference, -28.27 kPa; 95%CI: -29.30, -27.24 kPa; p<.001).(16, 29, 34, 37, 41) The PPT, measured at the gluteal site (figure 5) was significantly lower in patients with nonspecific LBP than in healthy controls (mean difference, 218.63 kPa; 95%CI: 49.69, 387.57kPa; *P*=.01).(32, 33, 35, 44) The PPT measured at the lower leg (figure 6) was significantly lower in patients with nonspecific LBP than in healthy controls (mean difference, 68.51 kPa; 95%CI: 19.15, 117.86 kPa; *P*=.007).(15, 36, 37, 43)

Three studies with PPT measurements could not be included in the meta-analysis. Two studies used the 'remote site' that did not fit within our subgroups (19, 39) and 1 study presented results by reporting the median.(17) All PPT values (lower back and remote site) of the group with nonspecific LBP in that study were significantly lower than those in healthy controls.(17) Özdolap et al. measured PPTs at the lower back, 12 sciatic Valleix points, and the fibromyalgia tender points. All mean PPT values in the group with nonspecific LBP were significantly lower than those in healthy controls.(19) Schenk et al. measured PPTs at the lower back and forehead. All PPT values measured at the lower back in people with nonspecific LBP did not differ from those measured in healthy controls, whereas PPT values measured at the forehead were lower (*P*=.049) compared to those in healthy controls.(39)

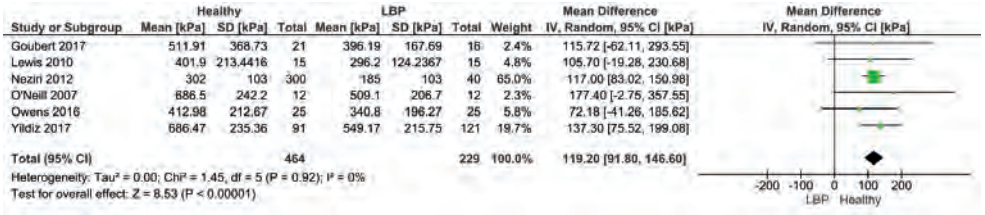

FIGURE 2. Pooled results of PPTs for cluster Scapula

PPTs: pressure pain thresholds; kPa: kilopascal; SD: standard deviation; LBP: low back pain; IV: inverse-variance; Random: random-effects; 95% CI: 95% confidence interval

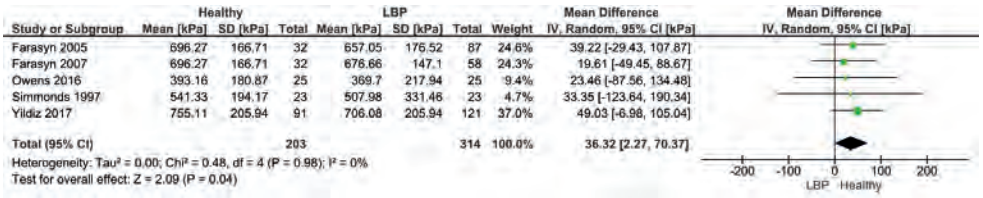

FIGURE 3. Pooled results of PPTs for cluster Arm

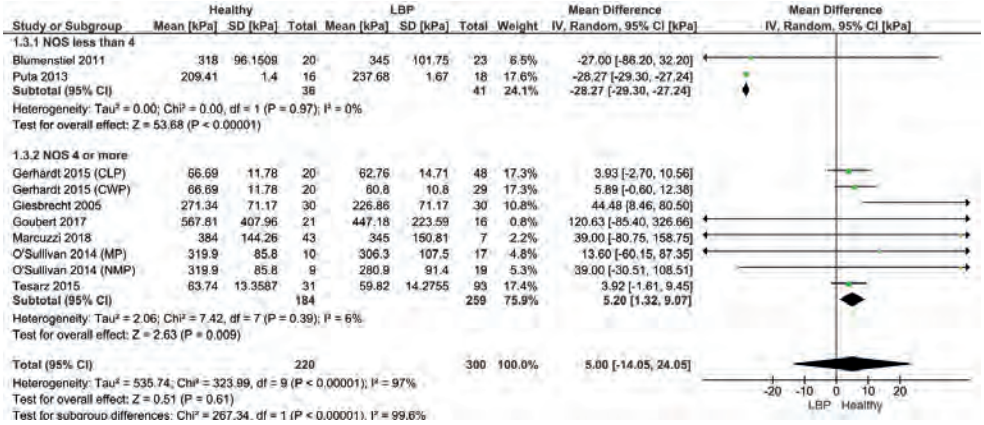

FIGURE 4. Pooled results of PPTs for cluster Hand

NOS: Newcastle-Ottawa quality assessment scale; CLP: chronic localized pain; CWP: chronic widespread pain; MP: mechanical pain; NMP: non-mechanical pain

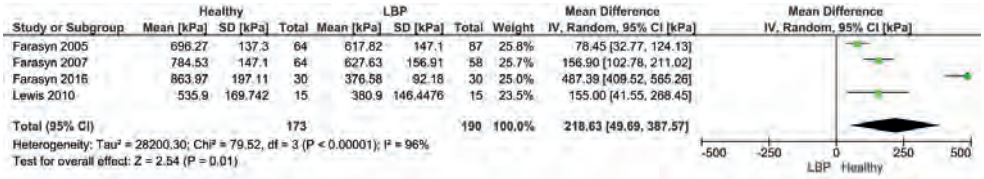

FIGURE 5. Pooled results of PPTs for cluster Gluteal

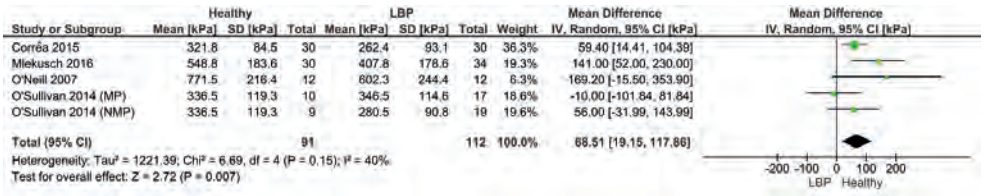

FIGURE 6. Pooled results of PPTs for cluster Lower leg

PPTs: pressure pain thresholds; kPa: kilopascal; LBP: low back pain; SD: standard deviation; IV: inverse-variance; Random: random-effects; 95% CI: 95% confidence interval; MP: mechanical pain; NMP: non-mechanical pain

Temporal Summation

The results of the meta-analysis are shown in figures 7 and 8. Funnel plots were symmetrical, and no sign of publication bias was noted. For temporal summation measured at the lower back (figure 7), heterogeneity was high (I^2= 72%). Subgroup analysis revealed that I^2 values dropped to 0% and 3% when considering studies with NOS less than 4 and 4 or greater, respectively. Pooled temporal summation values of studies with NOS score less than 4 were significantly higher in the healthy controls compared to patients with nonspecific LBP (mean difference, 1.04; 95%CI: 0.16,1.93; *P*=.02). Pooled temporal summation values of studies with NOS score of 4 or greater were significantly higher in patients with nonspecific LBP compared to healthy controls (mean difference, -0.84; 95%CI: -1.24, -0.44; *P*<.001).(13, 34, 38, 41, 46) The subgroup with temporal summation measured at the hand (figure 8), revealed no significant difference between patients with nonspecific LBP and healthy controls (*P*=.06).(13, 34, 38, 41, 46, 47)

Three studies using temporal summation were not included in the meta-analysis because of a different measurement protocol.(18, 29, 45) Goubert et al. reported that the temporal summation value of people with nonspecific LBP was higher (ie, more enhanced) than that in healthy controls.(29) Significance was not described. The temporal summation values reported by Owens et al. showed a significantly higher sensitivity in patients with nonspecific LBP compared with healthy controls.(45)

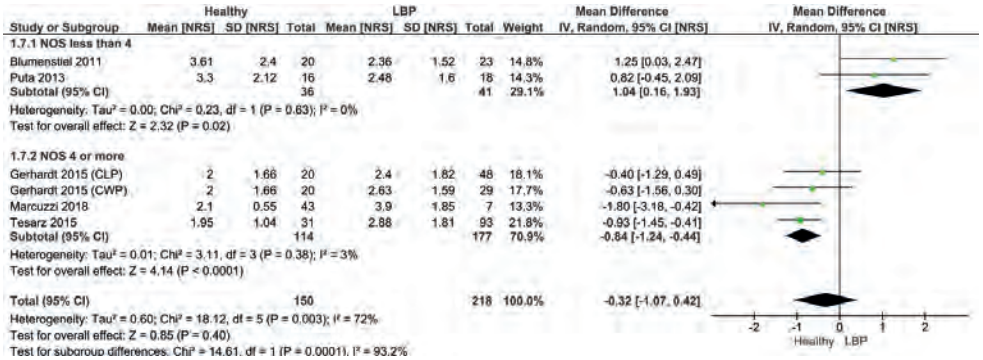

FIGURE 7. Pooled results of TS for cluster Lumbar

TS: temporal summation; NRS: Numeric Rating Scale; LBP: low back pain; SD: standard deviation; IV: inverse-variance; Random: random-effects; 95% CI: 95% confidence interval; NOS: Newcastle-Ottawa quality assessment scale; CLP: chronic localized pain; CWP: chronic widespread pain

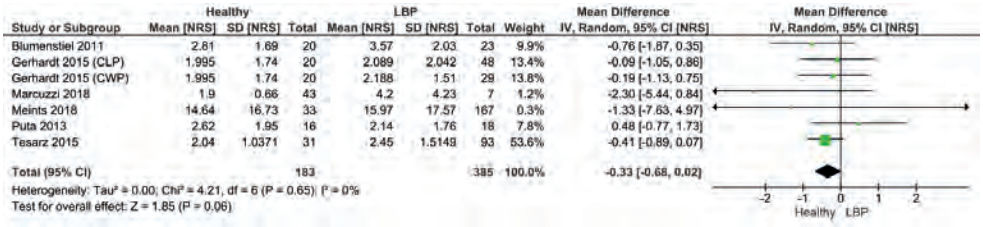

FIGURE 8. Pooled results of TS for cluster Hand

TS: temporal summation; NRS: Numeric Rating Scale; LBP: low back pain; SD: standard deviation; IV: inverse-variance; Random: random-effects; 95% CI: 95% confidence interval; CLP: chronic localized pain; CWP: chronic widespread pain

Conditioned Pain Modulation

In 6 studies, a conditioned pain modulation protocol was used. Results were not pooled because of differences between the protocols.(15, 29, 30, 43, 45, 46) The study of Rabey et al. found that more healthy controls showed a significant inhibitory effect than did people with nonspecific LBP.(30) In the study of Corrêa et al. conditioned pain modulation outcomes showed that PPT values at the lower back and the tibialis anterior in the group with nonspecific LBP were significantly lower compared to those in healthy controls. During conditioned pain modulation, the group with nonspecific LBP demonstrated a statistically significant decrease in the lumbar PPT, while healthy controls demonstrated a significant increase in the lumbar PPT.(15) Goubert et al. demonstrated no significant differences between patients with nonspecific LBP and healthy controls.(29) Mlekusch et al.(43) and Owens et al.(45) showed a normal conditioned pain modulation effect in both groups; PPT values were increased after the conditioned pain stimulus in both the group with nonspecific LBP and healthy controls. Marcuzzi et al. showed no significant differences between the group with nonspecific LBP and healthy controls.(46)

Discussion

The present systematic review and meta-analysis critically appraised the current literature on mechanical QST-measurements in patients with nonspecific LBP in order to examine signs of altered sensory functioning in this population. The meta-analysis found that overall PPT measurements at remote body parts are significantly lower in patients with nonspecific LBP compared with healthy controls. This finding is indicative of central sensitization in people with nonspecific LBP.(49) In the studies with superior methodological quality, temporal summation was enhanced in the lumbar region, but not at remote sites, in people with nonspecific LBP compared to healthy controls. Regarding conditioned pain modulation in patients with NSLBP, the findings were mixed. Although we did not find a clear picture of signs of central sensitization in people with nonspecific LBP, the available literature regarding mechanical somatosensory functioning provides some evidence of central sensitization in people with nonspecific LBP.

Central sensitization is a phenomenon characterized by enhanced nociceptive processing combined with disturbed top-down modulation. Quantitative sensory testing measures objectify these neurophysiological processes and are used to conclusions about the way the sensory systems processes different stimuli. In this study, only a small number of studies used temporal summation

and/or conditioned pain modulation, which hampered conclusions about changes in this type of QST measurement and may explain the inconsistent results, underscoring the importance of conducting a meta-analysis. Inconsistent findings regarding QST measurements may also be due to the presence of subgroups within the population with nonspecific LBP. Only 2 of the included studies separately reported on localized and widespread pain. Therefore, subgroup analyses were not possible. The present review was not designed to reveal or refute subgroups within people with nonspecific LBP. There is a need for more studies using more extended QST measurements in order to determine the existence of different QST profiles in patients with nonspecific LBP.

As mechanical QST measurements are most often used in studies of patients with nonspecific LBP, this review is limited to studies using mechanical QST-measurements only. How the somatosensory system responds to thermal and electrical stimuli in people with nonspecific LBP and central sensitization remains to be examined. Finally, it is currently unknown whether the different results in these static (PPT) and dynamic (temporal summation and conditioned pain modulation) measurements can be explained by methodological issues (eg, smaller sample sizes and different protocols) or by underlying physiological differences. Notably, a clear definition of nonspecific LBP was not reported in most studies.

The strength of this review is that it is the first meta-analysis to study and summarize QST measurements in people with nonspecific LBP. It should be taken into consideration that many of the included studies were rated as having low to moderate methodological quality. Based on their narrative analysis of the literature, Roussel et al. concluded that signs of central sensitization may be present in patients with LBP.(14) The results of our meta-analysis confirm that PPTs at remote body parts are significantly lower and temporal summation at the lower back is enhanced in patients with nonspecific LBP compared to healthy controls. This conclusion could be strengthened by studies with higher methodological quality. Because the reported standard error of measurement of QST measures may vary between measured populations, measured body parts, and different protocols, it is difficult to compare scores and evaluate the magnitude of pooled differences properly. However, the pooled difference for PPTs measured at the scapula (mean difference, 119.2 kPa; 95%CI: 91.8, 146.6 kPa) exceeds the range of previously reported standard error of measurement of 18.2-52 kPa.(50)

The results of this study should be interpreted with caution as we only included several types of observational study design that compared groups of patients with nonspecific LBP to healthy controls. Additionally, we currently lack clear cut-off scores for QST measurement that would enable health care professionals to make sound judgements in individual cases. However, health care professionals should be aware that altered sensory processing may be present in patients with nonspecific LBP and that this might require a different treatment approach.(51)

Conclusion

The PPTs at remote body parts and temporal summation at the lower back differed between people with nonspecific LBP and healthy controls. Results of studies using conditioned pain modulation measurement were mixed.

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Appendix 1

Search string for Medline:

("Central Nervous System Sensitization"/ OR hyperalgesia/ OR "Neural Inhibition"/ OR "pain threshold"/ OR hypersensitivity/ OR (sensitization* OR sensitisation* OR desensitization* OR desensitisation* OR hyperalgesi* OR hypoalgesi* OR (central* ADJ3 sensitivit*) OR hyperexcitab* OR (pain ADJ6 (modulat*)) OR ((inhibit* OR facilitat*) ADJ3 mechanism*) OR ((nerve OR neural*) ADJ3 inhibit*) OR (pain ADJ3 (threshold*)) OR algometr* OR hypersensitiv* OR (summat*) OR (quantitativ* ADJ3 sensor* ADJ3 test*) OR qst OR habituat* OR (cognit* ADJ6 modulat*)).ab,ti.) AND ("low back pain"/ OR "back pain"/ OR (((backpain OR backache)) OR (back ADJ3 pain*) OR lowback OR (low* ADJ back) OR ((lumbo* OR lumba*) ADJ6 pain*))) NOT (exp animals/ NOT humans/)

Appendix 2

The Newcastle-Ottawa quality assessment scale: case-control

Selection

Is the case definition adequate?

Representativeness of the cases

Selection controls

Definition of controls

Comparability

Study controls for (select the most important factor: we chose control matched age and sex)

Study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor)

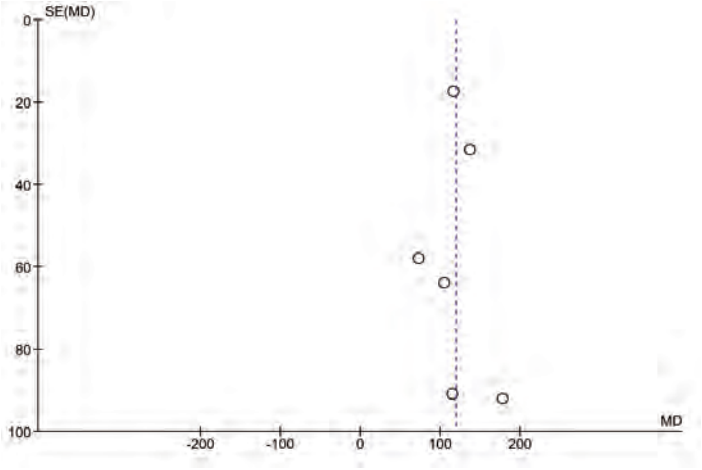
Exposure

Ascertainment of exposure

Same method of ascertainment for cases and controls

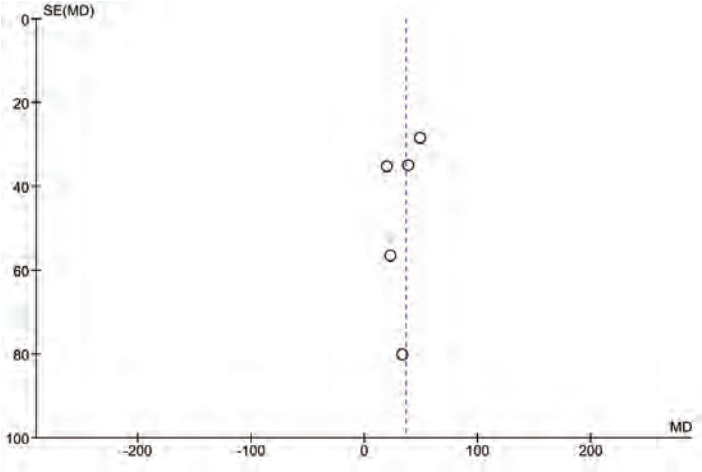
Non-response rate

Appendix 3



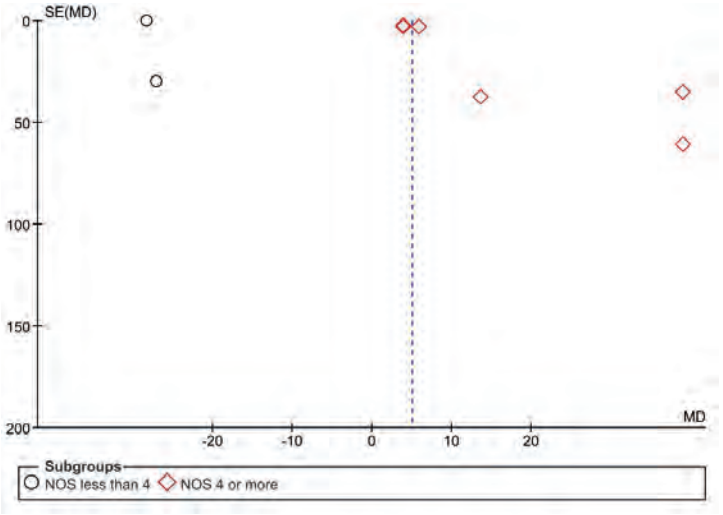
Funnel Plot of PPTs for cluster Scapula

SE: standard error; MD: mean difference



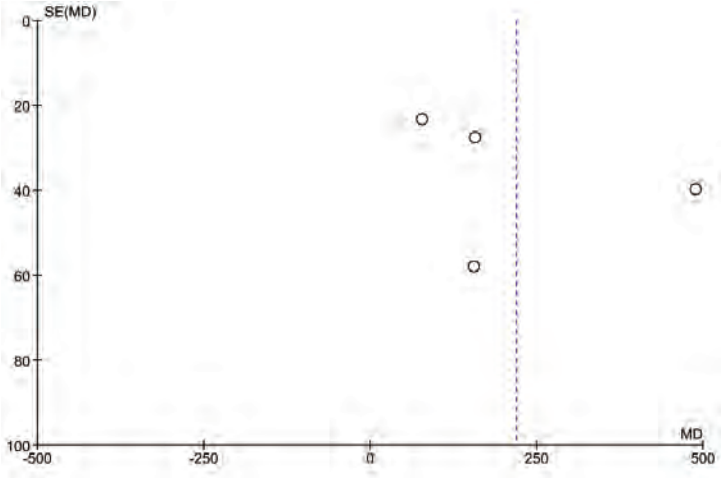
Funnel plot of PPTs for cluster Arm

SE: standard error; MD: mean difference



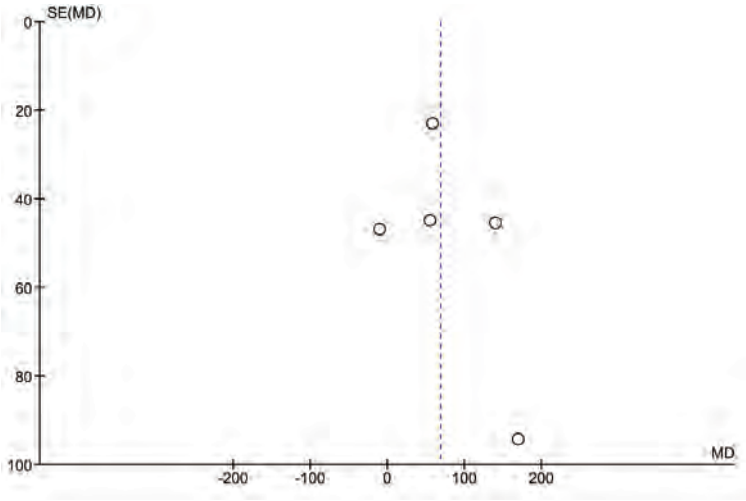
Funnel plot of PPTs for cluster Hand

SE: standard error; MD: mean difference



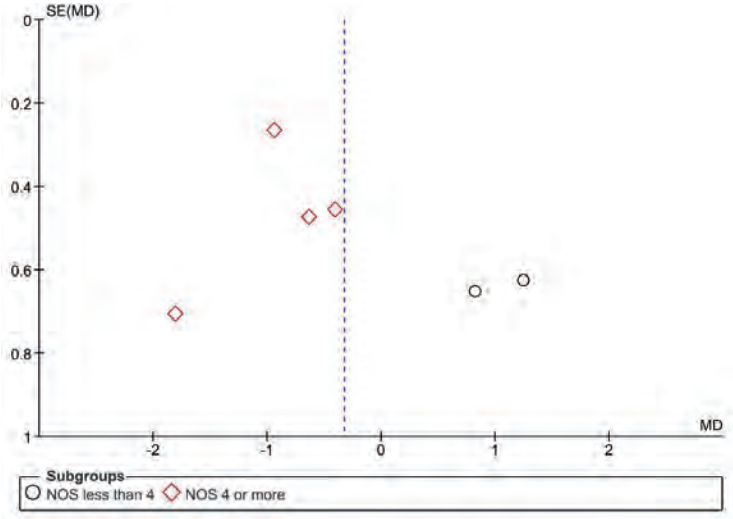
Funnel plot of PPTs for cluster Gluteal

SE: standard error; MD: mean difference



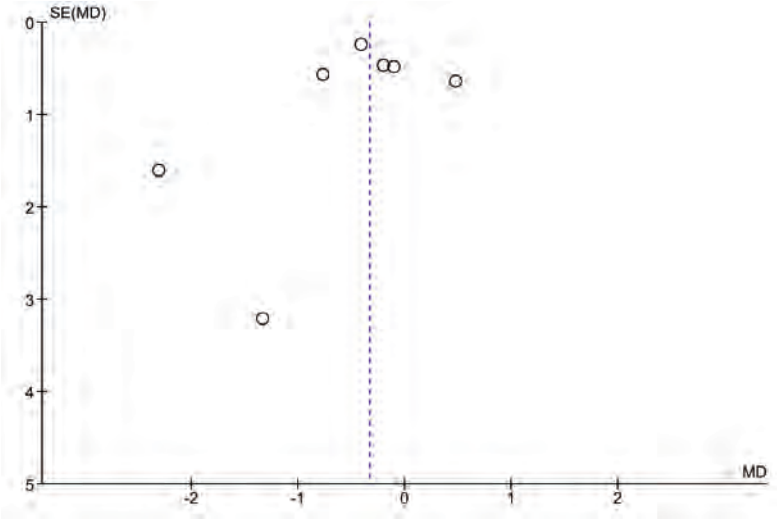
Funnel plot of PPTs for cluster Lower leg

SE: standard error; MD: mean difference



Funnel plot of TS for cluster Lumbar

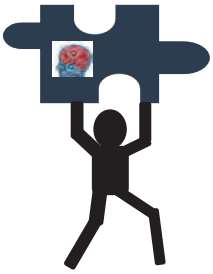
SE: standard error; MD: mean difference



Funnel plot of TS for cluster Hand

SE: standard error; MD: mean difference

Chapter three



Associations between Cognitive, Emotional and Behavioral Factors and Symptoms of Central Sensitization in People with Non-Specific Low Back Pain in Primary Care: a Cross-Sectional Study

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Abstract

Objectives: Main aim of this cross-sectional study is exploring associations between Central Sensitization (CS) and inflexibility pattern of behavior, cognitive fusion and perceived injustice in people with non-specific low back pain (NSLBP). Secondary aim is to compare pain intensity, widespread pain, functional disability, pain catastrophizing, inflexibility pattern of behavior, cognitive fusion, kinesiophobia and perceived injustice between NSLBP patients with and without the symptoms of CS.

