A comprehensive evaluation of somatosensory function in acute low back pain and pain-free individuals using Quantitative Sensory Testing

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Supervisors' statement

As supervisors of Anna Marcuzzi's doctoral work, we certify that we consider her thesis "A comprehensive evaluation of somatosensory function in acute low back pain and pain-free individuals using Quantitative Sensory Testing" to be suitable for examination.

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Candidate's statement

I, Anna Marcuzzi, hereby declare that the work contained within this Thesis, "A comprehensive evaluation of somatosensory function in acute low back pain and pain-free individuals using Quantitative Sensory Testing", is my own and has not been submitted to any other university or institution, in part or in whole, as a requirement of a degree.

I, Anna Marcuzzi, hereby declare that I was the principal researcher of all work included in this Thesis, including the work published with multiple authors. A statement of co-authors confirming the authorship contribution of the PhD candidate is provided in each of the relevant chapters.

I, Anna Marcuzzi, hereby declare that this Thesis is an original piece of work and it is written by me. Any assistance that I have received in the preparation of this Thesis has been appropriately acknowledged. In addition, I also certify that all information sources and literature are indicated in this Thesis.

Signed

8 December 2016

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Summary

Low back pain is a common complaint and has the highest global disability burden when measured as years lived with a disability. After an episode of low back pain, up to two-thirds of people will experience variable levels of chronic pain after one year and around 10% will be significantly disabled in association with low back pain. Recent research has revealed that people with chronic low back pain are characterised by widespread pain hypersensitivity, suggesting that neuroplastic changes at the central nervous system underlie this condition. While this knowledge has enhanced our understanding of pathophysiological processes in chronic low back pain, it is currently unclear how early these somatosensory changes develop. Therefore, the broad aims of this thesis are: to investigate the time course of somatosensory changes from the acute stage of low back pain without serious pathology; to examine the prognostic utility of this information in low back pain; and to address methodological aspects of such assessment using quantitative sensory testing (QST).

In order to meet these aims, several research approaches have been undertaken. Two systematic reviews of the literature were carried out to establish whether somatosensory changes are a feature of acute low back pain compared to healthy controls (Chapter 2) and to investigate the prognostic ability of QST in low back pain (Chapter 5). An inception cohort study, using a comprehensive QST assessment, was carried out to inform whether early somatosensory changes can be detected soon after low back pain onset compared to pain-free individuals (Chapter 3). The assessment included evaluation of endogenous pain modulation (Chapter 4) and tracked changes in somatosensory function over time, until 4 months after onset (Chapter 7). This comprehensive data set has also enabled the evaluation of important methodological issues related to the stability of QST over time in healthy individuals (Chapter 6).

Overall, the work presented in this thesis has contributed to the body of evidence regarding the evaluation of somatosensory function in the early stages of low back pain, as well as providing novel methodological insights into QST testing. This scholarly work has specific implications for clinicians and researchers addressing low back pain, the condition of highest disability burden worldwide.

Acknowledgments

Deciding to start a PhD for me was like deciding to give my life a new direction and, not only from a single perspective, to discover a new world. Today, I am happy to say that every day was a rich and challenging discovery. Every day was a step forward, both personally and professionally, and the best of this is that I was not alone. These three and a half years of discovery were only possible thanks to the people who supported me and shared this time with me.

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List of Publications and Presentations

Parts of the work presented in this thesis have been published and/or presented in the following forums:

Publications

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Other publications

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Conference presentations

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Marcuzzi A., Dean C.M., Wrigley P.J., Hush J.M. (2016) "Conditioned pain modulation in acute low back pain and pain-free controls: a comparison using two test paradigms" *Australian Pain Society (APS) 36th Annual Scientific Meeting*, Perth, Australia (oral rapid communication and poster presentation).