Methods: People with NSLBP were recruited from February 2018 to February 2019 while visiting a primary care physiotherapist. Pearson's correlation was used to analyze associations between CS and inflexibility pattern of behavior, cognitive fusion and perceived injustice, pain intensity, widespread pain, functional disability, pain catastrophizing and kinesiophobia. By using the Independent Sample t-test NSLBP patients with symptoms of CS were compared to patients without such symptoms.

Results: Patients with NSLBP (n=124) participated. For the primary aim, significant associations were found between the CSI and inflexibility pattern of behavior ($r=0.390, p<0.001$), cognitive fusion ($0.586, p<0.001$) and perceived injustice ($r=0.515, p<0.001$). The results of the Independent Sample t-test showed significant differences between the two subgroups ($p<0.01$), except for widespread pain ($p=0.053$) and kinesiophobia ($p=0.027$). The mean scores of the subgroup with symptoms of CS were significantly higher than the mean scores of the subgroup without symptoms of CS.

Conclusion: There are weak to moderate associations between CS and psychosocial and cognitive behavioral factors. Also, people with NSLBP with symptoms of CS scored significantly more poorly on several psychosocial variables compared to patients without symptoms of CS.

Key words: non-specific low back pain, central sensitization, psychological factors, associations

Introduction

Symptoms of central sensitization (CS) are increasingly recognized in people with (non-specific) low back pain (NSLBP).(1) CS is defined as "an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity".(2) Neurophysiological characteristics for CS are: dysfunctional endogenous analgesia, enhanced ascending nociceptive facilitation and increased brain activity in brain regions known as the dynamic pain connectome.(3, 4)

Clinically, symptoms of CS manifest as widespread pain, generalized hypersensitivity (hyperalgesia and/or allodynia), higher pain intensity, lowered pain thresholds, lower quality of life and poorer prognosis.(5, 6) Some research suggests there is a subgroup of people with symptoms of CS in NSLBP patients.(1, 7) Roussel et al. (2013) estimate that approximately 25% of the people with NSLBP exhibit signs of CS.(8)

Risk factors for symptoms of CS and somatosensory changes are several psychological factors such as stress, depression, fear, catastrophizing and inadequate illness perceptions.(9) Many studies investigated the association between symptoms of CS and various psychological risk factors in people with chronic (low back) pain.(10-12) These studies reveal a moderate association between symptoms of CS and sleep disturbance, depressive symptoms, pain intensity and perceived disability. Other studies reported a relationship between anxiety sensitivity and the experience of pain and reduced pain thresholds.(11, 12) A cross-sectional study investigated associations between symptoms of CS and illness perceptions, kinesiophobia, pain catastrophizing, functioning, pain behavior and pain intensity in people with chronic NSLBP. The results indicated that symptoms of CS were moderately associated with all the investigated variables.(10)

Another psychological factor that may be involved in the development of symptoms of CS is psychological inflexibility. This is defined as “being excessively entangled in experiential avoidance as a result being cognitively fused, lacking acceptance and openness to painful thoughts and feelings, disconnected from the present moment, and without commitment to living in accordance with personal values”. (13) It means that people with chronic pain avoid thoughts and situations that can provoke pain and as a result exhibit rigid behavioral patterns like avoiding activities. In the short term, this strategy can result in some relief. However, it prevents gaining satisfaction from these activities and has nothing but negative long-term consequences.(13) Another cognitive factor that influences pain perception is cognitive fusion, defined as “the tendency of behavior to be overly regulated by cognition, where, for example, a person acts on thoughts as though they are literally true”. (13) Suppose, a teenager with chronic pain and high cognitive fusion is convinced that no one believes him to be in pain. As a consequence, this teenager will experience fear and have less social contact with peers. In both, psychological inflexibility and cognitive fusion, thoughts dominate and influence behavior. This can be counterproductive in attempts to manage chronic pain.

Perceived injustice is a further important psychological factor for somatosensory changes. These changes are influenced by cognitive and emotional factors.(14) Where injury has occurred as a result of an offense by another, the injury victim might experience post-injury life with a sense of injustice.(15) The perception of injustice can appear in case of the experience of irreparable loss or unnecessary suffering as a result of someone else’s action.(15) This may represent a risk factor for recovery after musculoskeletal injury.(16) The focus of the study is the relation between the clinical

construct of central sensitization and its relation with psychological constructs like psychological inflexibility, cognitive fusion and perceived injustice as these constructs are important aspects of chronic pain problems stemming from the theory underlying Acceptance & Commitment Therapies.(17) This therapy is a new third generation of cognitive behavior therapy.(18) It intends for increasement of psychological flexibility (opposite of psychological inflexibility) and improvement of function instead of reducing pain.(19) Psychological inflexibility and cognitive fusion are direct derivatives and perceived injustice is an indirect derivative of the cognitive behavior therapy. It is hypothesized that these three constructs affect the phenomenon of CS.

To the best of our knowledge no research has been done to explore associations between symptoms of CS and 1) inflexibility pattern of behavior, 2) cognitive fusion and 3) perceived injustice in people with NSLBP in primary care. Hence, the main objective of the present explorative study is to examine the associations between symptoms of CS and inflexibility pattern of behavior, cognitive fusion and perceived injustice in people with NSLBP in primary care. The secondary aim is to compare pain intensity, widespread pain, functional disability, pain catastrophizing, inflexibility pattern of behavior, cognitive fusion, kinesiophobia and perceived injustice between NSLBP patients with and without symptoms of CS.

Methods

Study design and setting:

This cross-sectional study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement.(20)

Study participants were recruited from February 2018 to February 2019 while visiting Dutch primary care physiotherapists for low back pain complaints. The Ethical Committee of Maasstad Hospital, Rotterdam, the Netherlands, approved the study procedures. Prior to study participation, participants were all informed and they provided written informed consent. In a separate room, they completed several paper questionnaires after their first treatment session.

Participants:

Eligible participants had to meet the following criteria: age between 18-65 years, non-specific low back pain for at least one week with or without radiating leg pain and pain regularly experienced during the day. Exclusion criteria were: having neuropathic pain, a positive straight leg raise test, back pain due to referred pain from internal organs, back pain after trauma or surgery, back pain related to psychiatric diagnoses determined by psychiatrist, pregnancy and finally inability to read or write Dutch. Participants were screened for selection criteria by experienced physiotherapists, during routine intake and physical examination according to the guideline “Low back pain” of KNGF (Royal Dutch Society for Physical Physiotherapy) and were asked to participate in this study.(21)

Questionnaires:

Participants were asked to respond to demographic questions about their sex, age, duration of current low back pain episode and whether or not their low back pain was recurrent. In addition, they

completed various self-reported questionnaires about symptoms of CS, intensity and location of their pain, the degree of limitation in functional, cognitive and emotional aspects of their low back pain.

The *Central Sensitization Inventory* (CSI), consisting of part A and B, is a questionnaire used to measure the presence of symptoms of CS.(22) It contains 25 CS related questions on a 5-point Likert scale (0 = never, 4 = always).(23) Scores ≥40/100 imply the presence of clinically relevant symptoms of CS. A sensitivity of 81% and a specificity of 75% for this cut-off is reported for the presence of CS.(22) The Dutch CSI has excellent test-retest reliability, is equivalent to the original version and useful in the clinical setting to indicate the presence of symptoms of CS.(24)

The *Numeric rating Scale* (NRS) was used to measure highest, lowest and mean pain intensity. It varies from 0 (no pain) to 10 (the severest pain imaginable). The NRS shows a fair test-retest reliability.(25) The intraclass correlation coefficient (ICC) is 0.76; 95%CI 0.51-0.87.(26) The total score of the NRS can be interpreted in three subgroups: a score of ≤ 5 represents 'mild' pain-related interference with functioning, a score of 6-7 represents 'moderate' pain-related interference with functioning and a score of ≥ 8 'severe' pain-related interference with functioning.(27)

The *Patient Pain Drawing* is used to indicate the distribution of the patients' experienced pain. Patients are requested to shade the areas where they experience pain on an outline of a human figure. The human figure is divided into 45 body areas. Each body part is equal to a certain percentage of the total body surface.(28) The amount of shaded areas is an indication for widespread pain. The data obtained using this tool show acceptable test-retest reliability (r= 0.85).(29)

The level of functional disability for patients with low back pain is assessed by the *Quebec Back Pain Disability Scale* (QBPDS), a questionnaire containing 20 daily activities with a 6-point Likert scale (0 = no problem, 5 = not able to do).(30) The higher the total score, the more a patient is limited in daily activities.(31) The Dutch version of the QBPDS is considered to have high reliability.(32)

The *Pain Catastrophizing Scale* (PCS) is a questionnaire to measure the degree of pain catastrophizing. It contains 13 items on a 5-point Likert scale to explore pain-related cognitions (0 = not at all, 4 = all the time).(33) Scores vary from 0 to 52.(33) There is a cut-off score of ≥30/52, which means a clinical relevant degree of pain catastrophizing.(33) Pain catastrophizing is seen as a multidimensional construct which is questioned in the subscale on rumination, magnification and helplessness.(33) The scores obtained using the PCS show good internal consistency and test-retest reliability.(34-36)

The *Psychological Inflexibility in Pain Scale* (PIPS) questionnaire assesses the inflexibility pattern of behavior. This questionnaire originates in the Acceptance and Commitment Therapy.(37) This questionnaire contains two subscales: 'avoidance of pain' and 'cognitive fusion' related to pain. The PIPS consist of 12-items with a 7-point Likert scale (1 = never true, 7 = always true). The cut-off score of this questionnaire is ≥ 26.4/84.(37) The subscale scores show good internal consistency.(37) A confirmatory factor analysis indicated an acceptable to good fit of the model and good internal consistencies for the Dutch version.(38)

The *Cognitive Fusion Questionnaire 13* (CFQ13) indicates the degree to which behavior is influenced by cognition.(39) This questionnaire consists of 13 items with a 7-point Likert scale (1 = never true, 7 = always true). Gillanders et al. (2014) describe the higher the score, the higher the level of cognitive fusion.(39) The CFQ13 has an excellent internal consistency and good test-retest reliability.(39)

To assess kinesiophobia the *Tampa scale for kinesiophobia* (TSK) is used. When using the TSK, participants are asked to score 17 statements on a 4-points Likert scale (1 = highly disagree, 4 = highly agree). If the score is ≥37/68, it indicates kinesiophobia.(40) The scores obtained using the Dutch version of the TSK (TSK-DV) show good criterion validity, construct validity and are internally consistent.(41)

The *Injustice Experience Questionnaire* (IEQ) assesses the frequency in which patients experience different thoughts concerning the sense of unfairness in relation to their injury.(42) Patients are requested to provide their opinion regarding 12 statements on a 5-point Likert scale (0 = never, 4 = all the time). A cut-off score of ≥ 30/48 assumed to be a relevant clinical level for perceived injustice.(42) The test-retest reliability of the Dutch IEQ is good.(43)

Sample size

The (a priori) sample size calculation for this study was performed based on the results of the study of Huysmans et al. (2018), using G*Power (Düsseldorf, Germany)(44) for a correlation analysis with a moderate effect size (ρ=0.3), significance level of α=0.05 and power of 0.8.(10) The "two-tailed analysis" showed that the total sample must contain at least 82 participants.

Statistical Methods

To analyze the data IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.) was used. The characteristics were analyzed to specify the participants by calculating mean, standard deviation, minimum and maximum as regards distribution and percentage. To determine the normality of the data, the Kolmogorov-Smirnov test was used. Furthermore, data were checked for outliers and linear relationship between the variables. Data were also checked for completeness, prior to the analysis. If data were incomplete, the physiotherapist made a phone call in order to collect the missing elements. For the main purpose of this study, associations between symptoms of CS and inflexibility pattern of behavior, cognitive fusion and perceived injustice were analyzed. Pearson correlations were calculated between the total score of the CSI and the total score of PIPS, CFQ13 and IEQ. The interpretation of the correlation coefficient was done by the classification by Schober et al. (2018).(45) (0.00-0.10 negligible correlation, 0.10-0.39 weak correlation, 0.40-0.69 moderate correlation, 0.70-0.89 strong correlation and 0.90-1.00 very strong correlation).

For the second aim the results of the questionnaires of NSLBP patients with symptoms of CS were compared to those without symptoms of CS. The total score of the CSI was used to split the study sample into two subgroups using the above mentioned cut-off score ≥40/100 (22) : those patients with NSLBP having a total CSI score ≥40/100 were classified as the CS group, while those having a CSI total score <40 were classified as the no CS group. To investigate differences between these two subgroups for intensity, widespread pain, functional disability, cognitive, emotional and functional aspects of their low back pain, independent sample t-test (normally distributed data) or the Mann-Whitney U test (non-normally distributed data) was performed. Bonferroni correction was applied because of conducting multiple significance tests and therefore p-value was determined at 0.006.

Results

Participants

A total of 124 patients participated in this study. The mean age was 43 (SD: 13.70) years and 43 (34.7%) of the participants were male. All patients had had a duration of low back pain between 1-2080 weeks. Twenty-four patients had low back pain for the first time, while 93 patients had recurrent low back pain. Forty-nine participants had acute LBP (< 6 weeks) , sixteen of the patients had subacute LBP (6-12 weeks) and 38 of the participants had chronic LBP (> 12 weeks).(46) The NRS_{mean} was 5 (SD: 1.98) and the average level of functional disability (QBPDS) for all patients with NSLBP was 28 (SD: 16.17). During the recruitment two participants were excluded because of their age. Table 1 and 1A show the results of the descriptive statistics of all the participants divided into acute, subacute en chronic LBP.

Table 1: Descriptives of total investigated population (n=124).

	Mean ± SD	Min- max
Sex, male (%)	43 (34.7)	
Age in years (n=120)	43.27 ± 13.70	18-65
CSI (n=120)	28.93 ± 13.23	1-69
NRS_{mean} (n=123)	5 ± 1.98	0-9
Patient Pain Drawing (n=116)	11.37 ± 8.96	2-55.25
QBPDS (n=116)	28 ± 16.17	0-81
PCS (n=124)	13.40 ± 10.22	0-46
PIPS (n=122)	38.73 ± 13.51	12-79
CFQ13 (n=121)	37.23 ± 11.05	14-65
TSK (n=121)	30.13 ± 7.17	18-59
IEQ (n=122)	6.97 ± 7.63	0-37
Acute LBP	N= 49	
Subacute LBP	N= 16	
Chronic LBP	N= 38	

CFQ13, Cognitive Fusion Questionnaire; CSI, Central Sensitization Inventory; IEQ, Injustice Experience Questionnaire; LBP, low back pain; NRS, Numeric Rating Scale; PCS, Pain Catastrophizing Scale; PIPS, Psychological Inflexibility in Pain Scale; QBPDS, Quebec Back Pain Disability Scale; TSK, Tampa Scale for Kinesiophobia.

Table 1A: Descriptives of the studied population divided in acute, subacute and chronic low back pain.

	Acute LBP	Subacute LBP	Chronic LBP
Sex	Women n=29 Men n=20	Women n=9 Men n=7	Women n=25 Men n=13
Age in years mean ± SD	41.9 ± 13.69	45.4 ± 14.42	45.31 ± 15
NRS_{mean} mean±SD	4.98 ±2.18	4.88 ± 1.41	5.36 ± 1.82
CSI[a]	9	1	13
PCS[a]	5	0	3
PIPS[a]	37	12	34
TSK[a]	8	1	6
IEQ[a]	0	0	1

CSI, Central Sensitization Inventory; IEQ, Injustice Experience Questionnaire; LBP, low back pain; NRS, Numeric Rating Scale; PCS, Pain Catastrophizing Scale; PIPS, Psychological Inflexibility in Pain Scale; TSK, Tampa Scale for Kinesiophobia.

[a] number of participants who score above the cut-off value of the questionnaire

Outcomes

All variables were normally distributed. Positive moderate to weak significant associations were found between the symptoms of CS and inflexibility pattern of behavior, cognitive fusion and perceived injustice (Table 2). The CSI score correlated moderately with the cognitive fusion (r=0.586, P<0.001) and with the perceived injustice (r=0.515, p<0.001). The weakest correlation coefficient was found between the CSI and the inflexibility pattern of behavior (r=0.390, P<0.001) (Table 2).

Of the 124 patients, 120 completed the CSI. Twenty-seven patients had a score of ≥40 on the CSI and 93 patients had a score < 40. There was no significant difference in the variable age and sex between the two subgroups (Table 3). There was a significant difference in the positive score of the PIPS (p= 0.028) and TSK (p=0.017), using the cut-off scores, between the two subgroups. There was no significant difference in the positive score of the PCS (p=0.054) and IEQ (p=0.586) (Table 3). Nine participants with acute LBP had a CSI score of ≥40, one participant with subacute LBP had a CSI score of ≥40 and thirteen participants with chronic LBP had a CSI score of ≥40 (Table 3).

Table 4 shows the outcomes for both subgroups. The mean score of the subgroup with CSI ≥40 measuring pain intensity, functional disability, catastrophizing, inflexibility pattern of behavior, cognitive fusion and perceived injustice were significantly higher than the mean scores in the subgroup

with CSI< 40 (p<0.01), except for widespread pain (p= 0.053) and kinesiophobia (p=0.027). The subgroup having a CSI score of ≥40 demonstrated a NRS_{mean} score of 6.04 (SD:1.73) which is classified as 'moderate'.(27) While the subgroup with having a total CSI score of < 40 rated their pain as 4.73 (SD: 1.96), which is classified as 'mild'.(27)

Table 2: Measured outcomes of associations for Central Sensitization Inventory.

	N	r	p
NRS_{mean}	120	0.310	<0.001**
Patient Pain Drawing	113	0.413	<0.001**
QBPDS	112	0.531	<0.001**
PCS	120	0.413	<0.001**
PIPS	118	0.390	<0.001**
CFQ13	118	0.586	<0.001**
TSK	119	0.265	0.004*
IEQ	119	0.515	<0.001**

CFQ13, Cognitive Fusion Questionnaire; IEQ, Injustice Experience Questionnaire; NRS, Numeric Rating Scale; PCS, Pain Catastrophizing Scale; PIPS, Psychological Inflexibility in Pain Scale; QBPDS, Quebec Back Pain Disability Scale; TSK, Tampa Scale for Kinesiophobia.

*: statistically significant correlations (<0.05) tested with the Pearson test.

**: statistically significant correlations (<0.001) tested with the Pearson test.

Table 3: Descriptives for the studied participants with and without symptoms of CS.

	CSI ≥ 40 N=27			CSI < 40 N=93		
	Mean ± SD	Min-Max		Mean ± SD	Min-Max	Significance
Age	43.58±14.27[a]	22-64[a]		43.64±13.56[b]	18-65[b]	P= 0.984
Sex, male (%)	N=7[c] (25.9%)			N=36[d] (39.1%)		P= 0.209
PCS (%)	N=4[c] (14.8%)			N=4[h] (4.3%)		P= 0.054
PIPS (%)	N=25[a] (96.2%)			N=71[d] (77.2%)		P= 0.028*
TSK (%)	N=8[c] (29.6%)			N=10[d] (10.9%)		P= 0.017*
IEQ (%)	N=0[c] (0%)			N=1[d] (1.1%)		P= 0.586
Acute LBP	N=9[e] (19.1%)			N=38[e] (80.9%)		
Subacute LBP	N=1[f] (6.25%)			N=15[f] (93.8%)		
Chronic	N=13[g] (35.1%)			N=24[g] (64.9%)		

[a] N=26, [b] N= 91, [c] N=27, [d] N=92, [e] N=47, [f] N=16, [g] N=37, [h] N=93. CSI, Central Sensitization Inventory; IEQ, Injustice Experience Questionnaire; LBP, Low Back Pain; PCS, Pain Catastrophizing Scale; PIPS, Psychological Inflexibility in Pain Scale; TSK, Tampa Scale for Kinesiophobia.

*: statistically significant differences (<0.05) tested with the Chi-square test.

Table 4: Measured outcomes of questionnaires for population with and without symptoms of CS.

	CSI ≥ 40 N=26			CSI < 40 N=91			Independent T-test		
	Mean(SD)	Min-Max		Mean(SD)	Min- Max		df	F	Sign
NRS_{mean}	6.04(1.73)	1-8		4.73(1.96)	0-9		118	2.110	0.002*
Patient pain drawing (%)	15.42(12.84)	4-55.25		10.20(7.14)	2-37.25		111	7.564	0.053
QBPDS	38.69(17.87)	3-81		24.10(13.72)	0-64		110	2.553	<0.001*
PCS	20.26(10.90)	1-43		11.27(8.52)	0-44		118	4.681	<0.001*
PIPS	47.15(12.08)	20-68		36.03(12.49)	12-74		116	0.022	<0.001*
CFQ13	46.15(10.96)	22-65		34.80(9.65)	14-57		116	0.671	<0.001*
TSK	33.56(9.40)	22-59		29.10(6.15)	18-47		117	7.821	0.027
IEQ	13.04(8.20)	0-29		5.05(6.27)	0-37		117	5.485	<0.001*

CFQ13, Cognitive Fusion Questionnaire; IEQ, Injustice Experience Questionnaire; NRS, Numeric Rating Scale; PCS, Pain Catastrophizing Scale; PIPS, Psychological Inflexibility in Pain Scale; QBPDS, Quebec Back Pain Disability Scale; TSK, Tampa Scale for Kinesiophobia.