List of Abbreviations

QST	Quantitative sensory testing
ICD	International Classification of Disease
IASP	International Association for the Study of Pain
PAG	Periaqueductal grey
RVM	Rostroventral medulla
SDR	Subnucleus reticularis dorsalis
DNIC	Diffuse noxious inhibitory control
CPM	Conditioned pain modulation
NMDA	N-methyl-d-aspartate
PFC	Prefrontal cortex
ACC	Anterior cingulate cortex
fMRI	Functional magnetic resonance imaging
DFNS	German Research Network on Neuropathic Pain
NWR	Nociceptive withdrawal reflex
RRF	Reflex receptive field
PPT	Pressure pain threshold
TPD	Two-point discrimination
NRS	Numeric rating scale
ICC	Intraclass correlation coefficient
PCS	Pain catastrophising scale
PSEQ	Pain self-efficacy questionnaire

Glossary

Sensitisation: Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs

Central sensitisation: Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input

Peripheral sensitisation: Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields

Noxious stimulus: a stimulus that is damaging or threating damage to normal tissues

Pain threshold: the minimum intensity of a stimulus that is perceived as painful

Pain tolerance level: the maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation

Allodynia: pain due to a stimulus that does not normally provoke pain

Hyperalgesia: increased pain to a stimulus that normally provokes pain

Primary hyperalgesia: increased response to a stimulus that is normally painful at the site of injury or inflammation

Secondary hyperalgesia: increase in pain sensitivity when a noxious stimulus is delivered to a region surrounding but not including the zone of injury

Hypoalgesia: diminished pain in response to a normally painful stimulus

Hypoesthesia: decreased sensitivity to stimulation, excluding special senses

Temporal summation: progressive increased painful response following repeated administration of the same stimulus at a given interval of time

Sources:

- IASP taxonomy from http://www.iasp-pain.org/;
- Encyclopedia of Pain (2007), Springer Berlin Heidelberg

Preface

This thesis is arranged in eight chapters, and is structured so that each chapter can be read independently. It contains both traditional thesis chapters and published manuscripts embedded in PDF format. Each chapter contains its own reference list.

Chapter 1 is an introduction providing the theoretical background for this thesis. Chapter 2 is a systematic review investigating the current evidence on somatosensory changes in acute and subacute spinal pain and is presented as the paper published in *Pain*. Chapter 3 presents a cross-sectional analysis investigating somatosensory changes in acute low back pain compared to pain-free controls, and it is presented as the paper in the final stage of preparation for submission to a journal in the field of pain. Chapter 4 presents an additional cross-sectional analysis, which assesses the efficacy of conditioned pain modulation in acute low back pain and pain-free individuals, and addresses methodological aspects of this assessment. This study is presented as the paper in the final stage of preparation for submission to a journal in the field of pain. Chapter 5 is a systematic review investigating the prognostic value of QST in low back pain and is presented as the paper published in the *Journal of Pain Research*. Chapter 6 is a reliability study of QST in pain-free individuals and is presented as the paper accepted for publication in *Pain*. Chapter 7 presents a longitudinal analysis investigating the temporal development of somatosensory changes in acute low back pain, and is presented as the paper submitted to *Pain Practice*. Chapter 8 is the conclusive chapter providing an integrated discussion of the main findings, their implications, and future directions for research.

Ethical approval was granted from the Human Research Ethics Committees of Macquarie University prior to data collection. The ethical approval letter is provided in the appendix.

Chapter 1

Introduction

Low back pain is an extremely common complaint among the general population (Manchikanti, Singh et al. 2014). While underlying serious causes are a rare occurrence (Henschke, Maher et al. 2013), low back pain results in the highest disability burden worldwide (Vos, Flaxman et al. 2013). Recent research has challenged the traditional view of low back pain as a self-limiting condition with a predominantly favourable outcome (Bigos, Bowyer et al. 1994). While symptoms subside considerably within the first weeks, one third to two-thirds of people still experience low back pain after one year (Henschke, Maher et al. 2008, Vasseljen, Woodhouse et al. 2013). Most people will go on with activities of daily life despite variable levels of pain (Kent and Keating 2005), but a percentage of people (around 10%) will be significantly disabled in association with low back pain (Carey, Garrett et al. 2000). It is indeed this latter group that consumes the majority of healthcare resources (Becker, Held et al. 2010).