*: statistically significant differences (<0.01) tested with the independent samples t-test after Bonferroni correction (p<0.006)

Discussion

The primary aim of this study was to explore the associations between symptoms of CS and inflexibility pattern of behavior, cognitive fusion and perceived injustice in patients with NSLBP in primary care. The results showed weak to moderate significant associations between inflexibility pattern of behavior, cognitive fusion and perceived injustice and symptoms of CS in patients with NSLBP. The secondary aim was to compare pain intensity, widespread pain, functional disability, pain catastrophizing, inflexibility pattern of behavior, cognitive fusion, kinesiophobia and perceived injustice between NSLBP patients having a total CSI score of ≥ 40 and < 40. People with NSLBP with symptoms of CS scored significantly more poorly on pain intensity, functional disability, pain catastrophizing, inflexibility pattern of behavior, cognitive fusion and perceived injustice, compared to people without symptoms of CS. For widespread pain and kinesiophobia, there was no significant difference between the two subgroups. This study revealed the presence of symptoms of CS in 22% of patients with NSLBP seen in primary care.

Using established cut-offs, this study revealed that a large number of primary care patients with NSLBP show inflexibility pattern of behavior (100/122). This main finding is of prime importance to clinicians treating patients with NSLBP in primary care, as psychological inflexibility affects their behavior and emerges whenever pain or the possibility of pain occurs which may lead to avoidance behavior for situations with pain.(13) This behavior has its origin in pain-related fear and anxiety described in the fear-avoidance model. This model explains how acute LBP becomes chronic LBP and how a vicious

circle of avoidance behavior and disability arises.(47) This also explains the correlation between CSI and PIPS. Barke et al. (2015) describe that PIPS (especially the subscale "avoidance of pain") significantly predicts pain-related disability and is correlated with kinesiophobia.(48) In this study 94/121 patients have a positive score on CFQ13. In the process of cognitive fusion, thoughts about a pain-related event from the past merge with an actual pain-related event. These patients associate the actual pain-related event with the pain-related event from the past, which evokes the same emotional reaction. The patient is convinced that the thoughts are actual facts. However, in reality it is a misinterpretation of the actual pain-related event.(37) Also, this kind of cognitive factors can contribute to chronicity.(47) These behavior and cognitive factors can contribute and support the mechanism of CS.(8) Using the cut-off score for the IEQ, it appears minimally present in this population (one participant). Perceived injustice will occur in situations in which the injury is the result of another error or negligence.(15) The determination of the cut-off scores was investigated in a sample of people with musculoskeletal injuries due to work or vehicle accidents.(42) The cause of NSLBP is not attributable to a specific trauma or pathology.(49) This can explain why few people experience perceived injustice within the investigated patients with NSLBP. Because of its very low prevalence in the study population, the findings from the correlation analysis and independent sample t-test for the IEQ can be misleading. However it explains why there is no significant difference for the IEQ between the number of patients with NSLBP with and those without symptoms of CS.

In line with the study of Huysmans et al. (2018), the present study findings also suggest that patients with symptoms of CS have significantly more functional disability, pain intensity, pain catastrophizing, inflexibility pattern of behavior and cognitive fusion compared to patients with fewer symptoms of CS. Again, the fear-avoidance model could be an explanation: this may be due to the significantly higher scores in pain catastrophizing in patients with NSLBP with symptoms of CS. It is the cognitive element of risk factors to chronicity due to interpreted pain as being extremely threatening.(47) The significant higher score in inflexibility pattern of behavior and cognitive fusion in patients with NSLBP with symptoms of CS can be explained by the Acceptance and Commitment model. Patients with prolonged pain make great effort fighting against their pain experience.(50) For example, they avoid thoughts of pain or other people, reduce physical activities or distract themselves from activities or endlessly seek information. This inflexibility of pattern leads to reduced pain tolerance and increased severity of pain.(50) The patients with the significantly higher scores in cognitive fusion confuse pain-related thoughts with actual experience.(50) This evokes negative outcomes such as more pain and increased disability. (51) This contributes in developing or maintaining symptoms of CS.

This study shows that concepts like symptoms of CS and inflexibility pattern of behavior and cognitive fusion are moderately related and occur in people with LBP seen in primary care. For clinicians, it is important to realize that underlying principles as inflexibility pattern of behavior and/or cognitive fusion are highly prevalent in people with NSLBP seen in primary care. Psychological flexibility is the fundamental component of Acceptance and Commitment Therapy, an evidence-based treatment for patients with chronic pain (52) which focuses on reaching the client's most valued life goals rather than reducing pain.(17) In addition to psychological flexibility, cognitive fusion is also an important aspect within Acceptance and Commitment Therapy. Pincus et al. (2014) revealed that patients with chronic pain, treated by their physiotherapist, showed resistance to consult a psychologist for the Acceptance and Commitment Therapy.(53) It is a challenge for the physiotherapist to integrate Acceptance and Commitment Therapy in the treatment of patients with NSLBP. However, the available

evidence for Acceptance and Commitment Therapy provided by physiotherapists shows positive results, although effect size was small.(18)

The strength of this study is that all the participants visited a primary care physiotherapist. Many studies on this subject investigate participants from secondary or tertiary care setting. This cautiously suggests that this study is one of the few that describes the presence of symptoms of CS in primary care setting. Another strength is that this study is well powered.

For future research it would be interesting to describe general characteristics of people with NSLBP with CS as dominant pain mechanism. There is a need to improve the management of the large population with NSLBP. Future research can create subgroups using the CSI to stimulate the improvement of the management as Aoyagi et al. (2019) did in trying to create subgroups in people with chronic low back pain using the 2011 FM Survey.(7) This requires different associations combining with several agreements between psychological, cognitive, emotional and physiological factors. This study also confirms the presence of a subgroup of primary care patients with NSLBP with symptoms of CS similar to those observed in other studies that studied a secondary (or tertiary) care population.(1, 8) In this study the assessment of CS is done by using the CSI. Questionnaires are patient-reported, which creates a certain subjectivity. In addition, determining the content validity of the CSI is challenging(54). This is due to the lack of a gold standard for measuring CS, which implies that no statement can be made about the content validity of this questionnaire (54). Additionally, it is questionable whether a questionnaire can measure the complexity of the neurophysiological process such as CS. Combining self-reported data with Quantitative Sensory Testing (QST) measurements increases the validity of the assessment of CS-related symptoms in a clinical setting. For clinical practice a diagnostic algorithm is proposed to recognize CS pain in chronic pain patients.(55) This algorithm assesses CS pain and differentiates between neuropathic and nociceptive pain. The CSI is included in this algorithm, which is a useful tool for assessing symptoms of CS in clinical practice.(55) To our knowledge the psychometric properties of the proposed algorithm are yet to be explored. This will be a challenge for further research.

Limitations

The amount of missing data forms a study limitation. This was partly undone by approaching the relevant participants in order to collect the missing data. Not all descriptive data were completely filled in, except the sex. This makes analysis less precise. Another limitation is the small amount of information about the patient population that was collected. Demographics like BMI, race, income, educational level, smoking and physical deconditioning were not taken into account. This study lacks adjusted analysis which can reveal causal relationships. For some questionnaires the psychometric properties of the Dutch version are mentioned. Unfortunately, the study of psychometric properties of some of the used tools requires more study. The questionnaires were selected based on recommendations of guideline(21) and clinical expertise in pain rehabilitation in the Netherlands. Finally, the cross-sectional study design allows to study associations only. No conclusions on causal interactions can be made based on the present study.

Conclusion

Weak to moderate associations occur between symptoms of CS and inflexibility pattern of behavior, cognitive fusion and perceived injustice in people with NSLBP in the primary care. Pain intensity, functional disability, pain catastrophizing, inflexibility pattern of behavior, cognitive fusion and perceived injustice were higher in patients with symptoms of CS comparing with patients without the symptoms of CS. Although conclusions have to be interpreted with caution, this study justifies the 'biomedical' and 'psychological' components of the biopsychosocial approach of people with NSLBP.

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Chapter four

Differences in Quantitative Sensory Testing Outcomes between Patients With Low Back Pain in Primary Care and Healthy Controls

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Abstract

Objectives: Quantitative Sensory Testing (QST) is used to test somatosensory functioning in patients with low back pain (LBP) and most performed on people with chronic LBP in secondary/tertiary health care facilities. Studies using QST-testing in LBP populations in primary care are scarce. Central Sensitization Inventory (CSI) measures central sensitization (CS)-related symptoms. Studies which investigate differences between QST-testing in participants with LBP with a positive and negative score on the CSI questionnaire are rare. This case-control study investigates differences in extensive QST-measurements between patients with LBP (acute and chronic) in primary care and healthy controls. Secondary aim is to investigate differences of extensive QST-measurements between "CS" and "no-CS" groups.

Methods: Participants with LBP were recruited from November 2016 to October 2019. Demographic and clinical information was collected and a standardized QST-protocol was taken. Data-analysis involved determining differences between groups.

Results: Data of 100 participants with LBP and 50 healthy controls were analyzed. Heat pain thresholds, pressure pain thresholds, conditioned pain modulation local and remote were significantly affected by acute, chronic LBP versus healthy controls ($p<0.001$ to $p=0.036$). Lumbar temporal summation was significantly affected by acute, chronic LBP versus healthy controls ($p=0.002$). Only pressure pain thresholds showed significant difference between "CS" and "no-CS" group ($p=0.001$ to $p=0.002$).

Discussion: Signs of enhanced nociceptive processing and disturbed top-down nociceptive modulation is apparent in people with acute and chronic LBP in primary care. Results indicate existence of central mechanisms in LBP in primary care.

Key words: central sensitization, low back pain, primary care physiotherapy, quantitative sensory testing, case-control study

Introduction

Low back pain (LBP) is a major problem in current healthcare and is associated with significant personal burden and high socio-economic costs (1). Most people with LBP seem to recover within six weeks (2) but a lot of people with LBP (42-75%) still experience pain after 12 months (3). It has been shown that neuroplastic changes occur in the peripheral and central somatosensory system and also in motivational and emotional centers resulting in altered processing of (noxious) stimuli (4). Apkarian et al. (2013) indicated that the brain's corticolimbic circuitry plays a role in the transition from acute to chronic pain: it makes pain more emotional by learning mechanisms(5). Because of this, LBP is considered to be a complex and hard to treat health complaint(6).

Part of this complexity consists of the multiple neurophysiological processes that are involved (7). Enhanced ascending nociceptive facilitation, dysfunctional endogenous pain inhibition and increased brain activity have been identified as parts of this biology (7, 8) and these processes are labeled as central sensitization (CS). According to the International Associated for the Study of Pain (IASP) CS is defined as "an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input".(9) Using this narrow definition, CS is a neurophysiological phenomenon and cannot be measured directly in clinical practice. For clinical purposes, CS has been defined by Woolf as an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity (10). Under this definition, it is possible to study central (nervous system) sensitisation neurobiology in humans(11). Within this view, quantitative Sensory Testing (QST) measurements are used as a proxy of CS as these measurements aim to determine sensitivity changes in the somatosensory system (12). Studies suggest that CS is an important mechanism in LBP rehabilitation and hampers clinical recovery when linked to psychological factors (13).

Recent meta-analyses about QST-measurements in people with LBP show that the signs of CS are present in a subgroup of people with LBP (14-16). Based on the available literature, we previously concluded that Pressure Pain Thresholds (PPT) taken at remote body parts differ significantly between people with LBP and healthy controls (14). This result suggests the presence of CS in people with LBP (17). Temporal summation taken at lumbar region (TS) was increased in people with LBP compared to healthy controls.(14) These results are also suggestive of CS in LBP.(17) However, no significant differences at remote temporal summation (TS) measurements were found and the results of conditioned pain modulation (CPM) were mixed (14). McPhee et al. (2020) showed that CPM was impaired and TS facilitated in people with LBP compared to healthy controls (16). This also suggests CS in LBP (17).

The Central Sensitization Inventory (CSI) is frequently used in research and health care practices. The CSI measures CS-related symptoms (18) and is, in contrast to QST-measurements, easy to use in clinical practice. However, the relation between QST-measurements and the CSI is questionable which is described in a small number of studies showing mixed results (19, 20). Further research would be desirable.

The included studies in the meta-analyses were mostly underpowered, involved mainly people with LBP in secondary or tertiary health-care settings and limited to a few QST-measurements (14, 16). We wondered whether symptoms of CS are present in people with LBP in primary care. This population reported to have less pain and fewer functional limitations compared to people with LBP in secondary or tertiary care (21). Characteristics of the population with LBP attending primary care physiotherapy

are patients with less complicated LBP problems: they may experience acute or chronic LBP and possibly some psychosocial problems (22). In addition, people can visit physiotherapy through "direct access physiotherapy" (23).

Hence, the innovative nature of this observational case-control study is studying participants with acute and chronic LBP recruited in primary care and examining differences in QST outcomes between participants with acute and chronic LBP with CSI≥40/100 on the CSI and those with CSI<40/100. In addition, this fully-powered study aims to extend on current knowledge by using a comprehensive QST protocol (i.e. thermal and mechanical QST-measurements) in order to examine differences in QST outcomes between participants with acute and chronic LBP and healthy controls.

Primary aim of this study is to investigate whether differences in heat pain threshold, pressure pain threshold, temporal summation and conditioned pain modulation measurements exist between participants with acute and chronic LBP in primary care and healthy controls. Secondary aim is to investigate differences in heat pain threshold, pressure pain threshold, temporal summation and conditioned pain modulation measurements between participants with LBP with CSI-score of ≥40/100 and those with CSI-score of <40/100.

Materials and Methods

Study design and setting

This case-control study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement (24). People with LBP, visiting primary care physiotherapy practices, were recruited from November 2016 to April 2019. Healthy controls were recruited by word of mouth in the physiotherapy practices where people with LBP were measured and at the Rotterdam University, University of Applied Science between February 2019 and October 2019. Ethical approval was provided by the Ethical committee of Maasstad Hospital, Rotterdam, The Netherlands (T2016-38).

Participants

Inclusion criteria for people with LBP were: age between 18-65 years, having had LBP for at least one week with or without referred pain in one or two legs and having complained about at least 'mild' LBP during the last week (corresponding to pain intensity of ≥ 30 mm on a Visual Analogue Scale)(25). Exclusion criteria were: having a psychiatric diagnosis determined by a psychiatrist, pregnancy, LBP after surgery or trauma, LBP due to referred pain from internal organs as well as people suffering fibromyalgia, chronic fatigue syndrome or rheumatoid arthritis and those not in command of the Dutch language. The healthy controls were included if they had no physical complaints at the time of study participation and an attempt was made to match age and sex as much as possible with the participants with LBP. The exclusion criteria were similar to the LBP cohort.

Procedure

Attending physiotherapist screened people with LBP for eligibility and informed them about the study. Measurements were carried out by the first author (HdB), an experienced physiotherapist, trained in taking QST-measurements. Prior to enrollment, the participants received procedural information and they provided written informed consent.

Study participants with LBP answered demographic questions about age, sex, pain duration, pain intensity, the most painful site of their LBP, and they filled in the CSI and the painDETECT to characterize the sample. Acute LBP is defined as pain up to 12 weeks and chronic LBP as pain lasting at least 12 weeks (26). Healthy controls responded to questions about age and sex. The most painful site was taken for QST-measurements in participants with LBP and the right hand site was used in controls. All measurements were taken by the same researcher. QST-measurements were taken at the following anatomical locations: 1) the thumb mouse (Abductor Pollicis brevis muscle), 2) lower back (2 cm lateral to the processus spinosus vertebrae of L4), and 3) at the muscle-tendon transition of the Gastrocnemius muscle. Participants lied prone during all measurements. Test locations were localized and marked prior to the measurements. Heat pain thresholds (HPT) were measured prior to PPT (with a five minutes pause). Temporal summation (TS) was taken five minutes after PPT measurements. After another five minutes of rest, conditioned pain modulation (CPM) was assessed. The whole procedure took approximately one hour.

Measurements

The *Central sensitization Inventory (CSI)* is a questionnaire measuring the presence of symptoms related to CS (18). It contains a 5-point Likert scale (0 = never, 4 = always) and consists of 25 CS questions (27). The cut-off score is ≥40/100, indicating the presence of CS-related symptoms (18). The sensitivity and specificity are 81% and 75%, respectively (18). The test-retest reliability of the Dutch version is excellent (28). The *painDETECT* is a reliable and valid tool aiming to discriminate between neuropathic and nociceptive pain mechanisms (29). The Dutch version has been adequately translated for screening of neuropathic pain (30).

QST measurements

Heat Pain Threshold (HPT) measurements were conducted by using the TSA 2001-II (MEDOC, Israel). HPT was obtained by an increasing stimulus (1°C /sec, 32°C baseline and 50°C cut-off, 8 cm^2 thermode). When the sensation became uncomfortable, participants were instructed to say 'stop'. On each location HPTs were assessed twice with a 30 seconds interval. Mean scores were calculated and used for further analysis. Lower HPT's at remote level are indicative for enhanced sensitivity in the somatosensory system and are therefore indicative for the presence of CS in people with LBP (17). HPT measurements have acceptable reliability (31).

Pressure Pain Threshold (PPT) measurements were performed with a handheld digital pressure algometer (Wagner Instruments, FDX 50 Algometer, Greenwich, USA,) with a circular probe of 1 cm diameter. The measurement was conducted by applying an increasing stimulus (1 kg/s) and the instruction was to say 'stop' when the sensation became uncomfortable (32). The measurement was performed twice with a 30 seconds interval. The mean score was calculated and used for further analysis. Lower remote PPTs at remote level are indicative for CS (17). The PPT has acceptable test-retest reliability (31).

Temporal Summation (TS) or wind-up is measured by applying a train of identical nociceptive stimuli with a handheld pressure algometer (33). If the neuronal output amplifies, pain sensation will increase which mediates TS (33). Ten stimuli at the previously determined mean PPT intensity were applied and this pressure was maintained for one second before being released. The pressure was increased at a rate of approximately 2 kg/s for each stimulus and stimuli were presented with an one second interstimulus interval. A stopwatch was used to assure rate and time components (32). At the first,

fifth and tenth stimulus, the participant had to rate a numeric rating scale (0 = no pain, 10 = unbearable pain) for the pain intensity. The outcome measure for TS is the difference between the tenth and the first numeric rating scale score. If this difference is higher in participants with LBP compared to the difference of the controls, it will be interpreted as enhanced TS, which is a CS characteristic (33). Temporal summation has acceptable reliability (34, 35).

Conditioned Pain Modulation (CPM) measures the phenomenon that remote PPTs increase as a consequence of a painful stimulus. CPM was measured using The Thermo Scientific™ VersaCool™ Refrigerated Circulating Bath (ThermoFisher Scientific, Newington, U.S.A.) and the algometer. To induce a painful conditioning stimulus, participants had to immerse their hand, contralateral to the most painful site, into a 12°C cold water bath. Controls used their left hand. Participants were instructed to keep their hand in the water with a maximum of two minutes. Once the hand was removed, PPTs on each test location were taken. Mean score of two measurements was used for further analysis. In drawing a conclusion about the endogenous pain inhibitory capacity post-conditioning scores were subtracted from pre-conditioning scores. Negative values were classified as 'normal CPM' and positive scores (or zero-sum) as 'abnormal CPM' (36). The reliability of CPM is acceptable (31).

Analysis and statistics

IBM SPSS Statistics for Windows Version 25.0 (Armonk, NY: IBM Corp.) was used for data analysis. Data were assessed for normal distribution by Shapiro-Wilk. Demographic data were summarized using mean (standard deviation), minimum and maximum. Chi-square test and independent sample t-test were used to determine group differences regarding sex or age. Prior to the analysis, data were checked for completeness and outliers. Outliers were determined, defined as at least 1.5 times the inter quartile range (IQR) below the lower quartile or above the upper quartile, by viewing boxplots (37). Incomplete questionnaires were withdrawn from further analysis. For the primary aim one-way ANOVA (normally distributed data) was performed to compare the means of the three groups. Adjustments for sex and age were made and Bonferroni correction was applied because of conducting multiple significance tests. For the second aim, the participants with LBP were divided into two subgroups based on the cut-off score of the CSI-scores (≥40/100 the 'CS-group', <40/100 'no-CS-group') (18). There were no significant differences in QST-measurements between the people with acute versus those with chronic LBP. This clarifies the approach of combining the acute and chronic LBP groups. In addition, the group with chronic LBP contained the highest number of people with a CSI score ≥40/100. Independent sample t-test (normally distributed data) and Mann-Whitney U test (non-normally distributed data) were performed to compare the means of the two groups. Bonferroni correction was applied (37) because of conducting multiple significance tests and therefore p-value was determined at 0.004.

Sample size

Sample size was calculated for the main study aim using G*Power (Düsseldorf, Germany) (38). To determine differences between two groups with a medium effect size (ρ=0.5)(39), significance level of α=0.05 and power of 0.8 with an allocation ratio N2/N1, resulted in a final sample size of 100 people with LBP and 50 healthy controls. The "PPT local" data from Marcuzzi et al. (2018) was used for this

purpose.(40) It has been taken into account that approximately 25% of the people with non-specific LBP exhibit neurophysiological symptoms of CS.(15) This is the rationality for a N2/N1 allocation ratio.

Results

Participants and descriptive data

During recruitment of the people with LBP, two participants reported not to have time for this study and did not participate. During the test session, one participant appeared to be insufficiently proficient in the Dutch language. He was subsequently excluded. Two participants were excluded after the session, because of having fibromyalgia and one recently underwent surgery at the lower back. The recruitment continued until the 100 number of participants with LBP was reached. All recruited controls participated in this study.

A total of 150 people (100 participants with LBP and 50 healthy controls) participated. Mean age was 42.36 (SD 10.84) versus 43.4 (SD 11.78). Of the 100 participants with LBP, 44 (44%) were male and 56 (56%) were female. In the healthy control group 25 (50%) were male and 25 (50%) female. No significant differences were seen in age and sex between the two groups (p=0.591) versus (p=0.487). Of the 100 people with LBP, 47 (47%) have acute LBP and 53 (53%) have chronic LBP. The mean (SD) pain duration of the people with acute LBP was 3.15 (2.43) weeks and their mean (SD) pain intensity was 37.06 (21.1). The mean (SD) pain duration of the people with chronic LBP was 308.17 (481.5) weeks and their mean (SD) pain intensity was 55.77 (22.91). Of the 47 people with acute LBP, 37 (78.7%) participants scored <40/100 on the CSI and 10 (21.3%) participants scored ≥40/100 on the CSI. Of the 53 people with chronic LBP, 26 (49.1%) participants scored <40/100 and 26 (49.1%) participants scored ≥40/100 (Table 1). Forty-one people with LBP reported to have their most painful site on the left site of the body, while 59 participants reported to have more pain on the right site. Fifty seven point one percent (57,1%) of the participants with LBP scored negative on the painDETECT, 23.5% scored ambiguous, and 19.4% participants scored positive. Of the CSI≥40/100, 37.1% scored positive on the painDETECT. Of the CSI<40/100, 9.5% scored positive and 71.4% scored negative on the painDETECT. For the group with LBP, there was one incomplete questionnaire of the CSI and two incomplete questionnaires for the painDETECT; these were excluded. There were nine missing data for the HPT measurements in the group with LBP, due to technical problems.

Table 1. Descriptive statistics of the study sample of patients with low back pain in primary care.

	Acute LBP, n=47	Chronic LBP, n= 53	Healthy Controls, n= 50
Age (mean/SD)	43.7 (11.02)	41.17 (10.64)	43.4 (11.78)
Sex	Women, n=22 Men, n=25	Women, n= 34 Men, n=19	Women, n=25 Men, n=25
Pain intensity VAS (mean/SD)	37.06 (21.1)	55.77 (22.91)	3.88 (7.72)
Pain duration in weeks (mean/SD)	3.15 (2.43)	308.17 (481.5)	0
CSI[a]	CSI- , n= 37 (78.7%) CSI+, n=10 (21.3%)	CSI-, n=26 (49.1%) CSI+, n=26 (49.1%)	

CSI, Central Sensitization Inventory; SD, standard deviation; VAS, Visual Analogue Scale

[a] n=99

Comparisons between people with acute and chronic LBP and healthy controls (HC)

The outcomes of all QST-measurements are presented in Table 2.

Heat Pain Threshold

Pairwise comparisons with adjusted p-values showed significant differences for HPT-thumb between acute LBP and HC (p=0.009) and between chronic LBP and HC (p=0.006). For HPT-L4, pairwise comparisons with adjusted p-values showed a significant difference between acute LBP and HC (p=0.016), chronic LBP and HC (p=0.003). Pairwise comparisons with adjusted p-values showed significant differences for HPT-lower leg between acute LBP and HC (p<0.001), and between chronic LBP and HC (p=0.002) (Table 2).

Pressure Pain Threshold

Pairwise comparisons with adjusted p-values showed significant differences for PPT-thumb between acute LBP and HC (p<0.001), and between chronic LBP and HC (p<0.001). For PPT-L4, pairwise comparisons with adjusted p-values showed significant differences between acute LBP and HC (p<0.001), and between chronic LBP and HC (p<0.001). Pairwise comparisons with adjusted p-values showed significant differences for PPT-lower leg between acute LBP and chronic LBP (p=0.024), and between chronic LBP and HC (p<0.001) (Table 2).

Temporal Summation

TS-thumb was not significantly affected by acute LBP, chronic LBP and HC. For TS-L4, pairwise comparisons with adjusted p-values showed significant differences between acute LBP and HC

(p=0.002), and between chronic LBP and HC (p=0.002). TS-lower leg was not significantly affected by acute LBP, chronic LBP and HC (Table 2).

Conditioned Pain Modulation

Pairwise comparisons with adjusted p-values showed significant differences for δCPM-thumb between acute LBP and HC (p=0.036) and between chronic LBP and HC (p=0.015). For δCPM-L4, pairwise comparisons with adjusted p-values showed significant differences between acute LBP and HC (p<0.001), and between chronic LBP and HC (p<0.001). Pairwise comparisons with adjusted p-values showed significant differences for δCPM-lower leg between acute LBP and HC (p=0.012), and between chronic LBP and HC (p=0.005) (Table 2).

Table 2: Outcomes of the QST measurements between population with Low Back Pain (acute and chronic) and Healthy Controls in primary care.

	LBP, N=100					HC, N=50			ANOVA	
	LBP acute, N=47		LBP chronic, N=53							
	Mean (SE)		Mean (SE)			Mean (SE)			Sign.	
	Women	Men	Women	Men		Women	Men		HC/Acute LBP	HC/Chronic LBP
HPT thumb (N=91)/(N=50)	43.9 (0.69)	46.88 (0.62)	44.86 (0.54)	45.81 (0.74)		46.48 (0.6)	48.13 (0.61)		P=0.009	P=0.006
HPT L4 (N=91)/(N=50)	43.65 (0.62)	46.3 (0.56)	44.26 (0.49)	45.1 (0.66)		45.3 (0.54)	47.86 (0.54)		P=0.016	P=0.003
HPT lower leg (N=91)/(N=50)	44.99 (0.45)	46.99 (0.4)	45.42 (0.35)	47 (0.47)		46.68 (0.39)	48.62 (0.39)		P<0.001	P=0.002
PPT thumb (N=100)/(N=50)	6.67 (0.66)	10.17 (0.62)	6.36 (0.53)	8.5 (0.71)		9.62 (0.61)	13.24 (0.62)		P<0.001	P<0.001
PPT L4 (N=100)/(N=50)	6.14 (0.89)	11.03 (0.84)	5.42 (0.72)	8.68 (0.96)		11.13 (0.83)	16.66 (0.84)		P<0.001	P<0.001
PPT lower leg(N=100)/(N=50)	5.52 (0.56)	9.39 (0.53)	5.11 (0.45)	7.49 (0.60)		7.17 (0.52)	10.57 (0.52)		P=0.024	P<0.001
TS thumb (N=100)/(N=50)	2.63 (0.47)	1.46 (0.44)	2.64 (0.38)	1.69 (0.51)		1.67 (0.44)	2 (0.44)		n.s.	n.s.
TS L4 (N=100)/(N=50)	2.84 (0.44)	1.77 (0.42)	2.87 (0.35)	1.77 (0.47)		0.7 (0.41)	1 (0.41)		P=0.002	P=0.002

Table 2 (continued).

	LBP, N=100					HC, N=50			ANOVA	
	LBP acute, N=47		LBP chronic, N=53							
	Mean (SE)		Mean (SE)			Mean (SE)			Sign.	
	Women	Men	Women	Men		Women	Men		HC/Acute LBP	HC/Chronic LBP
TS lower leg (N=100)/(N=50)	2.56 (0.42)	1.33 (0.4)	2.66 (0.34)	1.93 (0.45)		1.7 (0.39)	1.5 (0.39)		n.s.	n.s.
ΔCPM thumb (N=100)/(N=50)	-1.74 (0.42)	-2.48 (0.4)	-1.7 (0.34)	-2.29 (0.46)		-3.03 (0.4)	-3.24 (0.4)		P=0.036	P=0.015
ΔCPM L4 (N=100)/(N=50)	-2.72 (0.46)	-3.33 (0.43)	-2.89 (0.37)	-3.24 (0.5)		-4.46 (0.43)	-5.26 (0.43)		P<0.001	P<0.001
ΔCPM lower leg (N=100)/(N=50)	-1.73 (0.31)	-2.37 (0.29)	-1.58 (0.25)	-2.35 (0.34)		-2.84 (0.29)	-2.99 (0.29)		P=0.012	P=0.005

HC, Healthy Controls; HPT, Heat Pain Threshold; LBP, Low Back Pain; Min-Max, minimum-maximum; n.s., non-significance; PPT, Pressure Pain Threshold; Sign, significance; SE, standard error; TS, Temporal Summation, Δ delta

* statistically significant difference tested with ANOVA adjustment for multiple comparisons by Bonferroni

Comparisons between people with LBP and CSI ≥40/100 versus CSI<40/100

QST-results were compared in the group with LBP after a split had been made based on the cut-off score (18) of the total scores of the CSI (≥40/100 versus <40/100) (Table 3).

Heat Pain Threshold

None of the HPT measurements between the two subgroups differed significantly from each other. HPT-thumb measured in participants with CSI≥40/100 group (m=45.18) compared to the CSI<40/100 group (m=46.27), p=0.406. HPT-L4 measured in participants with CSI≥40/100 (m=43.87) compared to participants with CSI <40/100 (m=45.81), p=0.049. HPT-lower leg measured in participants with CSI ≥ 40/100 (m=46.85) compared to participants with CSI<40/100 (m=46.60), p=0.655 (Table 3).

Pressure Pain Threshold

PPT-thumb was significantly lower in participants with CSI≥40/100 (m=6.36) compared to participants with CSI<40/100 (m=7.73), p=0.002. Similarly, PPT-L4 and PPT-lower leg were significantly lower in participants with CSI≥40/100 (m=4.97 and m=5.03) compared to participants with CSI<40/100 (m=7.45 and m=6.93). PPT-L4: p=0.002 and PPT-lower leg: p=0.001 (Table 3).

Temporal Summation

None of the TS measurements between the two subgroups differed significantly from each other. TS measured at the thumb in participants with CSI≥40/100 (m=2) compared to participants with CSI<40/100 (m=1), p=0.125. TS measured at L4 CSI≥ 40/100 (m=2) compared to participants with CSI<40/100 (m=2), p=0.982. TS measured at the lower leg CSI≥ 40/100 (m=2) compared to participants with CSI< 40/100 (m=2), p=0.994 (Table 3).

Conditioned Pain Modulation

None of the δCPM measurements between the two subgroups differed significantly from each other. ΔCPM-thumb in participants with CSI≥40/100 (m=-1.43) compared to participants with CSI<40/100 (m=-2.26), p=0.014. The mean scores of CPM-L4 (p=0.899) and CPM-lower leg (p=0.166) did not differ significantly between the two subgroups (Table 3).

Table 3: Outcomes of the QST measurements for the study population with low back pain CSI<40/100 and CSI≥ 40/100.

	CSI < 40			CSI ≥ 40			Mann-Whitney U test			
	Median	Interquartile range		Median	Interquartile range		Sign		U-test statistics	Z-Score
HPT thumb (N=58)/(N=32)	46.27	4.18		45.18	5.56		0.406		U=829.5	z=-0.830
HPT L4 (N=58)/(N=32)	45.81	3.91		43.87	5.42		0.049		U=694.5	z=-1.97
HPT lower leg (N=58)/(N=32)	46.60	3.26		46.85	3.56		0.655		U=875	z=-0.447
PPT thumb (N=63)/(N=36)	7.73	4.08		6.36	3.84		0.002*		U=702.5	z=-3.14
PPT L4 (N=63)/(N=36)	7.45	6.15		4.97	4.02		0.002*		U= 700	z=-0.32
PPT lower leg(N=63)/(N=36)	6.93	4.94		5.03	3.04		0.001*		U=678	z=-3.32
TS thumb (N=63)/(N=36)	1	4		2	3.75		0.125		U=926.5	z=-1.53
TS L4 (N=63)/(N=36)	2	4		2	2		0.982		U=1131	z=-0.022
TS lower leg (N=63)/(N=36)	2	4		2	3		0.994		U=1133	z=-0.007

Table 3: (continued)

	CSI < 40			CSI ≥ 40			Mann-Whitney U test			
	Median	Interquartile range		Median	Interquartile range		Sign		U-test statistics	Z-Score
ΔCPM thumb (N=63)/(N=36)	-2.26	2.39		-1.43	1.82		0.014		U=797	z=-2.45
	Mean	SD		Mean	SD		Independent t-test			
ΔCPM L4 (N=63)/(N=36)	-3.04	1.81		-2.99	2.13		0.899			
ΔCPM lower leg (N=63)/(N=36)	-2.11	1.57		-1.70	1.12		0.166			

CSI, Central Sensitization Inventory; HPT, Heat Pain Threshold; Min-Max, minimum-maximum; PPT, Pressure Pain Threshold; Sign, significance; SD, standard deviation; TS, Temporal Summation

* statistically significant difference tested with Mann-Whitney U test after Bonferroni correction (p<0.004)

Discussion

The primary aim of this study was to investigate differences in HPT, PPT, TS and CPM measurements between primary care patients with acute and chronic LBP versus healthy controls. The results showed that HPT, PPT and δCPM measurements at remote body parts were significantly affected by acute LBP and chronic LBP versus HC. This is indicative for CS and for a decreased functioning of the endogenous inhibitory system in patients with acute and chronic LBP (17). Of the TS measurements, only TS-L4 was affected by acute LBP and chronic LBP versus HC. For the secondary aim, only PPT local and at remote body parts were significantly different in the "CS"group.

The results of the first aim are partly in line with the results of Marcuzzi et al. (2015;2018), McPhee et al. (2020) and our meta-analysis (14, 16, 40, 41). Marcuzzi et al. (2015) showed significant differences for PPT local between people with subacute LBP and HC and no significant differences for PPT at remote body parts between people with subacute LBP and HC (41). Our study showed the same results for PPT local, however it also showed significant differences for PPT at remote body parts for both acute as well as chronic LBP compared to HC. Comparing both studies with regard to CPM measurements, Marcuzzi et al. (2015) showed no significant differences in people with acute LBP compared to HC which our study did (41). The longitudinal study of Marcuzzi et al. (2018) showed no significant differences for the HPT measurements between the group with persistent LBP and HC, however our study showed for all HPT measurements significant differences between both acute as well as chronic LBP compared to HC (40). Marcuzzi et al. (2018) showed significant differences for the TS measurement at the hand in the group of persistent LBP compared to HC while in our study it was shown that TS-L4 measurement was significantly affected by acute LBP, chronic LBP versus HC (40). This latter was also demonstrated in our meta-analysis (14). Marcuzzi et al. (2018) showed the same results for the PPT local as our study: significant difference between the people with persistent LBP compared to HC. While our study showed significant differences for the PPT remote between the acute LBP, chronic LBP compared to HC, Marcuzzi et al. (2018) did not show this (40). Our results regarding CPM and TS-L4 measurements are in line with the result of McPhee(16). Looking at the subgroups (acute and chronic LBP) our study showed significant differences between both acute and chronic LBP compared to HC (16). The results of the second aim are in line with the study of Kregel et al. (2018) and Bezerra et al. (2021) (42, 43) Their study showed weak associations between the CSI total scores and PPT measurements (43) and no associations between the CSI total scores and CPM measurement (42, 43). It can be concluded that the CSI does not replace the QST measurements: the use of both measuring instruments is complementary. CSI questionnaire measures emotional and somatic symptoms related to Central Sensitivity Syndrome (44) and the QST measures the functional state of the somatosensory system (45).

The descriptive statistics showed that approximately an equal number of people with acute and chronic LBP visit the primary care physiotherapy. It was also shown that there are fewer people with CS-related symptoms in acute LBP compared to people with chronic LBP in primary care (Table 1). Because people score above the cut-off of the CSI it appears that signs of CS are apparent in a subgroup of people with LBP which was currently unknown in primary care. Realization of this result is essential for clinicians working in primary care. Awareness of the need for biopsychosocial treatment due to the complexity of LBP should remain (21).

The strength of this study is its innovative objective to analyze differences in QST-measurements between the "CS"group and "no-CS"group. Another innovative element is that the included

participants with LBP were recruited from primary care setting. The sample size is well powered and this study contains an extensive QST protocol which are strong points of this research.

Study results should be interpreted with caution as potential confounders as demographics like race, BMI, smoking, physical condition, educational level and income were not taken into account. This is a potential limitation of this study. To use a cut-off score of the CSI questionnaire in the clinical setting can be arbitrary. It provides an indication of whether a patient meets or does not meet the criteria for the presence of CS-related symptoms. In such a situation, a practitioner is alerted to this. From the intervention point of view it is more nuanced to interpreted the results of the questionnaire based on the 'severity levels'. Dividing the group of people with LBP into two groups ("CS"-group and "no-CS" group) in this study, made the existing cut-off of the CSI suitable for this purpose.

The knowledge that CS is present in patients seen in primary care, makes it important to apply interventions that take the role of the central nervous system into account.(46) The intervention 'pain neuroscience education' will focus on the neurophysiology of pain and maladaptive thoughts and behaviors about pain. It reconceptualizes pain as a "source of tissue damage" and will ultimately contribute to increased pain inhibition.(46) In addition, it is important that people start moving. This can be general strength exercises or aerobic training to stimulate the exercise-induced analgesia and thus the pain-inhibiting system.(46) If one wants to consider testing the somatosensory system in a physiotherapy practice, PPT measurements may be suitable because a comprehensive QST-test battery is time consuming. From this study PPT measurements appear to measure significant differences between acute and chronic LBP versus HC. Like Wang et al. (2019), in a study of people with neck- and shoulder pain, suggest that using the algometer is an easy and accessible tool to measure mechanosensitivity changes in individuals. (47) If such results are known for the lumbar region, PPT measurements could be implemented in primary care to objectify individual changes in the somatosensory system during their treatment.

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Chapter five

Multifactorial Differences Between People with Low Back Pain in the Various Risk Levels of the Start Back screening Tool and Central Sensitization Inventory in Primary Care: a Cross-sectional Study

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Abstract

Study design: cross-sectional study

Objective: This study aimed to investigate whether linear trends in psychological factors (kinesiophobia, pain catastrophizing), disability and somatosensory characteristics exist in a sample of people with acute and chronic low back pain (LBP) in primary care across severity levels based on the Start Back screening Tool (SBT) and Central Sensitization Inventory (CSI).

Backgrounds: Current LBP treatment might be improved by tailoring treatments to subgroup characteristics. SBT and CSI classify people with LBP into subgroups. It is currently unknown whether linear trends exist regarding somatosensory changes, psychological characteristics and physical disability across severity levels of the SBT and CSI in patients with LBP.

Methods: Participants with LBP were recruited in primary care from November 2016 until April 2019. Demographic information was obtained and psychological and disability questionnaires were filled in. A comprehensive Quantitative Sensory Testing (QST) protocol was followed. Linear contrast analysis was conducted.

Results: Psychological variables show significant positive linear trends across the subgroups based on the SBT ($p<0.001$) and CSI ($p<0.001$ to $p=0.013$). Heat pain threshold lower leg ($p=0.005$), pressure pain threshold L4 and lower leg ($p=0.025$ respectively $p=0.043$) show significant negative linear trends within the SBT. Negative linear trends in sensory changes exist within CSI for all pressure pain thresholds and a positive linear trend was seen in δ conditioned pain modulation thumb ($p=0.035$).

Conclusion: Kinesiophobia, pain catastrophizing, disability and pain intensity are positively related with the risk levels based on the SBT and CSI in primary care patients with LBP. For somatosensory changes, measured by QST, the results are mixed.

Introduction

Low back pain (LBP) is a complex health problem that can be characterized by the many neurophysiological and psychosocial factors that might be involved.(1-4) People with LBP can be divided into subgroups based on clinical characteristics and current treatments might be improved when they are tailored to these characteristics. Stratified care is defined as grouping people with LBP in risk levels to target interventions specific to that risk level managing the complexity of LBP.(5-7) Stratified care has been suggested in LBP-rehabilitation and evidence shows promising outcomes for both cost-effectiveness and patient outcomes when treatments are directed to these subgroups.(7, 8)

A commonly used questionnaire to stratify people with LBP in primary care into risk levels is the Start Back screening Tool (SBT) which indicates the odds of unfavorable prognosis.(9, 10) The SBT contains several pain-related and psychological questions. The pain-related questions concern referred leg pain, widespread pain and disability in walking and dressing.(10) The psychological questions concern kinesiophobia, fear, feelings of depression, pain catastrophizing and back pain bothersomeness.(9) Each risk level (low, medium, high) facilitates appropriate treatment choices, varying from analgesia, to advice regards physical and cognitive-behavioral approaches.(9) In addition to the SBT, there is another questionnaire that assists clinicians in the clinical decision-making of an appropriate treatment at the corresponding risk level: the Central Sensitization Inventory (CSI) also allows dividing people with LBP into subgroups. It has been indicated that symptoms of CS may be present in a subgroup of people with LBP.(11, 12) The CSI has been developed to identify the main symptoms of Central Sensitivity Syndrome and symptoms related to Central Sensitization (CS).(13) It contains questions concerning somatic, cognitive and emotional health-related symptoms which occur in CS-related disorders.(14) The subgroups represent CS-related symptom severity into three categories (low, medium, high) which could aid treatment choices.(14)

CS is a neurophysiological process that might be part of the complex biology underlying LBP. Quantitative Sensory Testing (QST) is used as a proxy for CS in clinical studies. QST-measurements attempt to objectify sensitivity changes in the somatosensory system.(15) Marcuzzi et al. (2018) showed that such sensitivity changes in the somatosensory system are present when acute LBP develops into persistent LBP.(16) They also concluded that pain-related psychological variables were significantly lower in those with recovered LBP compared to those with persistent LBP.(16)

Stratifying patients fits within the idea of precision medicine, which is defined as the ability to classify patients into subgroups that differ in their susceptibility, biology or prognosis of a particular disease or in their response to a specific treatment.(17) A tentative step towards precision medicine for primary care patients with LBP is taken with this exploratory study to outline psychological and somatosensory characteristics per SBT- and CSI-defined subgroups. The changes in the psychological factors are not innovative as such, but these changes in combination with the alterations in the somatosensory system are new. In our view this represents a knowledge gap. If characteristics are present in these subgroups, this can support clinicians in interpreting SBT- and/or CSI-defined subgroup classification, which in turn might assist in determining appropriate treatment for primary care patients with LBP.

Hence, aims of this study are 1) to investigate whether linear trend exists across low, medium and high risk levels based on the Start Back screening Tool with regard to kinesiophobia, pain catastrophizing, pain intensity, disability and sensitivity changes in the somatosensory system in people with acute and

chronic LBP in primary care, 2) to investigate whether a linear trend exists across low, medium and high severity levels based on the Central Sensitization Inventory with regard to kinesiophobia, pain catastrophizing, pain intensity, disability and sensitivity changes in the somatosensory system in people with acute and chronic LBP in primary care. The final aim is to assess the level of agreement in identifying subgroups between the SBT and CSI in people with LBP in primary care.

Methods

Study design and setting

This cross-sectional study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement.(18) From November 2016 to April 2019, people with LBP, visiting Dutch primary care physiotherapy practices, were recruited. Ethical approval was provided by the Ethical committee of Maasstad Hospital, Rotterdam, The Netherlands (T2016-38).

Participants

People with LBP were included if: their age was between 18-65 years, having had LBP for at least one week with or without referred pain in one or two legs and having had a mean pain intensity reported on the Visual Analogue Scale of ≥ 30 mm during the last week. Exclusion criteria were: pregnancy, LBP after surgery or trauma, psychiatric diagnosis determined by a psychiatrist, people with fibromyalgia, chronic fatigue syndrome or rheumatoid arthritis, LBP due to referred pain from internal organs and inability to write or read Dutch.

Procedure

People with LBP were screened for eligibility according to the Dutch LBP guideline of the Royal Dutch Society for Physiotherapy by their treating physiotherapist and were informed about this study.(19) Patients received an information leaflet about the objectives and content of the study. The first author (HdB), an experienced physiotherapist trained in performing QST-measurements, carried out all measurements. HdB was blinded to the medical record and all other study data of the study participants. Prior to enrollment, all study participants provided written informed consent.

First, included participants provided demographic information to describe the sample. Therefore, the following information was obtained: sex, age, most painful site of their LBP, and information about the present type of pain (by means of the painDETECT). Then they filled in the following questionnaires: SBT, CSI, Tampa scale for kinesiophobia, Pain Catastrophizing Scale, Roland Morris Disability Questionnaire and Visual Analogue Scale. Questionnaires were administered in an alternately structured order: participant A started the questionnaires with the sequence 1 till 9, participant B started with the sequence 2 till 9, then questionnaire number 1 and so on. After participants had completed the questionnaires the study was continued with carrying out QST-measurements.

Measurements

The *Start Back screening Tool (SBT)* is a questionnaire that identifies to what extent primary care patients with LBP are at risk for a poor prognosis. It classifies patients in one of three risk levels (low, medium, high-risk).(9) An overall score of ≤ 3 indicates "low-risk", an overall score of ≥ 4 indicates "medium or high risk" of which a sub score of ≤ 3 indicates "medium-risk".(9) The SBT consists of nine questions of which eight questions need to be answered with "true/false" and one on a 5-point Likert-scale.(20) The Dutch version generates sufficient valid and reliable data.(20)

The *Central Sensitization Inventory* (CSI) measures CS related symptoms and consists of 25 CS related questions which need to be answered on a 5-point Likert-scale (0 = never, 4 = always). The Central Sensitization Inventory Symptom Severity Calculator determines the severity level (low, medium, high) of the CSI which the patient belongs to. The calculator uses as reference the results of the Hierarchical Cluster Analysis with the pooled sample.(14) The test-retest reliability of the Dutch version is excellent.(21) The sensitivity and specificity of the questionnaire are 81% and 75%, respectively.(22)

The *Tampa scale for kinesiophobia (TSK)* assesses kinesiophobia. The TSK consists of 17 statements that need to be scored on a 4-point Likert scale (1 = highly disagree, 4 = highly agree).(23) A cut-off score of ≥37/68 indicates kinesiophobia.(23) The Dutch version of the TSK (TSK-DV) shows high internal consistency (Cronbach's alfa range .68 - .80) and shows good construct validity and criterion validity.(24)

The *Pain Catastrophizing Scale (PCS)* measures the degree of pain catastrophizing. This questionnaire assesses three related subscales: magnification, rumination and helplessness.(25) It consists of 13 statements that need to be scored on a 5-point Likert scale (0 = not at all, 4 = all the time).(25) A cut-off score of ≥30/52 declares a clinical degree of pain catastrophizing.(25) The PCS shows good test-retest reliability and internal consistency.(26, 27)

The *Roland Morris Disability Questionnaire (RDQ)* assesses the functional status of people with LBP.(28) This questionnaire contains 24 items in which the answer options are "yes/no". (29) The total score is calculated by adding up the number of "yes" answers ranging from 0 (=no disability) to 24 (= maximal disability).(30) Higher scores indicating a higher level of disability.(30) The Dutch version of the RDQ is a reliable questionnaire to evaluate functional status of people with LBP.(28)

The *Visual Analogue Scale (VAS)* measures pain intensity of people with LBP. This self-reported scale has a horizontal line of 100 mm. The score varies from 0 mm (no pain) to 100 mm (unbearable pain).(31) Participants are requested to mark the line that corresponds most closely with the pain intensity they currently experience.(31) Despite the low content validity the VAS is recommended to measure and report in clinical trials in people with LBP.(31, 32)

The *painDETECT* discriminates between nociceptive and neuropathic pain mechanisms.(33) It consists of seven questions about the quality of neuropathic pain symptoms with a 5-point Likert-scale (0=never, 5=very strongly), one question about radiating pain answered by "yes/no" and four pictures that describe the pain course pattern. The participant has to mark the picture that describes the pain course best. The interpretation of a total score ≤ 12 is predominantly nociceptive pain and a total score of ≥ 19 is predominantly neuropathic pain.(33) It is a valid and reliable screening tool and it has been adequately translated into Dutch.(33, 34)

QST-measurements

To determine the testing site for the QST-measurements, participants indicated the most painful site of their LBP. QST-measurements were performed at the following locations: 1) thumb mouse, 2) lower back (2 cm lateral to the processus spinosus vertebrae of L4) and 3) at the muscle-tendon transition of the M. Gastrocnemius. During the measurements the participants lied prone and the locations were localized and marked prior to the measurements. The measurements started with heat pain threshold (HPT). After a five minutes pause pressure pain threshold (PPT) was measured. After another five minutes, temporal summation (TS) was assessed. Subsequently, after another five minutes pause, conditioned pain modulation (CPM) was assessed. The whole procedure took one hour.

Heat Pain Threshold (HPT) measurements were conducted with an increasing stimulus (1°C /sec, 32°C baseline and 50°C cut-off, 8 cm^2 thermode), using the TSA 2001-II (MEDOC, Israel). Participants were instructed to say 'stop' when the sensation first became uncomfortable.(35) The measurements were performed twice on each location (i.e., thumb mouse, lower back (2 cm lateral to the processus spinosus vertebrae of L4) and the muscle-tendon transition of the M. Gastrocnemius) with an interval of 30 seconds. For further analysis, the mean scores were calculated and used. Indication for enhanced sensitivity in the somatosensory system is lower HPTs at non-segmental level.(36) HPT measurements have proved to be of acceptable reliability.(37)

With a handheld digital pressure algometer (Wagner Instruments, FDX 50 Algometer, Greenwich, USA,) *Pressure Pain Threshold* (PPT) measurements were performed. The circular probe was 1 cm diameter and the measurement was carried out by applying an increasing stimulus (1 kg/s). Again, the instruction was to say 'stop' when the sensation first became uncomfortable.(35) PPTs were also assessed twice at the same locations as the HPT with an interval of 30 seconds and the mean was calculated and used for further analysis. Lower remote PPTs at non-segmental levels are also indicative for CS.(36) The PPT shows acceptable test-retest reliability.(37)

Temporal summation (TS) was measured by applying ten consecutive identical nociceptive stimuli.(38) Pain sensation will increase if the neuronal output amplifies, which mediates TS.(38) The stimuli were applied at the previously determined mean PPT intensity. This pressure was maintained for one second before starting the measurement. At a rate of approximately 2 kg/s for each stimulus, the pressure was increased. With an interstimulus interval of one second, stimuli were presented. By means of a verbal numeric rating scale (0=no pain, 10 =unbearable pain) for the pain intensity the participants had to rate the first, fifth and tenth stimulus. The result for TS is calculated by the difference between the tenth and the first verbal numeric rating scale score. The reliability is acceptable.(37)

Endogenous pain inhibition is measured by means of the *Conditioned Pain Modulation* (CPM) paradigm (39) using the Thermo Scientific™ VersaCool™ refrigerated circulating bath (ThermoFisher Scientific, Newington, U.S.A.) and the pressure algometer. The painful conditioning stimulus was immersing the participant's hand, ipsilateral to the most painful site, in a cold water bath of 12°C. Participants were instructed to keep their hand in the water as long as they could bear with a maximum of two minutes. On each test location PPTs were taken as the test stimulus, after they had removed their hand. Mean score was calculated and used for further analysis. For drawing a conclusion about endogenous pain inhibitory capacity, post-conditioning scores were subtracted from pre-conditioning scores. The reliability is acceptable.(37)

Analysis and statistics

This study was carried out as secondary analysis of a case-control study which investigated whether differences in QST-measurements exist between people with acute and chronic LBP and healthy controls.(40) For data analysis IBM SPSS Statistics for Windows Version 25.0 (Armonk, NY: IBM Corp.) was used. Demographic data were represented as mean (standard deviation), minimum and maximum. The participants were divided into acute (0-12 weeks) and chronic LBP (≥ 12 weeks).(41) The entire set of data were checked for completeness. If questionnaires were incomplete, the whole questionnaire was removed for further analysis. Outliers were identified by checking boxplots. Viewing the boxplots, outliers were recognized as values that exceeded at least 1.5 times the inter quartile range (IQR).(42) Correlation analysis was done in order to assess whether participants belonging to the high risk level of the SBT also belonged to the high severity level of the CSI. Cohen's kappa was calculated to assess the agreement in identifying subgroups by the SBT and CSI. One-way ANOVA was performed, based on the significance of the Levene's test ($p<0.01$). After the one-way ANOVA, linear contrast analysis was performed because of the expectation of linear trend in outcomes across the various risk/severity levels based on the SBT and CSI. Adjustments were made for sex and age.

Results

Participants and descriptive data

A hundred participants with LBP and a mean age of 42.36 (SD 10.84) years participated. Forty-four participants were male and 56 were female. For 59 participants their right hand side of the body was the most painful side, while for 41 participants their left hand side was the most painful one. Forty-seven participants had acute LBP and 53 had chronic LBP. Of the 47 participants with acute LBP, 30 patients belonged to the low risk level of the SBT, 16 to the medium risk level, and 1 to the high risk level. Of the 53 participants with chronic LBP, 21 patients belonged to the low risk level of the SBT, 22 to the medium risk level and nine to the high risk level. Of the 47 participants suffered from acute LBP, twelve patients belonged to the low severity level of the CSI, 26 to the medium severity level, and 9 to the high severity level. Of the 53 participants suffered from chronic LBP, four patients belonged to the low severity level of the CSI, 27 to the medium severity level, and 21 to the high severity level. Participants with acute LBP scored a mean of 32.31 (SD 6.58) on the TSK, and those with chronic LBP 34.78 (SD 7.99). For the PCS, participants with acute LBP showed a mean of 15.23 (SD 8.42), and those with chronic LBP 21.85 (SD 12.81). Participants with acute LBP had a mean pain intensity of 37.06 (SD 21.1) on the VAS, and those with chronic LBP 55.77 (SD 22.91). For the RDQ, participants with acute LBP showed a mean of 7.4 (SD 4.81), and those with chronic LBP 10.53 (SD 5.18) (Table 1). On the painDETECT 57,1% of the participants scored negative (nociceptive pain), 23.5% scored ambiguous (unclear which pain mechanism) and 19.4% participants scored positive (neuropathic pain). The CSI scores correlated moderately with the painDETECT scores ($r=0.475$; $p<0.001$).(43)

During recruitment two participants reported this study too time consuming and discontinued their participation. One participant appeared to be insufficiently proficient in the Dutch language during the test session and was subsequently excluded. Additionally, two participants were excluded: one suffering from fibromyalgia and one recently having received lower back surgery. The recruitment ended on reaching the required 100 participants. For the SBT, CSI and painDETECT questionnaires were

excluded for further analysis due to incompleteness. Due to technical problems, the HPT measurements consisted of 91 data instead of 100.

Table 1. Descriptive statistics of the study sample of patients with low back pain in primary care.

	Acute LBP, N=47	Chronic LBP, N=53	
Age (mean/SD)	43.7 (11.02)	41.17 (10.64)	
Sex	Women, n=22 Men, n=25	Women, n= 34 Men, n=19	
TSK	32.31 (6.58)	34.78 (7.99)	
PCS	15.23 (8.42)	21.85 (12.81)	
VAS_{mean} (mean/SD)	37.06 (21.1)	55.77 (22.91)	
RDQ	7.4 (4.81)	10.53 (5.18)	
SBT	Low risk level, n= 29 (61.7%)	Low risk level, n= 20 (37.7%)	N=4 missing data
	Medium risk level, n= 16 (34%)	Medium risk level, n= 21 (39.6%)	
	High risk level, n= 1 (2.2%)	High risk level, n=9 (17%)	
CSI	Low sev. Level, n=12 (25.5%)	Low sev. Level, n=4 (7.5%)	N= 1 missing data
	Medium sev. Level, n=26 (55.3%)	Medium sev. Level, n=27 (50.9%)	
	High sev. Level, n=9 (19.1%)	High sev. Level, n=21 (39.6%)	

CSI, Central Sensitization Inventory; LBP= Low Back Pain; PCS, Pain Catastrophizing Scale; RDQ, Roland Morris Disability Questionnaire; SD, standard deviation; SBT, Start Back screening Tool; TSK, Tampa Scale for Kinesiophobia; VAS, Visual Analgue Scale

Level of agreement between SBT and CSI

The level of agreement between the SBT and CSI was (95%CI) 0.104 (-0.03, 0.23) which indicates "slight" agreement.(44)

Linear trends across the risk levels based on the Start Back Screening Tool with psychosocial and disability questionnaires and QST-measurements

Table 2 presents the results of the linear trends across the risk levels based on the SBT of the psychological and disability variables and somatosensory changes in people with LBP in primary care.

All the questionnaires showed positive significant linear trends across the risk levels (TSK,PCS, VAS_{mean}, RDQ, all $p< 0.001$) with adjustments for sex and age. Both HPT_{thumb} and $HPT_{low\ leg}$ showed negative significant linear trends across the risk levels (HPT_{thumb}, $p=0.037$; $HPT_{low\ leg}$, $p=0.005$). HPT_{L4} showed no significant linear trend across the risk levels (HPT_{L4}, $p=0.051$). Both PPT_{L4} and $PPT_{low\ leg}$ showed negative significant linear trends across the risk levels (PPT_{L4}, $p=0.025$, $PPT_{low\ leg}$, $p=0.043$). The PPT_{thumb} showed no significant linear trend across the risk levels. None of the TS measurements showed significant linear trends across the risk levels. Only the δCPM_{thumb} showed a positive significant linear trend across the risk levels (δCPM_{thumb}, $p=0.040$). Both δCPM_{L4} and $\delta CPM_{low\ leg}$ showed no significant linear trend across the risk levels with adjustments for sex and age with all QST-measurements (Table 2).

Table 2. Descriptive statistics of the study sample of patients with low back pain per risk level and results of linear trends based on the Start Back Screening Tool.

Variable	Acuut LBP (N=47)	Results Mean (SD)	Chronic LBP (N= 53)	Results Mean (SD)	Linear contrast sig.
TSK[a]					
Low risk	29	30 (6.16)	20	31.2 (6.74)	P<0.001
Medium risk	14	36.64 (5.29)	19	36.37 (8.14)	
High risk	1	40	9	40.44 (6.52)	
PCS[b]					
Low risk	29	11.17 (6.3)	19	11.95 (8.04)	P<0.001
Medium risk	16	21.63 (7.29)	21	23.9 (12.13)	
High risk	1	30	9	35.89 (7.08)	
VAS_{mean}					
Low risk	29	27.9 (15.58)	20	40.7 (21)	P<0.001
Medium risk	16	54.06 (19.39)	21	64.14 (21.75)	
High risk	1	56	9	67.78 (13.16)	
RDQ					
Low risk	29	5.18 (3.22)	20	6.65 (3.54)	P<0.001
Medium risk	16	11 (4.65)	21	12.62 (4.99)	
High risk	1	17	9	12.78 (4.24)	
HPT thumb[c] (°C)					
Low risk	26	45.74 (3.4)	18	45.66 (2.94)	P=0.037
Medium risk	15	45.85 (2.66)	20	45.18 (2.74)	
High risk	1	38.86	8	44.29 (4.92)	
HPT L4[c] (°C)					
Low risk	26	45.25 (3.44)	18	44.85 (2.59)	P=0.051
Medium risk	15	45.31 (2.71)	20	44.56 (2.93)	
High risk	1	40.92	8	43.38 (3.45)	
HPT Low leg[c] (°C)					
Low risk	26	46.24 (2.23)	18	46.38 (1.67)	P=0.005
Medium risk	15	46.53 (2.09)	20	46 (2.79)	
High risk	1	42.67	8	43.9 (4.13)	
PPT thumb (kg/cm^2)					
Low risk	29	8.58 (3.81)	20	7.93 (3.73)	P=0.151
Medium risk	16	8.54 (3.17)	21	6.97 (2.63)	
High risk	1	7.79	9	6.30 (2.97)	
PPT L4 (kg/cm^2)					
Low risk	29	9.69 (5.5)	20	7.9 (4.05)	P=0.025
Medium risk	16	7.16 (4.29)	21	5.82 (2.92)	
High risk	1	10.81	9	4.56 (2.29)	
PPT low leg (kg/cm^2)					
Low risk	29	7.77 (3.77)	20	6.74 (3.19)	P=0.043
Medium risk	16	7.32 (2.8)	21	5.58 (1.85)	
High risk	1	5.27	9	5.21 (1.7)	
TS thumb (NRS)					
Low risk	29	1.97 (2.08)	20	2.25 (2.57)	

Medium risk	16	1.94 (2.72)	21	2.29 (2.81)	P=0.619
High risk	1	4	9	2 (1.58)	
TS L4 (NRS)					
Low risk	29	2.24 (1.9)	20	2.6 (2.46)	P=0.668
Medium risk	16	2.13 (2.25)	21	2.33 (2.06)	
High risk	1	2	9	1.89 (1.76)	
TS Low leg (NRS)					
Low risk	29	2.1 (2.19)	20	2.65 (1.93)	P=0.748
Medium risk	16	1.38 (2.55)	21	2.1 (1.84)	
High risk	1	4	9	2.33 (1.58)	
δCPM thumb (kg/cm^2)					
Low risk	29	-2.28 (1.88)	20	-2.49 (1.59)	P=0.040
Medium risk	16	-1.92 (2.38)	21	-1.59 (1.57)	
High risk	1	-2.26	9	-1.08 (1.35)	
δCPM L4 (kg/cm^2)					
Low risk	29	-3.11 (1.85)	20	-3.27 (2.12)	P=0.160
Medium risk	16	-3.11 (1.74)	21	-3.27 (2.07)	
High risk	1	-3.97	9	-1.93 (1.61)	
δCPM Low leg (kg/cm^2)					
Low risk	29	-2.19 (1.47)	20	-2.05 (1.74)	P=0.091
Medium risk	16	-2.04 (1.24)	21	-1.79 (1.17)	
High risk	1	-1.21	9	-1.44 (1.41)	

CPM, Conditioned Pain Modulation; HPT, Heat Pain Threshold; LBP, Low Back Pain; Low leg, lower leg; NRS, Numeric Rating Scale; PCS, Pain Catastrophizing Scale; PPT, Pressure Pain Threshold; RDQ, Roland Morris Disability Questionnaire; SD, Standard Deviation; Sig, significance; TS, Temporal Summation; TSK, Tampa Scale for Kinesiophobia; VAS, Visual Analogue Scale

[a] n=96, [b] n=99, [c] n=9 missing

Linear trends across the severity levels based on the Central Sensitization Inventory with psychosocial and disability questionnaires and QST-measurements

Table 3 presents the results of the linear trends across the severity levels based on the CSI of the psychological and disability variables and somatosensory changes in people with LBP in primary care. All the questionnaires showed positive significant linear trends across the severity levels (TSK and PCS, $p<0.001$; $VAS_{mean,}$ p=0.013; RDQ= 0.001) with adjustments for sex and age. None of the HPT measurements showed significant linear trends across the severity levels. All PPT measurements showed negative significant linear trends across the severity levels (PPT_{thumb}, p=0.009, PPT_{L4}, p=0.012, $PPT_{low\ leg}$, p=0.001). None of the TS measurements showed significant linear trends across the severity levels. The δCPM_{thumb} showed a positive significant linear trend across the severity levels (p=0.035). The δCPM_{L4} and $\delta CPM_{low\ leg}$ showed no significant linear trends across the severity levels with adjustments for sex and age with all QST-measurements (Table 3).

Table 3. Descriptive statistics of the study sample of patients with low back pain per severity level and results of linear trends based on the Central Sensitization Inventory.

Variable	Acuut LBP (N=47)	Results Mean (SD)	Chronic LBP (N= 53)	Results Mean (SD)	Linear contrast sig.
TSK[a]					
Low sev. Level	11	31.55 (5.91)	4	28.75 (3.77)	P<0.001
Medium sev. Level	25	30.92 (5.91)	26	33.46 (8.2)	
High sev. Level	9	37.11 (7.56)	20	37.35 (7.58)	
PCS[b]					
Low sev. Level	12	12.67 (7.43)	4	5.5 (2.89)	P<0.001
Medium sev. Level	26	14.19 (7.82)	26	21.5 (11.86)	
High sev. Level	9	21.67 (8.96)	21	24.71 (13.01)	
VAS_{mean}					
Low sev. Level	12	32.58 (17.52)	4	35.75 (20.79)	P=0.013
Medium sev. Level	26	34.12 (21.27)	27	55.56 (23.71)	
High sev. Level	9	51.56 (20.7)	21	59.67 (21.71)	
RDQ					
Low sev. Level	12	5.33 (4.05)	4	5.5 (3.7)	P=0.001
Medium sev. Level	26	7.15 (4.43)	27	10.22 (4.66)	
High sev. Level	9	10.89 (5.35)	21	11.9 (5.67)	
HPT thumb[c] (°C)					
Low sev. Level	12	46.54 (1.78)	4	47.21 (2.48)	P=0.284
Medium sev. Level	23	45.21 (3.52)	24	44.7 (3.27)	
High sev. Level	8	44.97 (4.18)	19	45.52 (3.34)	
HPT L4[c] (°C)					
Low sev. Level	12	46.63 (1.97)	4	45.06 (1.73)	P=0.247
Medium sev. Level	23	44.56 (3.03)	24	44.8 (3.03)	
High sev. Level	8	44.61 (4.42)	19	43.96 (2.84)	
HPT Low leg[c] (°C)					
Low sev. Level	12	47.44 (1.43)	4	46.42 (1.24)	P=0.434
Medium sev. Level	23	45.55 (2.15)	24	45.98 (2.42)	
High sev. Level	8	46.25 (2.7)	19	45.67 (3.46)	
PPT thumb (kg/cm^2)					
Low sev. Level	12	10.25 (2.87)	4	9.81 (4.45)	P=0.009
Medium sev. Level	26	8.43 (3.38)	27	7.18 (3.18)	
High sev. Level	9	6.53 (3.74)	21	6.61 (2.81)	
PPT L4 (kg/cm^2)					
Low sev. Level	12	11.23 (4.19)	4	10.09 (6.33)	P=0.012
Medium sev. Level	26	8.49 (5.32)	27	6.76 (4.34)	
High sev. Level	9	6.13 (4.65)	21	5.84 (2.57)	
PPT low leg (kg/cm^2)					
Low sev. Level	12	9.49 (2.77)	4	9.29 (3.67)	P=0.001
Medium sev. Level	26	7.28 (3.47)	27	6.06 (2.75)	
High sev. Level	9	5.76(2.76)	21	5.39 (1.66)	
TS thumb (NRS)					
Low sev. Level	12	2 (2.22)	4	0.75 (0.96)	

Medium sev. Level	26	2.19 (2.25)	27	2.15 (2.92)	P=0.575
High sev. Level	9	1.67 (2.69)	21	2.67 (1.98)	
TS L4 (NRS)					
Low sev. Level	12	2.42 (2.35)	4	1 (2.58)	
Medium sev. Level	26	2.08 (1.94)	27	2.74 (2.57)	P=0.553
High sev. Level	9	2.78 (2.28)	21	2.19 (1.83)	
TS Low leg (NRS)					
Low sev. Level	12	2 (2.45)	4	1.5 (1.29)	
Medium sev. Level	26	2.08 (2.04)	27	2.59 (1.91)	P=0.698
High sev. Level	9	1.44 (3.05)	21	2.29 (1.79)	
δCPM thumb (kg/cm^2)					
Low sev. Level	12	-2.46 (1.36)	4	-3.44 (0.75)	
Medium sev. Level	26	-2.3 (2.16)	27	-1.97 (1.8)	P=0.035
High sev. Level	9	-1.14 (2.22)	21	-1.64 (1.57)	
δCPM L4 (kg/cm^2)					
Low sev. Level	12	-3.48 (1.36)	4	-2.54 (1.98)	
Medium sev. Level	26	-2.74 (1.93)	27	-3.1 (1.92)	P=0.744
High sev. Level	9	-3.42 (1.99)	21	-2.97 (2.24)	
δCPM Low leg (kg/cm^2)					
Low sev. Level	12	-2.72 (1.61)	4	-2.92 (2.69)	
Medium sev. Level	26	-1.82 (1.37)	27	-1.88 (1.44)	P=0.085
High sev. Level	9	-1.86 (1.1)	21	-1.67 (1.16)	

CPM, Conditioned Pain Modulation; HPT, Heat Pain Threshold; LBP, Low Back Pain; Low leg, lower leg; NRS, Numeric Rating Scale; PCS, Pain Catastrophizing Scale; PPT, Pressure Pain Threshold; RDQ, Roland Morris Disability Questionnaire; SD, Standard Deviation; sev, severity; Sig, significance; TS, Temporal Summation; TSK, Tampa Scale for Kinesiophobia; VAS, Visual Analogue Scale

[a] n=96, [b] n=99, [c] n=9 missing

Discussion

This study investigated linear trends in psychological factors, pain-related disability and somatosensory sensitivity across SBT- and CSI-defined risk and severity levels in primary care patients with acute and chronic LBP. All questionnaire data (TSK, PCS, VAS_{mean} and RDQ) showed positive linear trends across the SBT- and CSI-defined risk and severity levels in primary care LBP patients. This indicates that the SBT- and CSI-defined risk and severity levels increase the degree of psychological factors, pain related disability and pain intensity in primary care patients with acute and chronic LBP.

Regarding the QST-measurements, HPT_{thumb}, $HPT_{low\ leg}$, PPT_{L4} and $PPT_{low\ leg}$ showed negative linear trends across the SBT-defined risk levels. This indicates that when the risk levels increase, these heat and pressure pain thresholds become more sensitive in primary care patients with acute and chronic LBP. The δCPM_{thumb} showed positive linear trends across the risk levels based on the SBT. This indicates that the endogenous inhibitory system functions more poorly when the risk levels increase. Concerning the severity levels based on the CSI, all PPT measurements showed negative, and δCPM_{thumb} showed positive linear trends. This shows that as the severity level increases, the pressure pain thresholds

become more sensitive, and also that the endogenous inhibitory system is working less efficiently in patients with LBP seen in primary care. None of the TS measurements, HPT_{L4}, δCPM_{L4} or $\delta CPM_{low\ leg,}$ showed a significant linear trend across the SBT- and CSI-defined risk and severity levels. All analyses were adjusted to sex and age. The results showed a slight level of agreement between the SBT and CSI total scores in patients with acute and chronic LBP seen in primary care (Cohen's kappa=0.104).(44) Clinically, this means that both questionnaires measure two different yet related constructs.

When comparing the mean scores of psychological factors, pain related disability, pain intensity, all HPT, PPT, TS measures and $\delta CPM_{low\ leg}$ between the patients with acute and chronic LBP in the SBT-defined low and medium risk levels, several differences were observed (Table 2). The differences indicate that people with chronic LBP score higher on the various psychological, pain related disability factors, and also have lower HPT and PPT scores compared to those with acute LBP for both risk levels. The means of the TS indicate a stronger pain facilitation in people with chronic LBP compared to those with acute LBP, and the mean of $\delta CPM_{low\ leg}$ of the people with chronic LBP indicates poorer endogenous analgesia compared to those with acute LBP (Table 2). Likewise, on comparing the means of psychological factors, pain related disability, pain intensity, HPT_{thumb}, all PPT, TS_{L4}, $TS_{low\ leg}$ and δCPM_{thumb} between the people with acute and chronic LBP in the CSI-defined medium severity level, several differences were observed (Table 3). The people with chronic LBP score higher on the various psychological factors, pain related disability and pain intensity, indicating poorer outcome for these factors compared to those with acute LBP. For the HPT_{thumb} and all PPT measures the people with chronic LBP are more sensitive compared to those with acute LBP. For the TS_{L4}, $TS_{low\ leg}$ and $\delta CPM_{thumb,}$ the pain is more facilitated respectively less inhibited in people with chronic LBP compared to those with acute LBP. These findings of differences in sensitivity and pain-related emotions between people with acute and chronic LBP are consistent with findings from Glare et al. (2020) and Marcuzzi et al. (2018).(16, 45) Sustained nociceptor activity can induce neuroplastic changes in peripheral and central somatosensory circuits, and in higher brain regions containing motivational and emotional centers. This in turn can contribute to the development of chronic pain. (16, 45)

The questionnaires for the psychological and disability factors in this study are commonly used in primary care. Although results regarding the linear trends across the risk and SBT- and CSI-defined severity levels are not surprising, the psychological factors provide further insight into the characteristics for the different SBT- and CSI-defined risk and severity levels for kinesiophobia and pain catastrophizing in both people with acute and chronic LBP using the cut-off values. Using these values, there is a difference in the amount of people with kinesiophobia and pain catastrophizing. In primary care, these psychological factors are less common in the people with acute LBP compared to those with chronic LBP. When the risk profile of the medium risk level based on the SBT and severity level based on the CSI are considered, it becomes clear that they have the highest percentage of people with kinesiophobia and pain catastrophizing (Table 4A,B and 5A,B). It can also be concluded that kinesiophobia and pain catastrophizing in both acute and chronic LBP are present in this studied population in primary care.

Some characteristics that emerged in this study based on 1) significant linear trends across the SBT- and CSI-defined risk and severity levels, 2) the absolute values of the means of the variables between the people with acute and chronic LBP; and 3) the cut-off values of the TSK and PCS that as the risk levels, increase psychological and pain-related disability and HPTs and PPTs become more sensitive. In addition, people with chronic LBP have worse outcomes on psychological and pain-related factors in

combination with a more sensitive pain system compared to those with acute LBP. Looking at the risk levels based on the SBT and CSI using the cut-off values, there is an increase in percentage of people with kinesiophobia and pain catastrophizing. Due to differences in numbers per risk profile, this study does not show to what extent the increase in percentage continues for the high risk level based on the SBT and CSI.

From a scientific point of view we were curious to know to what extent there is a level of agreement between the SBT and CSI in primary care patients with LBP. A moderate level of agreement between the SBT and CSI scores was observed in primary care patients with LBP. These two questionnaires each measure their own construct. It is therefore recommended to use both questionnaires for their own purposes. With the critical note that the CSI is supposed to measure CS-related symptoms, but the content validity is unknown to date.(46)

The strength of this study is its innovative character. Investigating linear trends across the various risk/severity levels based on the SBT and CSI for psychosocial, disability and QST-variables in people with LBP in a primary care setting. Another strength is the representativeness of the included participants. Most scores (51%) of SBT were “low risk level”. This was expected because generally people with LBP visiting primary care have uncomplicated LBP.(47) However, clinicians should be aware that some patients in primary care have more LBP problems in which psychological and disability factors play a role as shown in “medium risk level” of the SBT (38.5%) and the large number of “medium severity level” of the CSI (53.3%).

A limitation of the study is the difference in numbers of participants per subgroup. Despite homogeneity of variance, the results should be interpreted with caution. A limitation of a cross-sectional study is that it is only about an association. The results do not reflect causality.

Lack of information caused some limitation; a better interpretation of results can be achieved if more demographic potential confounders such as income, race, BMI, physical condition and educational level were included. It may be questionable to use the SBT in this heterogeneous group with both acute and chronic LBP. Based on the results of Hill et al. (2008) it appears that there are good opportunities for screening for a duration of LBP between 1-6 months.(9) It also appeared that as the duration of LBP increased the specificity of the cut-off value of the screening tool decreased and the sensitivity remained fairly constant.(9) It is important to realize that the screening of poorer prognosis becomes less accurate over time, however it appears to be possible.

With this study a tentative step has been made to outline characteristics in the SBT- and CSI-defined subgroups of the population of primary care patients with LBP, with the idea of moving towards tailor-made treatments.

The appropriate treatment for the “low levels” could consist of reassuring, educating, promoting self-management and some simple analgesics.(47) As the risk/severity level increases, the psychological approach becomes more dominant in combination with desensitizing strategies such as cognitive behavioral therapy, biofeedback, relaxation training, exercise therapy and pain neuroscience education (PNE).(48) Several studies have shown that PNE, on its own or combined with other kinds of therapy, has a positive influence on psychological and sensory variables and CSI scores.(49, 50) To further develop the idea of precision medicine within LBP rehabilitation clearly, more research is needed. New studies on phenotyping LBP using biomarkers, (epi-) genetics and clinical characteristics of patients with LBP is mandatory before tailoring LBP-treatments to individual characteristics can be

scrutinized. Clinical studies about the (cost-) effectiveness of interventions based on the idea of precision medicine should be conducted in order to see which type of subgrouping is beneficial for people suffering from LBP.

Table 4A. Classification of the LBP patients with a high score on the Tampa Scale Kinesiophobia according to the Star Back Screening Tool.

	Low risk level SBT	Medium risk level SBT	High risk level SBT
Acute LBP	6/15 (40%)	8/15 (53.3%)	1/15 (6.7%)
Chronic LBP	6/21 (28.6%)	9/21 (42.9%)	6/21 (28.5%)

LBP, Low Back Pain; SBT, Start Back screening Tool

Table 4B. Classification of the LBP patients with a high score on the Pain Catastrophizing Scale according to the Star Back Screening Tool.

	Low risk level SBT	Medium risk level SBT	High risk level SBT
Acute LBP	0/4 (0%)	3/4 (75%)	1/4 (25%)
Chronic LBP	1/16 (6.3%)	8/16 (50%)	7/16 (43.7%)

LBP, Low Back Pain; SBT, Start Back screening Tool

Table 5A. Classification of the LBP patients with a high score on the Tampa Scale Kinesiophobia according to the Central Sensitization Inventory.

	Low sev. level CSI	Medium sev. level CSI	High sev. level CSI
Acute LBP	1/15 (6.7%)	7/15 (46.7%)	7/15 (46.6%)
Chronic LBP	0/22 (0%)	10/22 (45.5%)	12/22 (54.5%)

CSI, Central Sensitization Inventory; LBP, Low Back Pain; sev., severity

Table 5B. Classification of the LBP patients with a high score on the Pain Catastrophizing Scale according the Central Sensitization Inventory.

	Low sev. level CSI	Medium sev. level CSI	High sev. level CSI
Acute LBP	0/4 (0%)	1/4 (25%)	3/4 (75%)
Chronic LBP	0/17 (0%)	9/17 (52.9%)	8/17 (47.1%)

CSI, Central Sensitization Inventory; LBP, Low Back Pain; sev., severity

Conclusion

This cross-sectional study revealed linear trends in kinesiophobia, pain catastrophizing, pain intensity, disability and some somatosensory changes across SBT- and CSI-defined low, medium and high risk/severity levels in primary care patients with LBP. Significant positive linear trends showed more psychological and disability factors and enhanced sensory sensitivity (only the PPT measurements) as the SBT- and CSI-defined risk/severity levels increased, which suggests that both the SBT and CSI identify relevant subgroups within the primary care LBP population. This holds potential for tailoring treatment for the specific subgroups, although further work is needed to examine the possible treatment implications. To identify more precise subgroup characteristics within the primary care LBP population, further research is needed (e.g. studies exploring possible biomarkers, phenotypes or (epi)genetic changes to characterize subgroups in the LBP population).

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General Discussion

General discussion

Low back pain (LBP) is a huge and complex problem with several impacts on daily life.(1, 2) A small group of people recover from LBP, but the majority retain low back pain complaints.(3, 4) LBP can lead to absenteeism, reduced quality of life and possibly social isolation.(2, 5) The complexity of LBP is that it is characterized by changes in the somatosensory system and maladaptive cognitions.(5, 6) Despite the different types of interventions, LBP remains a major health problem because the effect sizes of established treatments are small.(7) It invites clinicians and researchers to continue to critically examine the phenomenon of LBP and the different types of interventions with their results. More specific knowledge with regard to the pain mechanisms in LBP with the associated psychosocial characteristics is fundamental in order to link appropriate interventions to this. More efforts should be made towards this in the future, resulting in more tailor-made treatment. The present work attempted to account for all of this.

The main aim of this dissertation is to obtain further information on central sensitization (CS) investigated from the different components of the biopsychosocial model. From the biological component: 1) to examine whether sensory function, measured with quantitative sensory testing (QST), was altered in people with nonspecific LBP compared with healthy controls and 2) to investigate whether differences in various QST measurements exist between people with acute and chronic LBP versus healthy controls in primary care. From the psychological component: to examine the associations between symptoms of CS and inflexibility pattern of behavior, cognitive fusion and perceived injustice in people with non-specific LBP in primary care. From the biopsychological component: to investigate whether linear trends in kinesiophobia, pain catastrophizing, disability, pain intensity and somatosensory characteristics exist in a sample of people with acute and chronic LBP in primary care across severity levels based on the Start Back screening Tool and Central Sensitization Inventory.

To answer this main aim several research questions have been investigated:

- To what extent is sensory functioning, measured with quantitative sensory testing (QST), altered in people with LBP?
- Are there associations between symptoms of CS and inflexibility pattern of behavior, cognitive fusion and perceived injustice in people with non-specific LBP in primary care? Are there differences between people with non-specific LBP with and without symptoms of CS in primary care regarding pain intensity, widespread pain, functional disability, pain catastrophizing, inflexibility pattern of behavior, cognitive fusion and perceived injustice?
- Do differences exist between people with acute and chronic LBP in primary care and healthy controls in heat pain threshold, pressure pain threshold, temporal summation and conditioned pain modulation? Do differences exist between people with LBP with Central Sensitization Inventory (CSI)-score 40≥100 and those with CSI-score <40/100 in heat pain threshold, pressure pain threshold, temporal summation and conditioned pain modulation?
- Does a linear trend exist in acute and chronic people with LBP in primary care across low, medium and high risk/severity level based on the Start Back screening Tool and based on the CSI with regard to kinesiophobia, pain catastrophizing, pain intensity, disability and sensitivity changes in the somatosensory system? What is the level of agreement in identifying subgroups between the SBT and CSI in people with LBP in primary care?

Main results

Chapter 2: Pain mechanisms in low back pain: comparison of QST-measurements between people with LBP and healthy controls

Due to minimal intervention effects it is suggested that altered somatosensory function may play an important role in LBP.(8, 9) It consists of biological processes such as augmentation of peripheral nociceptive information at the level of the dorsal horn and amplification of nociceptive information within several brain nuclei and is summarized as CS.(8, 10) From a clinical point of view it is important to know whether CS is present in the large group of people with LBP. There is a lack in overview and critical evaluation of current literature regarding QST-measurements. Therefore a systematic review and meta-analysis was performed to determine whether there are differences in mechanical QST-outcomes (pressure pain threshold, temporal summation and conditioned pain modulation) between people with non-specific LBP and healthy controls.(11) The systematic review and meta-analysis contained 24 articles. The main result was that overall pressure pain threshold (PPT) measurements at non-segmental related body areas were significantly lower in people with non-specific LBP compared to healthy controls which indicates widespread hyperalgesia. This result is indicative of CS.(9, 11) In addition it was found that temporal summation (TS), performed in the lumbar region, was enhanced in people with NSLBP compared to healthy controls. Enhanced TS is also considered indicative of CS.(9) The result of the conditioned pain modulation (CPM) measurements were mixed: varying from no significant differences between the people with LBP and healthy controls to significantly decreased CPM-outcomes, the latter being indicative of CS.(9, 11)

Many promising results have been found in the systematic review and meta-analysis.(11) Yet no firm conclusions can be drawn from it. This systematic review and meta-analysis focused only on mechanical QST-measurements, but the results of thermal or electrical QST-measurements are not known. The aim was initially to perform a systematic review and meta-analysis over different types of QST measurements in people with nonspecific LBP. During the process, it became clear that too few data were available about non-mechanical QST measurements to perform a meta-analysis in people with nonspecific LBP. As a result, only the mechanical QST measurements were considered. Most of the included articles performed PPT-measurements and to a lesser extent the TS- and CPM-measurements. Many PPT-measurements showed significant differences while the TS- and CPM-measurements showed mixed results. This could be due to the use of different QST protocols for TS- and CPM-measurements across studies. The results were based on non-experimental observational studies which is not positioned high in the 'level of evidence' and describes the situation at the time of measurement; causal inferences cannot be derived from this.(12) Hence, because of the observational nature of the included studies, study findings should be interpreted with caution.(13) Despite these weaknesses, this first systematic review and meta-analysis on this topic shows that alterations are present in the somatosensory system within the group of people with LBP.(11) It is important for clinicians to know that increased pain sensitivity may be present in segmental and non-segmental related body areas in people with LBP. They are advised to adjust their treatment accordingly. Some discrepancies have arisen between the description of the article and the registration on Prospero. Because the search only resulted in articles in English, the proposed plan to include also Dutch and German articles was dismissed. As registered in the Prospero database the included articles covered people with non-specific LBP. Later, during the actual review process, it became clear that these articles on non-specific LBP could include people with subacute as well as people with chronic LBP. For reasons of clarity and correctness it was therefore decided to also make this classification based on the duration of the complaints.

Chapter 3: Associations between cognitive, emotional and behavioral factors and symptoms of central sensitization in people with non-specific low back pain in primary care.

Several psychological factors such as catastrophizing, stress, fear, inadequate illness perception and depression could be risk factors for the development of symptoms of CS and changes in somatosensory functioning.(14) Many associations between symptoms of CS and psychological factors such as symptoms of depression, sleep disturbance, kinesiophobia, pain catastrophizing, pain behavior, pain intensity and functioning in patients with chronic pain were studied.(15, 16) Psychological constructs such as psychological inflexibility and cognitive fusion, concepts from the Acceptance and Commitment model, may also contribute to the development of the symptoms of CS.(17) It was assumed that this also applies to perceived injustice. These three psychological constructs have not been previously investigated in relation to symptoms of CS. From a scientific point of view, this represents a knowledge gap. This innovative study was able to examine the associations between symptoms of CS and inflexibility pattern of behavior, cognitive fusion and perceived injustice in people with non-specific LBP in primary care. In addition the results of the outcomes of the comparison between pain intensity, widespread pain, functional disability, pain catastrophizing, inflexibility pattern of behavior, cognitive fusion, kinesiophobia and perceived injustice between patients with non-specific LBP with and without symptoms of CS were examined. The main finding showed weak to moderate associations between symptoms of CS and inflexibility pattern of behavior, cognitive fusion and perceived injustice in people with LBP in primary care. It was also shown that pain intensity, functional disability, pain catastrophizing, inflexibility pattern of behavior, cognitive fusion and perceived injustice showed significantly poorer outcomes in people with symptoms of CS compared to those without symptoms of CS. This in contrast to widespread pain and kinesiophobia, where there were no significant differences between the two subgroups.(18)

Both psychological inflexibility and cognitive fusion are concepts that originate from Acceptance and Commitment model. Cognitive fusion is part of psychological inflexibility: all questions of the CFQ13 focus on the extent to which a person is influenced by his thoughts. The PIPS contains four questions about cognitive fusion and the remaining eight questions are about avoidance of activities. While psychological inflexibility notifies various elements such as avoidance of situations, thoughts, feelings, and non-acceptance of pain, cognitive fusion is very specific to a person's thoughts. In addition, the researcher performed a Pearson correlation between the PIPS and CFQ13 resulting in r=0.313 (p=0.001). This indicates that there is a weak correlation between these two constructs. Using the cut-off scores of the Psychological Inflexibility in Pain Scale (PIPS) as well as of the Cognitive Fusion Questionnaire 13 (CFQ13), many of the included participants revealed inflexibility pattern of behavior and cognitive fusion. This is in contrast with the findings from the data obtained with the Injustice Experience Questionnaire (IEQ); only one participant scored above the cut-off score for perceived injustice. The cut-off score of the IEQ was established in a study participated by people with musculoskeletal injuries due to work or vehicle accidents.(19) The emotion of 'perceived injustice' will be more applicable in such situations caused by someone else's action instead of the situation with people suffered from non-specific LBP. From this point of view, the outcome of the moderate association between perceived injustice and symptoms of CS is misleading. Additional research into the extent to which the PIPS plays a role in the level of the CSI score was performed in people with non-specific LBP in primary care by means of a regression analysis. The result showed that only 15% of the CSI score predicted by the PIPS score and 85% by other factors. This may explain the 'weak' association between the PIPS and the CSI. The regression analysis of the CFQ13 with the CSI showed that 34% of the CSI score is predicted by the CFQ13 score and 66% by other factors. This may explain the slightly stronger association between the CFQ13 and the CSI. Taking these results into account, the hypothesis needs to be adjusted: it is not so much the psychological construct of psychological

inflexibility and cognitive fusion that affect the phenomenon of CS-related symptoms. The other finding confirms the manifestations of the symptoms of CS: higher pain intensity, increased functional disability, expression of adverse behavior and cognition in inflexibility pattern of behavior, cognitive fusion, more pain catastrophizing and more perceived injustice.(18) The classification according to Boonstra et al. (2016) was used to interpret the degree of pain that the participants scored.(20) Due to the lack of a classification from the primary care setting, this choice was made knowing that the classification is based on people from the rehabilitation setting. This can influence the interpretation of the score. Another critical note relates to the PIPS. The PIPS has been validated in people with chronic pain. We could not scientifically use this questionnaire in people with acute low back pain. This questionnaire was used with all participants because it provides a good overview of the extent of psychological inflexibility. This has been taken into account in the interpretation of the results.

It is important for clinicians to realize that inflexibility of pattern behavior and cognitive fusion occur in large numbers of people with non-specific LBP. Recognizing this behavior and this cognition, the challenge for the clinician is to use Acceptance and Commitment Therapy in these people with non-specific LBP in primary care.(21)

Chapter 4: Differences in quantitative sensory testing outcomes between people with low back pain and healthy controls

QST measures the sensitivity of the somatosensory system and can detect dysfunctions which can be interpreted as CS.(22) Many studies included in our systematic review with meta-analysis, show that CS is present in people with LBP.(11, 23) The CSI measures CS related symptoms.(24) To what extent the QST-measurements and the CSI are related is still unknown. The included studies in the systematic review and meta-analysis were often underpowered and their participants were recruited from the secondary or tertiary health-care settings.(11) The systematic review and meta-analysis was limited to mechanical QST-measurements. This observational case-control study examined whether differences in heat pain threshold (HPT), PPT, TS and CPM measurements exist between participants with acute and chronic LBP in primary care versus healthy controls. This study also investigated whether differences in HPT, PPT, TS and CPM-measurements exist between participants with LBP with CSI-score of ≥40/100 and participants with LBP with CSI-score of <40/100. The results of the primary aim were that all HPT, PPT and δCPM-measurements at remote body areas were significantly different between people with acute and chronic LBP versus healthy controls. All HPT and PPT-measurements were significantly lower in people with acute and chronic LBP compared to healthy controls and all CPM-measurements were smaller in people with acute and chronic LBP compared to healthy controls. Only TS at the L4 level was significantly higher in people with acute and chronic LBP compared to healthy controls.(25) The results of the secondary aim were that all PPT-measurements were lower in people with LBP with CSI-score of ≥40/100 compared to those with CSI-score of <40/100.

The results of the primary aim are in line with our systematic review and meta-analysis: all PPT-measurements of the people with chronic LBP were significantly lower compared to healthy controls and TS at the L4 level of the people with chronic LBP were significantly higher compared to healthy controls.(11, 25) In this study all CPM-measurements of people with chronic LBP were significantly smaller compared to healthy controls while results of the CPM-measurements in the systematic review and meta-analysis were mixed. In addition this study showed that all HPT-measurements also were significantly lower in people with acute and chronic LBP compared to healthy controls. The results of the secondary aim of this study were innovative. Until now it was known from the systematic review and meta-analysis that the CS pain type occurs in secondary and tertiary health-care settings, these results indicated that CS also occurs in primary care to a similar extend as to what is seen in secondary/tertiary care. The results should be interpreted with caution because some social and

physical components such as BMI, income, smoking, race, education level and physical condition were not taken into account. Knowing that the CS type of pain can occur in people with LBP in primary care, the advice for clinicians would be screen for it. And if CS is present the clinician should adapt the treatment accordingly. Treatment should target the central nervous system; this means that the clinician pays attention to the explanation of the neurophysiology of pain, maladaptive cognitions and behavior, referred as 'pain neuroscience education', and exercise-induced analgesia. Studies show positive results in people with chronic spinal pain: less pain sensitivity, fewer symptoms of CS, improved physical and mental functioning and improved pain-inhibition system.(26, 27) Based on these studies, this treatment would be the appropriate treatment for the CS subgroup within the primary care LBP population.

Chapter 5: Multifactorial differences between people with low back pain in the various risk level of the Start Back screening Tool and Central Sensitization Inventory in primary care

Low back pain is complex due to the fact that it includes different types of pain and that various psychosocial factors may play a role in the development of LBP or in the persistence of LBP.(14, 15, 28) Because the effects of the treatment of LBP are small, it should be considered to personalize the treatment. A suggestion is to make subgroups based on the different pain types or on the different psychosocial characteristics of the patient as is done in stratified care. Evidence reveals that treating directly related to a specific subgroup leads to more favorable outcomes than usual care in patients with musculoskeletal pain.(29) The questionnaires Start Back screening Tool (SBT) and Central Sensitization Inventory (CSI) divide people into subgroups (risk levels) with regard to the likelihood of chronicity in LBP respectively CS-related symptom severity.(30, 31) Little was known whether there is a linear trend across the risk levels based on the SBT and the CSI with regard to psychosocial factors, disability and neurophysiology in patients with LBP. The cross-sectional study included in this dissertation investigated whether linear trends exist across low, medium and high risk levels based on the SBT and CSI with regard to kinesiophobia, pain catastrophizing, pain intensity, disability and sensitivity changes in the somatosensory system in people with acute and chronic LBP in primary care. The results showed a significant positive linear trend across the risk levels based on the SBT for kinesiophobia, pain catastrophizing, pain intensity, disability and a significant negative linear trend across the risk levels based on the SBT for the HPT at the thumb and lower leg level, PPT at the L4 level and PPT at the lower leg level in patients with LBP in primary care. In addition, a significant positive linear trend was present across the risk levels based on the SBT for δCPM at the thumb level. Significant positive linear trends were shown across the severity levels of the CSI for kinesiophobia, pain catastrophizing, pain intensity, disability in patients with LBP in primary care. For all PPT-measurements, significant negative linear trends were present across the severity levels of the CSI. In addition, significant positive linear trend across the severity levels of the CSI was present for the δCPM at the thumb level.(32)

This is one of the first studies investigating linear trends across the risk levels with regard to comprehensive psychosocial factors and functional disability in combination with QST-measurements. Another study also subgrouped their participants after completing the CSI and had comparable outcomes regarding the psychosocial and disability factors in patients with musculoskeletal disorders in primary care setting.(33) In our study, the number of participants per subgroup was different, however there was homogeneity of variance. For that reason these innovative results should be treated with caution. The means of the psychological factors and the QST measures showed a difference between the people with acute LBP and those with chronic LBP. The people with acute LBP showed the presence of psychological factors to a lesser extent than those with chronic LBP. For the QST measurements, it was apparent that people with acute LBP had a less sensitive pain system compared to those with chronic LBP. The knowledge of these results may have important implications for clinical practice. It is essential to be aware that a different treatment is carried out for each subgroup. This can vary from promoting self-management with some education for patients with a low

risk level, to more psychosocial approach such as cognitive behavioral therapy in combination with e.g. relaxation training, biofeedback and pain neuroscience education to desensitizing the central nervous system in the high risk level.(34)

Reflections

This dissertation concentrates on CS in people with LBP in primary care. As described in the general introduction, the concept of CS has evolved during this PhD. At the time, this concept was widely used and today a distinction is made between the neurophysiological understanding and the clinical understanding. After the content of various chapters were taken into account, it became clear that the concept of CS had not always been used correctly. In the general introduction is described per chapter whether the term central sensitization or nociplastic pain applies to the current view. In the general discussion both terms will be used as they are defined according the IASP.

The CSI was used several times in this dissertation. This questionnaire acts as a screening tool and measures emotional, cognitive and somatic symptoms.(35) It is a subjective measure of a person's general sensitivity. Several cut-off scores have been published in recent years. It may seem tempting to use the existing cut-off score of ≥ 40, determined by Neblett et al. (2013) in order to indicate the presence of CS.(36) The presence of CS can never be proven directly from a questionnaire. The idea, having arisen in recent years, that the CSI shows whether people do or do not have CS based on the cut-off value is a fallacy. The CSI provides insight into the CS-related symptoms that are present in that person.(16) In chapter 3, this cut-off score was used only to screen the study population for an increased risk of having central sensitivity syndrome and thereby segregate them. In chapter 5 the severity levels of the CSI, determined by Cuesta-Vargas et al. (2020), were used. This choice is based on dividing the study population according to the severity of the CS-related symptoms.(31) From this perspective, using a cut-off score falls short for its purpose. The cut-off score and the different severity levels of the CSI have been determined in research populations with chronic pain.(24, 31) In this dissertation the population is heterogenous: people with acute and chronic LBP are included. From a scientific point of view, no conclusions should be drawn from the results of the CSI score of the people with acute LBP. In the clinical setting of primary care, the CSI is the available questionnaire to use. A critical remark is needed: the results of the people with acute LBP should be viewed with some caution. Looking at the acute phase of LBP, the neurophysiological process of CS is normal. The literature indicates that acute LBP is considered to last no longer than six weeks.(37) During this six weeks, psychological factors can take on a more dominant role, which is predisposing to chronic LBP.(38) The sensation of pain is often associated with factors such as feelings, emotions, behavior, beliefs and fears. Located in the brain is a network referred to as the 'dynamic pain connectome' which integrates the sensorimotoric, cognitive and affective aspects of pain.(10) These aspects together are persistent and increasingly dominant in influence on pain; the development leads to chronic LBP.(38) From this point of view, the use of the CSI in this phase of LBP may be of more value than has been assumed so far. This is a consideration from the clinical reasoning process, where the absolute realization is that the validation of the CSI must be performed in people with acute LBP, in order to have scientific value. A critical remark regarding the use of the CSI is the lack of knowledge regarding the content validity of this questionnaire. The lack of a gold standard for assessing CS makes it difficult to determine the content validity of the CSI.(39) The question is to what extent a questionnaire can completely overcome the above-described complexity of the neurophysiology associated with CS.

In this dissertation a lot of information was obtained from QST measurements in people with LBP in primary care. Partly derived from the systematic review and meta-analysis (chapter 2) and partly by

performing QST itself (chapter 4 & 5). By using QST measurements an attempt was made to objectify the neurophysiological process of CS in people with acute and chronic LBP in primary care. Reflecting on this process, it can be concluded that the word 'objectification' as such conflicts with practice. These measurements are somewhat subjective even though there is a desire to think that *only* the somatosensory system is measured. Contextual factors such as the temperature in the room where the measurements are taken, the explanation and voice of the researcher, the starting position ((not) comfortable), the reaction time and a person's ability to concentrate to be measured can influence the QST measurements.(40) It is essential to realize that pain sensation is always accompanied by affective and cognitive factors. When a stimulus is given, these three 'systems' become active. During the instruction for the QST measurements, the person may already have certain (anxiety) expectations and this can influence the moment of ending the measure: has the person actually felt the pain threshold or is the person afraid of feeling pain and does he end the measurements prematurely? This actually happened when a test person already indicated pain before the 2nd PPT measurement had started. Individual QST measurements are not interpretable. Comparing results within the individual on the contralateral side is possible in case of primary hyperalgesia, but may be misleading when secondary hyperalgesia is present.(27) If the suspicion is nociplastic pain, comparison with the contralateral side will not be possible if one of the symptoms is widespread pain. The results will have to be compared with those obtained in healthy controls. This makes interpretation of QST data difficult for individual use. It should also be taken into account that different parts of the body have significant regional differences: from cranial to caudal, for example, the PPT will show an increasing score.(41) As a result, it is not possible to compare individual differently measured locations and therefore our three test locations were interpreted independently.

In this dissertation the most common QST measurements and the performance were chosen based on scientific literature.(42-46) We are aware that we have not complete the entire QST protocol. QST is time consuming; as a result, scientific interests and the cooperation of the participants sometimes come into conflict. The situations makes it necessary to make decisions from a practical view. The 'methods of limits' (defined as "the perception and pain thresholds are measured as the first identified stimulus under increasing stimulus intensities") were chosen instead of 'methods of levels' (defined as stimulations is applied repeatedly below and above the perception or pain thresholds").(41) Although the 'methods of levels' allow stable responses the former is less time consuming.(47) The disadvantage of 'methods of limits' is that it requires a lot of attention from the participant to say 'stop' at the right time at his pain threshold. To keep the participant's the ability of concentration optimal, two measurements were chosen instead of three per QST test. As a result, the learning effect will also be minimal and bias will be minimized by calculating the mean. In addition to static QST measurements, the limitation of which lies in measuring at one point within the complex neurophysiological pain process, a dynamic test was also chosen. This method allowed us to obtain information about the central integration and the descending control.(47) The QST tests are interpreted separately: it was expected that if a static QST test could indicate CS, a dynamic test would also indicate this. The reality turned out to be different. Many TS measurements showed no significant results and some CPM measurements showed significant differences in people with acute and chronic LBP versus healthy controls. Presumably, undergoing a TS measurement requires more concentration and cognitive skills from the person compared to the CPM. In the TS measurement, the person has to rate the pain sensation three times in a short time. Not everyone is equally skilled at this. The question is whether QST actually measures CS. For example TS measurements: this process takes places at the synaptic level in the dorsal horn of the spinal cord.(41) We measured this process indirectly. Results from this dissertation show that differences are measured at group level between people with acute and chronic LBP compared to healthy controls. Significant differences were not measured between the people with

acute LBP versus chronic LBP. However, there were significant differences for the PPT measurements only between the people with CS versus without CS. The other QST test indicated no significant difference. Valid statements cannot be made on the underlying mechanism between them. From the knowledge about the network, known as the 'dynamic pain connectome' where the cognitive, affective and sensorimotoric processes are integrated, it is inconceivable that the somatosensory system is objectified in itself. Purely the neurophysiological processes cannot be measured in this way. QST measurements are interesting from a scientific point of view. Implementing these measurements in primary care is not applicable due to the absence of cut off values for individual measurements. The IASP describes clinical criteria for nociplastic pain and this should provide sufficient practical guidance.

The way forward: bridging the gap between research results and clinical practice

An attempt has been made to obtain information about CS in the large group of people with LBP in a primary care setting. Several studies have been carried out and it can be concluded that:

- Neurophysiological changes are present in people with acute and chronic LBP compared to healthy controls;
- An association was found between symptoms of CS and inflexibility pattern of behavior, cognitive fusion and perceived injustice in patients with non-specific LBP;
- A difference was shown between people with acute and chronic LBP versus healthy controls with regard to several psychosocial factors and QST-measurements in primary care;
- A difference is present between people with LBP with CS symptoms and those with no CS symptoms regarding to psychosocial factors and some QST-measurements in primary care;
- Psychosocial factors and disability increase and the somatosensory system became more sensitive as the risk and severity levels based on the SBT and CSI increase.

Considering the entire physiotherapeutic process, this dissertation is applicable to the physiotherapeutic diagnostic part. As a clinician it is valuable to include significant results from this dissertation in practicing the profession in people with LBP in primary care. Realizing that the results have significance at group level in this dissertation, and that no intervention research has been done, there is a need to provide some implications for practice: physiotherapists in primary care see a heterogeneous group of people with LBP. Based on this dissertation, heterogeneous means: people with acute and chronic LBP, people with and without de presence of CS-related symptoms, people with LBP with different degrees of psychological factors present. In addition, the described characteristics of people with LBP visiting the primary care, by Morso et al. (2013), are of course also present.(48) Despite the presence or absence of significant differences in the somatosensory system and the degree of presence of psychological factors within the heterogeneous group, as a clinician you cannot approach/treat these people generically. It remains a personal health problem that requires a tailor-made treatment. If the heterogeneous group of people with LBP continues to be treated generically, the "LBP problem" will continue. It is important for the clinician to realize that nociplastic pain may be present in people with LBP attending primary care. Frequently used questionnaires such as SBT and CSI can be used for their intended purpose. As described by Hill et al. (2008), the SBT as a screening tool is best used for LBP lasting between 1-6 months. The longer the duration of LBP, the less accurate the screening for poorer prognosis.(30) The CSI can be used to obtain information about the level of severity of the CS-related symptoms in patients. For the people with chronic LBP, the results will be more valid than for the patients with acute LBP because of the validation of this questionnaire was

done in populations with chronic pain. Using the SBT or the CSI, clinicians may realize that as the risk or severity level increases, the somatosensory system shows changes: it becomes more sensitive. Based on the reflections on the QST, it can be concluded that this tool is not useful for the individual and therefore not for clinical practice. If the clinician wishes to differentiate between neuropathic, nociceptive and nociplastic pain the algorithm according to Kosek et al. (2021) is recommended.(49) It describes several clinical criteria for chronic nociplastic pain, such as de duration (> 3 months) and the degree of widespread pain (regional), as well as whether nociceptive or neuropathic pain is responsible for the pain felt. The clinical criteria also includes asking about the history of pain hypersensitivity to different types of stimuli (touch, movement, pressure, heat/cold) and the presence of co-morbidities (fatigue, sleep disturbance, increased sensitivity to odors, light and sound). For the physical examination the clinical criteria lead to the advice to elicit the pain hypersensitivity in the region of pain.(49) This helps the clinician in choosing further treatment. Although this is beyond the scope of this dissertation, the intention is to help the clinician with advice: the type of intervention in primary care balances between all locally/peripherally related approach versus a central approach. If nociplastic pain is dominant, it is advisable to focus treatment on central mechanism.(27) Interventions such as pain neuroscience education (explaining the neurophysiology of pain, addressing maladaptive cognitions and behavior, reconceptualization of the concept of pain) in combination with exercise at moderately intensive level (aerobic training) will lead to an increase in pain inhibition and the stimulation of exercised-induced analgesia.(27) Patients will experience a better quality of life because they obtain more control over their pain.(50)

This dissertation also shows that there are significant associations between the CS-related symptoms and inflexibility pattern of behavior and cognitive fusion in primary care patients with LBP. If during the intake and/or during the physical examination it appears that primary care patients with LBP exhibit pain avoidance behavior or that people misinterpreted their current pain-related event due to a pain-related event from the past, the approach according to Acceptance and Commitment Therapy is advisable.(21, 51) This approach is concentrated on the person's most valuable goals and does not focus on the pain, resulting in improved person's functionality. This therapy uses mindfulness and acceptance strategies.(21) It results in a flexible pattern of behavior with their LBP and a realistic view of their back pain itself. It is clear from this dissertation and many newer studies that nociplastic pain is a complex process involving interactions between psychology, neurophysiology and also immunology.(50) Outside the scope of this dissertation, however, it is important for clinicians to consider the potential for sleep and stress related problems in people with LBP with nociplastic pain which negatively affects pain thresholds.(52) For this, it is recommended to apply sleep or stress management.(52) In addition, it remains important to motivate the person to exercise. It has been shown that cognition-targeted motor control training in combination with pain neuroscience education is more effective than best-evidence physiotherapy (including general exercises and traditional education) in people with chronic spinal pain.(26) Due to many influencing factors on the development of CS-related symptoms and many associated therapies, it is important to form subgroups in the large group of people with LBP.

The results of the innovative study, described in chapter 5, are an important start for 'the way forward'. It is a start to objectify characteristics in existing risk and severity levels by which the large group of people with LBP are classified when completing the SBT and CSI. This fits the idea of precision medicine. This term has gained popularity in recent years and although it does not yet have a definitive definition, it means that people are receiving tailor-made treatment.(53) It is becoming increasingly clear that more knowledge is needed about various aspects that characterize the persistence of LBP. There is a lot of knowledge about the neurophysiology of the somatosensory system and about several psychosocial factors that influence the persistence of LBP to which this dissertation also contributed.

It is important to broaden the knowledge about information with regard to lifestyle, genetics and other biomarkers. This allows to focus the treatment specifically on the characteristics. It is also necessary to further investigate which treatment is effective for which characteristics.

Directions for future research

All studies in this dissertation have an explorative research design. A weakness of this is that it provides information about one moment. Essential remaining questions are: why does acute LBP develop into chronic LBP in one person and not in another person? Which factors play a role in the development of maladaptive beliefs and cognitions, for example, thoughts, behavior, fear and emotion in people with LBP? What alterations occur in the somatosensory system in people with LBP? Which treatments have positive effects on the somatosensory system in primary care patients with LBP? What effects do the treatments have on thoughts, behavior, fear and emotion in primary care patients with LBP? A longitudinal study would be more appropriate as Marcuzzi et al. (2018) did.(6) They conducted the first longitudinal exploratory study in which people with acute LBP were followed for four months.(6) They found that there was an increased mechanical pain sensitivity in people who developed persistent LBP. They also concluded that higher pain-related cognitions at baseline distinguished between the 'persistent LBP group' and the 'recovered LBP group'.(6) Recommendation would be to obtain more understanding of this process by longitudinal studies in which the psychosocial factors and the somatosensory system are monitored. The effects of interventions can also be monitored in longitudinal studies on psychosocial factors as well as the somatosensory system in people with LBP. If people with chronic LBP with dominant psychosocial factors subjected to an intervention in which the psychosocial factors are significantly reduced, does the sensory system also change? To understand in more detail the thoughts, behavior, fear and emotion of people with LBP, a mixed method could provide this additional information instead of just questionnaires related to these items.

QST can be used to increase scientifically oriented insights. The use of the CSI provides us with information into the degree of presence of CS-related symptoms. In order to keep the patient's health problem manageable, it is desirable to be able to predict the extent of the patient's developing CS-related symptoms. The CSI questionnaire will then be used as a 'predictor'. If this idea has support, it is eligible to investigate this.

Would the riddle of LBP with the influence of CS now have been further unraveled?

Conclusion

The initial ambition of this PhD, was to create subgroups in the large group of people with LBP. During this period, the ambition was adjusted because our sample size was too small to perform a thorough cluster hierarchical analysis for creating subgroups. However, this dissertation has provided new information regarding nociplastic pain in primary care. Much has been written about LBP, CS, nociplastic pain, different types of psychologically oriented questionnaires, associated cut-off values, but most studies have included participants in secondary and/or tertiary setting. In spite of 'ifs and buts' this is an innovative point of this dissertation.

CS-related symptoms manifest in the large group of people with acute and chronic LBP in primary care. Within this group QST measurements show different outcomes in the somatosensory system that can be interpreted as CS. CS-related symptoms can be measured using the CSI questionnaire. Using the cut-off score (≥40/100), it was shown that some QST-measurements in the group of people with LBP with CSI ≥40/100 scored poorly compared to those with CSI <40/100 in primary care. The scores of

several psychosocial factors were also poorer in people with LBP with CSI ≥40/100 compared to those with CSI <40/100 in primary care. Several associations have already been demonstrated between CS-related symptoms and various psychosocial factors. Innovative constructs revealed that there are also associations between CS-related symptoms and inflexibility pattern of behavior, cognitive fusion and perceived injustice in people with LBP in primary care. The SBT and CSI subgroup people with LBP into low, medium and high risk and severity levels. It was demonstrated that there are significant linear trends in psychosocial factors, disability and some QST outcomes between the three risk and severity levels in people with acute and chronic LBP in primary care. This is a first step to investigate characteristics that are present per risk and severity level based on the SBT and CSI.

This dissertation forms a solid foundation for further research. The CSI measures CS-related symptoms but does not seem to measure to what extent the patient develops CS-related symptoms. A possibility for further research is to investigate the establishment of a predictive value for the development of CS-related symptoms. Other research is needed about characteristics of the subgroups based on the SBT and CSI. Expanding the knowledge about lifestyle, genetics and other biomarkers provides more specific information about subgroups of people with LBP. In the future, this knowledge may provide more specific and tailor-made treatments. Hopefully, this will eventually make the riddle of LBP less puzzling.

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Summary

Low back pain (LBP) is seen a lot in the physiotherapy primary care setting. Patients can suffer from LBP for short or long-time and sometimes it will be recurrent. Listening to the narratives of the patients, they often experience disability in their work, daily activities, hobbies and have different thoughts, beliefs and/or emotions. This is precisely what LBP makes complex: there is a neurophysiological component, various psychosocial factors, immunological and endocrine elements. A systematic review and meta-analysis has been carried out to investigate if the somatosensory system (neurophysiological component), measured by quantitative sensory testing (QST) is modified in people with non-specific LBP (chapter 2). The results showed significant differences in all pressure pain threshold measurements at remote body parts and at temporal summation at lumbar level between people with non-specific LBP and healthy controls. Regarding the conditioned pain modulation measurements, mixed results were found in people with non-specific LBP compared to healthy controls. We were curious to know to what extent there were differences in QST-measurements of people with acute and chronic LBP versus healthy controls in primary care setting. An extensive QST-measurement (mechanical as well as thermal) has performed (chapter 4). The results showed that all heat pain threshold, pressure pain threshold and conditioned pain modulation measurements at remote body areas differed significantly between people with acute and chronic LBP and healthy controls in primary care. Only the temporal summation measurement at the L4 level was significant different compared to healthy controls in primary care.

Several studies have shown that certain psychological factors (depression, fear, pain catastrophizing, inadequate illness perception and stress) affect the somatosensory system and can be a risk factor for developing symptoms of central sensitization (CS). The Acceptance and Commitment model indicates that inflexibility pattern of behavior and cognitive fusion can be psychological factors that affect the phenomenon of CS. In addition, people can sometimes have the feeling of 'injustice' in their experience of LBP. To what extent there is an association between CS-related symptoms and these three psychological factors in people with non-specific LBP in primary care is still unknown and will be investigated (chapter 3). In addition to this objective, it was also investigated to what extent there was a difference between the outcomes of people with non-specific LBP in primary care with a positive Central Sensitization Inventory (CSI) score and a negative CSI score with regard to different psychological factors, pain intensity, widespread pain and functional disability. There was a positive association (weak to moderate) between CS-related symptoms and inflexibility pattern of behavior, cognitive fusion and perceived injustice in people with non-specific LBP in primary care. There were significant differences between people with non-specific LBP with a positive CSI and a negative CSI regarding to various psychological factors in primary care. The people with non-specific LBP with a positive CSI had poorer outcomes compared to those with a negative CSI.

A growing idea is to tailor the treatment to the characteristics that (may) be present in LBP. The innovative cross-sectional study (chapter 5) starts with this idea by dividing the group of people with acute and chronic LBP in primary care into subgroups (risk levels) formed by the questionnaires Start Back screening Tool (SBT) and CSI. This study investigated whether linear trends exists across low, medium, high risk and severity level, based on the SBT and CSI, with regard to psychological factors, pain intensity and pain-related disability and QST-measurements in people with acute and chronic LBP in primary care. The results showed positive significant linear trends across the SBT and CSI- defined risk and severity levels for all psychological factors, pain-related disability and pain intensity in people with acute and chronic LBP in primary care. Negative significant linear trends were presented in some QST measurements across the risk and severity levels based on the SBT and CSI in people with acute and chronic LBP.

Researchers are invited to establish a predictive value for the development of CS-related symptoms. They are also invited to conduct further research in characteristics of subgroups in people with LBP in primary care in order to finally work towards tailor-made treatments.

Samenvatting

Lage rugpijn wordt veel gezien in de eerste lijn fysiotherapie praktijk. Patiënten kunnen hier kort- of langdurig last van ervaren en soms is lage rugpijn recidiverend van aard. Het verhaal van de patiënt horende, ervaren zij vaak een beperking in hun werkzaamheden, dagelijkse activiteiten, hobby's en hebben zij verschillende gedachtes, overtuigingen en/of emoties ten aanzien van hun lage rugpijn. Dit is nu juist wat lage rugpijn complex maakt: er is een neurofysiologisch component en immunologische en endocriene systemen die voor de pijnsensatie zorgt. Daarbij kunnen er verschillende psychosociale factoren aanwezig zijn die lage rugpijn een aanhoudend karakter geven. Een systematische review met meta-analyse is uitgevoerd om te onderzoeken of het somatosensorisch systeem (neurofysiologisch component), gemeten middels quantitative sensory testing (QST), veranderd is bij mensen met a-specifieke lage rugpijn (hoodfstuk 2). De resultaten toonden significante verschillen aan bij alle 'pressure pain threshold' metingen op het 'niet segmentaal gerelateerd locatie' aan de lage rug én bij de temporele summatie op het lumbale niveau tussen mensen met a-specifieke lage rugpijn en gezonden. Ten aanzien van de conditioned pain modulation metingen waren de significante verschillen wisselend tussen de mensen met a-specifieke lage rugpijn en gezonden. We waren benieuwd in hoeverre er verschillen zijn in QST metingen tussen mensen met acute en chronische lage rugpijn gerekruteerd uit de eerste lijn fysiotherapie praktijk en gezonden. Een uitgebreide QST meting (zowel mechanisch als thermisch) is uitgevoerd (hoofdstuk 4). De resultaten toonden aan dat alle heat pain threshold, pressure pain threshold en conditioned pain modulation metingen op het 'niet segmentaal gerelateerd locatie' aan de lage rug significant verschilden tussen de mensen met acute en chronische lage rugpijn uit de eerste lijn fysiotherapie praktijk en gezonden. De temporele summatie meting op het niveau van L4 verschilde significant tussen de mensen met acute en chronische lage rugpijn uit de eerste lijn fysiotherapie praktijk en gezonden.

Verschillende studies hebben aangetoond dat bepaalde psychologische factoren (depressie, angst, pijn catastroferen, inadequate ziekte perceptie en stress) het somatosensorisch systeem beïnvloeden en kunnen een risico factor zijn voor centrale sensitisatie (CS). Het "Acceptance en Commitment model" geeft aan dat inflexibel gedragspatroon en cognitieve fusie, psychologische factoren zijn die het fenomeen van CS kunnen beïnvloeden. Tevens kunnen mensen met lage rugpijn het gevoel van 'onrecht' ervaren tijdens hun lage rugpijn episode. In hoeverre er een verband is tussen de CS-gerelateerde symptomen en deze drie psychologische factoren (inflexibel gedragspatroon, cognitieve fusie en het ervaren van onrecht) is nog niet bekend en zal worden onderzocht (hoofdstuk 3). Tevens werd er onderzocht in hoeverre er een verschil is tussen de uitkomsten bij mensen met a-specifieke lage rugpijn, uit de eerste lijn fysiotherapie praktijk, met een positieve Central Sensitization Inventory (CSI) score en een negatieve CSI score ten aanzien van verschillende psychologische factoren, pijn intensiteit, wijdverspreide pijn en functionele beperking. Er was een positieve associatie (zwak tot matig) tussen de CS-gerelateerde symptomen en het inflexibel gedragspatroon, cognitieve fusie en onrecht voelen bij mensen met lage rugpijn in de eerste lijn fysiotherapie praktijk. Er was een significant verschil tussen de mensen met a-specifieke lage rugpijn, uit de eerste lijn fysiotherapie praktijk, met en zonder een positieve CSI ten aanzien van verschillende psychologische factoren, pijn intensiteit en functionele beperking. Mensen met a-specifieke lage rugpijn met een positieve CSI hadden slechtere uitkomsten dan diegenen met een negatieve CSI score.

Een idee wat in ontwikkeling is, is om de behandeling van lage rugpijn af te stemmen op de kenmerken die aanwezig (kunnen) zijn bij lage rugpijn. De innovatieve cross-sectioneel studie (hoofdstuk 5) maakt een begin met dit idee door de groep mensen met acute en chronische lage rugpijn, uit de eerste lijn fysiotherapie praktijk, te verdelen in bestaande subgroepen (risico niveaus), welke gevormd zijn door de vragenlijsten 'Start Back screening Tool' en de 'CSI'. Deze studie onderzocht in hoeverre er een

lineaire trend aanwezig is tussen de ‘laag’, middelmatig’ en ‘hoog’ risico level én de ‘mate van ernst’ level, gebaseerd op de vragenlijsten SBT en CSI, met betrekking tot psychologische factoren, pijn intensiteit, pijn gerelateerde beperking en QST metingen bij mensen met acute en chronische lage rugpijn in de eerste lijn fysiotherapie praktijk. De resultaten toonden positieve significante lineaire trends aan tussen de risico levels en ‘de mate van ernst’ levels, vanuit de SBT en de CSI, voor alle psychologische factoren, pijn gerelateerde beperking en pijn intensiteit bij mensen met acute en chronische lage rugpijn in de eerste lijn fysiotherapie praktijk. Negatieve significante lineaire trends werden aangetoond bij sommige QST metingen tussen de risico levels en ‘de mate van ernst’ levels, vanuit de SBT en de CSI, bij mensen met acute en chronische lage rugpijn in de eerste lijn fysiotherapie praktijk.

Onderzoekers worden uitgenodigd om een voorspellende waarde vast te stellen bij de CSI op het ontwikkelen van CS-gerelateerde symptomen. Zij worden ook uitgenodigd verder onderzoek te doen naar karakteristieken per subgroep bij de mensen met lage rugpijn met als doel toe te werken naar de behandeling specifiek af te stemmen op de persoon met lage rugpijn.

Curriculum Vitae

In April 2000, Hester den Bandt graduated from the bachelor program physiotherapy at the "Hogeschool van Amsterdam", Amsterdam, the Netherlands. She started as an acting physiotherapist for a half year to orientate herself in possibilities within the physiotherapy profession. Since the autumn of 2000, she works in a primary care physiotherapy setting.

From January 2008 to September 2010 Hester attended training as a manual therapist at the "Transfer groep Rotterdam", Rotterdam, the Netherlands. From August 2011 she combined her practical work as physiotherapist with lecturer at the "University of Applied Sciences Rotterdam", Rotterdam, the Netherlands. As lecturer, she provides the students theoretical subjects with the emphasis on neurophysiology of pain, modulation of pain, influences of stress on pain, pain education and clinical reasoning. Additionally she supports the students in various practical skills and writing of case reports.

In August 2015, she started her PhD part-time at the "Vrije Universiteit Brussel", Brussels, Belgium and became member of the international research group "Pain in Motion". During her PhD she contributed to several national and international scientific congresses such as an oral presentation at the "Pain in Motion" congress in Stockholm (2017), a poster presentation at the World Confederation of Physical Therapy (WCPT) congress in Genève (2019) and to be a guest lecturer at the "Roskilde University", Roskilde, Denmark (2018). In addition, she co-authored in several international peer-reviewed journals.

In addition to lecturing Hester recently became responsible for the coordinator ship of the minor "Pain Basics for Health Professionals" for 4th year bachelor students and the module "clinical reasoning in people with complex musculoskeletal pain" for 3th year bachelor physiotherapy students. In the spring of 2022 she exchanged her membership of the Assessment Committee for her membership in the Curriculum Council of the bachelor program physiotherapy for the "University of Applied Sciences Rotterdam".

Currently Hester participates in a group of paramedics to develop more efficient care pathways for patients with chronic pain within the healthcare section in Friesland, the Netherlands. In the future she intends to give courses to paramedics and/or colleagues physiotherapists on the subject of this dissertation.

She feels privileged combining scientific research with her lecturing position and clinical practice.

Dankwoord

Eindelijk is het zover: ik mag mijn 'dank woord' écht gaan schrijven. In de afgelopen jaren ben ik er al vaak mee bezig geweest tijdens het hardlopen. Vaak was het hardlopen voor mij een moment van reflectie. Dit gebeurde regelmatig, nadat ik feedback had gekregen bij het schrijven van de verschillende artikelen. Mijn stelling is dan ook: "van promoveren val je af". Na het hardlopen lukte het me om op een andere manier naar de feedback te kijken, de mogelijkheden/oplossingen hierin te zien en weer verder te schrijven. De afgelopen zes en een half jaar ben ik gaan beschouwen als een vorm van topsport. Het gehele proces van mij verdiepen in het onderwerp, mij inlezen in de literatuur, het overleggen over de verschillende onderzoeksvragen en hoe dit verder vorm te geven, het organiseren van mijn promotie in combinatie met het docentschap en praktiserend fysiotherapeute, het plannen van de participanten die ik moest meten, het analyseren van de resultaten, het schrijven van de artikelen en het balanceren tussen mijn eigen belasting en belastbaarheid is mij gelukt met een fijn team mensen om mij heen. Ik wil dan ook graag stil staan bij hen:

Allereerst wil ik stilstaan bij mijn begeleiders: Lennard, Jo, Kelly en Winifred. We zijn in september 2015 met elkaar aan een reis begonnen die op 29 april 2022 zal eindigen in Brussel. Fijn om de ruimte en tijd te krijgen voor het me bekwamen in de wereld van de wetenschap. Langzamerhand werd mij duidelijk wat en hoe ik de wetenschap moest gaan uitvoeren. Hierin kreeg de samenwerking ook steeds meer en beter vorm. Wat ik altijd als bijzonder heb ervaren is de vorm van feedback die ik kreeg van jullie. Het was altijd opbouwend en positief! Terwijl ik mijn eigen stukken tekst soms achteraf tenen krommend vond (nadat ik de feedback ontvangen had), merkte ik daar niets van bij jullie. Ik kreeg ook alle ruimte van jullie om mijn eigen onderzoeksproject vorm te geven. Mocht ik een afslag in willen gaan die niet gepast of handig was voor het onderzoek, werd mij dat op een duidelijke doch prettige manier verteld. Winifred, fijn dat je in de begin fase van mijn promotie betrokken was. Gedurende het ontstaan van ons eerste artikel heb ik fijn en leuk met je samengewerkt. De kneepjes van het wetenschapsvak heb je mij aangeleerd, het heeft mij verder geholpen dat jij verschillende soorten knelpunten in het proces benoemde en het aanvoelen van de situatie van 'in het diepe springen' in de wetenschap gaf mij een fijn luisterend oor bij jou. Op een gegeven moment ben jij je eigen ambities achter na gegaan, maar je tips bleven! Jo, senior onderzoeker, ik (beginneling) kreeg alle ruimte om mij te ontplooien, waarbij ongetwijfeld de startende onwetenschappelijkheden ongemerkt door je vingers werden gezien. Je relativeringsvermogen werkte verhelderend en fijn dat je soms even stil stond bij de mens achter het gezicht. Heel veel dank! Kelly, naast het meedenken in de antwoorden voor 'respons to the reviewers', het meedenken met de analyses was er ook altijd de gelegenheid om andere zaken de revue te laten passeren zoals sport of andere luchtige zaken in privé sfeer. De wetenschap verbond ons, maar leuk dat het contact ook ruimte bood voor dit soort elementen. Fijn om jou bij me in het team gehad te hebben. Heel veel dank voor jouw tijd en inzet! Lennard, we werken al heel lang samen met elkaar. Dit varieert van gelijkwaardig collega van elkaar zijn tot begeleiden van mij tijdens deze promotie. Ik vind het mooi en fijn dat we gemakkelijk en heel natuurlijk van de soort samenwerking konden switchen en dat dit de stemming niet beïnvloedde. Heel veel dank dat je in de ochtend, avond en soms zelfs in vakanties beschikbaar bleef voor mij. Ik ben mij ervan bewust van wat hier beschreven is, is een schijntje waarvoor ik jullie dankbaar ben. Jo, Kelly en Lennard: heel heel heel veel dank voor de samenwerking met voor mij fijne, kritische, relativerende en humoristische begeleiders.

In 2015 heeft de manager, Rob Tijssen, binnen de opleiding voor fysiotherapie de kennisagenda geïntroduceerd. Hiermee kwamen samenwerkingsmogelijkheden tussen het Kennis Centrum van de Hogeschool Rotterdam en de opleiding voor fysiotherapie tot stand. Dit gaf mij de kans om mijn ambitie voor promoveren waar te maken. Ik kreeg tijd voor mijn onderzoek binnen mijn aanstelling als

docent en heb daar uiteraard dankbaar gebruik van gemaakt. De managers, Annemarie Meulenberg en Tim Kuipers, ben ik dan ook dankbaar voor het overnemen van deze voorziening in mijn onderzoek tijd.

Voor mijn metingen had ik 150 participanten nodig en ik ben hen heel erg dankbaar (zowel de mensen met en zonder lage rugpijn). Mooi om te ervaren hoeveel mensen zich willen inzetten voor wetenschappelijk onderzoek. Het was elke keer weer spannend wat de reactie zou zijn op de vraag of zij een uur wilde vrijmaken om 'hun lichaam ter beschikking te stellen voor de wetenschap'. Wat mij opviel, ten tijde van de metingen, was de kracht van de behandelbank: mensen moesten voor de metingen op hun buik liggen en tussen de verschillende metingen door ontstonden vele gesprekken. Bijzonder hoe snel mensen zich open stelden en hun verhaal deden. Ook dank daarvoor! Om überhaupt te kunnen meten, had ik fysiotherapie praktijken nodig. Dat verliep in het begin stroef, maar op een gegeven moment had ik een 'meet circuit' tussen verschillende praktijken gelegen in Rotterdam, Dordrecht, Vlaardingen, Dokkum, Kootstertille en Groningen. Heel fijn dat jullie: Suzanne, Erwin, Paul en Amarins, in dit traject met mij meedachten en jullie praktijk ter beschikking stelden voor mijn onderzoek. Heel veel dank, het heeft mij erg geholpen! Tige tank, it hat my in protte holpen!

Beste kollega's út de praktyk yn Dokkum: tige tank foar it opnimmen fan de dielnimmers!

Beste praktyk managers, ik ben jim noch tige tankber foar de fjouwer moanne ûnbetelle ferlof. It hat in fersnelling yn it heule ûndersyksproses mooglik makke. De romte dy't jimme my dernei joegen (minder ynsetberens) wie ek tige moai en waard goed brûkt. Sjoch hjir it resultaat 😉. Nochris tige tank!!!

Bij een promotie traject bezoek je ook weleens congressen of symposia waar je een poster dan wel een mondelinge presentatie mag houden of gewoon luisteren om kennis te vergaren. Het heeft mij in leuke steden gebracht zoals o.a. Stockholm, Genève en wat dichterbij in Antwerpen. Als ik aan Antwerpen denk, voel ik de moeheid weer opkomen; we overnachtten naast een bouwput waarbij de werklui het blijkbaar normaal vonden om 's nachts door te werken. We (Tineke, Rinske, Amarins en ik) hebben ons uiterste best gedaan om overdag alle interessante presentaties mee te krijgen. We waren wel zo geïnspireerd door die dag dat er op de terugweg een plan was ontstaan om zo af en toe bij elkaar te komen en dan als 1^{e}) te gaan bijkletsen en als 2^{e}) wat wetenschappelijk gebabbel met elkaar te hebben. Op de terugtocht is ook de profielfoto gemaakt van onze groepsapp die een prachtige weergave geeft van waar wij de prioriteit aan geven als we elkaar zien. Ik wil jullie laten weten dat ik het contact met jullie erg fijn vindt: er wordt met elkaar meegedacht, het contact inspireert mij, daar waar we elkaar kun helpen doen we dat, we willen tijd investeren in elkaar. Heel fijn om jullie 'in het noorden' te hebben.

Tijdens de voorbereidingen voor mijn interne verdediging heb ik mij kritisch laten bevragen door enkele collegae van de Hogeschool Rotterdam en gepromoveerden. Dieuwke, Winifred, Amarins, Rinske, Jurryt, Sanneke, Maaike, Renske en Lennard: heel veel dank dat jullie tijd hebben vrijgemaakt ter voorbereiding op deze sessies én de sessies zelf voor het stellen van de kritische vragen. Fijn dat jullie in je drukke agenda hier tijd voor wilden inruimen.

Tegen het einde van het promotie traject worden de deadlines steeds 'steviger'. Het zijn data waar geen ontkomen meer aan is. Dat is prima, maar kan een keerzijde hebben: ik merkte bij enkele mensen dat ze me wilden behoeden voor 'door het ijs te gaan zakken'. Dat was op zo'n moment ongelofelijk lief om te ervaren! Dank je wel Diane dat je met we wilde wandelen in de duinen/strand (alleen laten we het nog eens een keer écht laten slagen 😉). Dank je wel Hannah dat je naar Beetsterzwaag kwam om samen met Anne naar de speeltuin te gegaan. Dank je wel Mirjam voor je

‘relativeringsfoto’s’ als ik die even nodig had. Dank je wel Tiny voor de foto’s van de kleine katjes die regelmatig verstuurd werden om mij kort van de laptop af te halen. Het liet mij weer even ‘onder mijn steen’ vandaan komen en de wereld te zien hoe die ook kan zijn.

Voor het Engels in dit gehele proefschrift wil ik mijn wenden tot Ateke: ongelofelijk veel dank hoe je je hebt door geploeterd door de taaie artikelen. Met name de paragraaf ‘results’ waren je favoriet. Ik geef toe dat in de laatste fase van het afronden van dit proefschrift ik minder (interpreteer ‘geen’) interesse had in de theorie van de Engelse grammatica. Je bevlogenheid voor Engels heb ik absoluut gewaardeerd, een volgende keer heb ik er meer tijd en ruimte voor het opnemen van je uitleg. Ik ben je ook écht heel erg dankbaar dat je je hebt kunnen voegen in de snelheid waarmee dit allemaal moest gebeuren. Ik besefte me dat ik aanspraak deed op jouw vrije tijd, maar het was fijn om te merken dat je mee ging denken in de mogelijkheden voor het bespreken van de correcties.

Willem, in september 2015 ben ik dit avontuur gestart, maar al snel kwamen we erachter dat dit eigenlijk voor ons samen gold. Uiteraard veel dank voor de ondersteuning in de kopjes thee, cappuccino’s en eten. Ik vind het wel zo leuk dat ik nu ook weer meer kan gaan koken. Al snel werd duidelijk dat het een gewoonte werd om de laptop mee te nemen op vakanties en dat er weleens een week afging van de zomervakantie voor een summer school. Zoals we dan tegen elkaar zeiden: “alles voor de wetenschap”. Waar ik je dankbaar voor blijf, is de mogelijkheid om alles te bespreken. Op een gegeven moment voelde het wel een beetje bezwaarlijk om weer met de laptop aan te komen, of weer met een summer school. Uiteindelijk hebben we er altijd wat moois van kunnen maken. Heel erg veel dank dat je mij in de laatste weken geholpen hebt met de tabellen, de figuren in de power point en de oplossingen aandragen als het ‘knippen en plakken’ in Word weer zijn eigen leven ging leiden. Dankzij jou is de laptop nog net niet uit het raam gevlogen! Het was voor jou dan ook meeveren en incasseren. Ook nu besef ik mij dat wat hier beschreven is, dekt niet de gehele 6.5 jaren waar ik je allemaal dankbaar voor ben. Het zit soms in kleine dingetjes, maar die groots kunnen zijn. Heel veel dank dat je überhaupt open stond voor mijn ambitie van promoveren en mij hierin hebt ondersteund. Je bent een mooi en heel fijn maatje!

List of publications

Pain mechanisms in low back pain: A systematic review with meta-analysis of mechanical quantitative sensory testing outcomes in people with nonspecific low back pain

Hester L. den Bandt (PT), Winifred D. Paulis (PhD), David Beckwee (PhD), Kelly Ickmans (PhD), Jo Nijs (PhD), Lennard Voogt (PhD)

Journal of Orthopaerdic & Sports Physical Therapy. 2019 Oct;49(10):698-715

Associations between cognitive, emotional and behavioral factors and symptoms of central sensitization in people with non-specific low back pain in primary care: a cross-sectional study

Hester L. den Bandt (PT), Kelly Ickmans (PhD), Winifred D. Paulis (PhD), Lynn Leemans (PhD), Jo Nijs (PhD), Lennard Voogt (PhD)

Revision submitted, March 2021, in Journal of Manipulative and Physiological Therapeutics

Differences in quantitative sensory testing outcomes between patients with low back pain in primary care and healthy controls

Hester L. den Bandt (PT, MT), Kelly Ickmans (PhD), Lynn Leemans (PhD), Jo Nijs (PhD), Lennard Voogt (PhD)

Revision submitted and under review, February 2022, in the Clinical Journal of Pain

Multifactorial differences between people with low back pain in the various ris levels of the Start Back screening Tool and Central Sensitization Inventory in primary care: a cross-sectional study

Hester L. den Bandt (PT), Kelly Ickmans (PhD), Ronald Buyl (PhD), Lynn Leemans (PhD), Jo Nijs (PhD), Lennard Voogt (PhD)

Submitted, March 2022

It hurts to move! Interventional effects and assessment methods for movement-evoked pain in patients with musculoskeletal pain: a systematic review and meta-analysis

Lynn Leemans (PhD), Andrea Polli (PhD), Jo Nijs (PhD), Timothy H. Wideman (PhD), Hester den Bandt (PT), David Beckwee (PhD)

Journal of Orthopaerdic & Sports Physical Therapy.2022 Febr 5;1-52

Transcutaneous electrical nerve stimulation and heat to reduce pain in a chronic low back pain population: a randomized controlled clinical trial

Lynn Leemans (PhD), Ömar Elma (MSc), Jo Nijs (PhD), Timothy H. Wideman (PhD), Carolie Siffain (MSc), Hester den Bandt (PT), Sven van Lare (MSc), David Beckwee (PhD)

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Transcutaneous electrical nerve stimulation reduces movement-evoked pain in people with chronic low back pain: a randomized crossover study

Lynn Leemans (PhD), Ömar Elma (MSc), Jo Nijs (PhD), Timothy H. Wideman (PhD), Hester den Bandt (PT), Sven van Lare (MSc), David Beckwee (PhD)

Under review in European Spine Journal

Do psychological factors relate to movement-evoked pain in people with musculoskeletal pain? A systematic review and meta-analysis

Lynn Leemans (PhD), Jo Nijs (PhD), Luna Antonis, Timothy H. Wideman (PhD), Hester den Bandt (PT), Zoe Franklin (PhD), Patrick Mullie (PhD), Maarten Moens, (MD,PhD), Erika Joos (MD), David Beckwee (PhD)

Under review in Journal of Orthopaerdic & Sports Physical Therapy

Do measures of central sensitization relate to movement-evoked pain in people with chronic low back pain? A longitudinal and prospective study

Lynn Leemans (PhD), Jo Nijs (PhD), Timothy H. Wideman (PhD), Hester den Bandt (PT), Maarten Moens, (MD,PhD), Erika Joos (MD), David Beckwee (PhD)

Under review in Journal of Pain

In the spine or in the brain? Recent advances in pain neuroscience applied in the intervention for low back pain.

Jo Nijs (PhD), Jacqui Clark (PhD), Anneleen Malfliet (PhD), Kelly Ickmans (PhD), Lennard Voogt (PhD), Sanneke Don (PhD), Hester den Bandt (PT), Dorien Goubert (PhD), Jeroen Kregel (PhD), Iris Coppieter (PhD), Wim Dankaerts (PhD)

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