With current socioeconomic data showing an increasing level of disability and associated costs due to low back pain (Manchikanti, Singh et al. 2014), it is apparent that the management of this common condition is far from ideal. The identification of a patho-anatomic cause of low back pain is not possible for the majority of cases (Deyo 2002). Therefore recommended first line care is mostly not specific, and includes education, advice to stay active, exercise and use of simple analgesics (Goertz, Thorson et al. 2012). Results from clinical trials show that current treatments seem not to have an effect beyond that of the spontaneous recovery (Artus, van der Windt et al. 2010) and, more importantly, they do not prevent the development of chronic pain. Once the chronic stage is reached, little or no improvement occurs thereafter (Pengel, Herbert et al. 2003). It is clear that a better knowledge of the underlying factors that contribute to low back pain is needed in order to improve management (Van der Windt and Dunn 2013).

In recent decades, advances in pain research have provided insight into the neurophysiological mechanisms involved in chronic pain conditions. A large body of

evidence has accumulated, and shows that people with chronic low back pain display exaggerated responses to experimental noxious stimuli applied to the back as well as to unrelated sites, compared with healthy individuals (Derbyshire, Jones et al. 2002, Giesecke, Gracely et al. 2004, Giesbrecht and Battié 2005, O'Neill, Manniche et al. 2007, Puta, Schulz et al. 2012). Such pain hypersensitivity expanding beyond the area of injury is commonly attributed to central amplification resulting from increased central nervous system excitability as well as altered central mechanisms of pain modulation (Curatolo, Arendt-Nielsen et al. 2006), and is clinically relevant (Van Wijk and Veldhuijzen 2010, Curatolo 2011), particularly for the common condition of low back pain. Nonetheless, it is important to note that heterogeneity in pain sensitivity profiles has been reported in chronic low back pain (Rabey, Slater et al. 2015).

While this knowledge has greatly enhanced our understanding of the pathophysiological processes underlying chronic low back pain, it remains unclear whether these somatosensory changes precede the onset of chronic pain, or rather develop after chronic pain has been established. Therefore an in-depth characterisation of changes in somatosensory function occurring in acute and subacute low back pain would provide important knowledge to better understand processes involved in the development of chronic back pain. This knowledge may have also value in the identification of potential factors associated with poor outcomes.

At present, it is unclear whether, and to what extent, changes in somatosensory function occur in acute and subacute low back pain. Also, longitudinal data regarding the time course of somatosensory changes are lacking in low back pain. One of the most commonly used methods to assess pain-related somatosensory changes is quantitative sensory testing (QST). However, if these tests are to be used to investigate long-term changes in somatosensory function, it is essential to understand whether the measures are stable and reproducible. The long-term reliability of QST is currently unknown.

The aims of thesis are to address these gaps in current knowledge, specifically to investigate changes in somatosensory function with QST from the acute stage of low back pain, and examine the prognostic utility of this information in low back pain. In addition, the long-term reliability of QST will be evaluated in pain-free individuals.

The following sections provide relevant background for the thesis: Section 1 provides a perspective of low back pain; Section 2 briefly describes the mechanisms involved in

somatosensory processing in normal and pathological conditions and reviews the evidence for somatosensory dysfunction in chronic low back pain; Section 3 discusses the assessment of somatosensory function using QST, and explores current methodological issues with this assessment; Section 4 outlines the specific aims of the thesis.

1.1 The clinical picture of low back pain

1.1.1 Definition and classifications of low back pain

Low back pain is currently defined as "pain and discomfort, localised below the costal margin and above the inferior gluteal folds with or without leg pain" (Van Tulder, Becker et al. 2006). Low back pain can arise from trauma or an insidious onset and rarely involves serious underlying pathology (e.g. spinal fracture, infection, neoplasm) (Henschke, Maher et al. 2013) or nerve root compromise (Chou, Qaseem et al. 2007). Once such specific conditions are excluded, the common diagnostic triage approach is to classify low back pain as *non-specific* which represents around 85% of cases (Deyo 2002, Chou, Qaseem et al. 2007). For this thesis, individuals with low back pain with or without leg pain were investigated, excluding those with possible serious spinal pathology.

Another common classification approach for low back pain is based on the duration of the current episode. Acute low back pain is defined as an episode lasting for less than 6 weeks; sub-acute low back pain as an episode persisting between 6 and 12 weeks; and chronic low back pain as an episode persisting beyond 12 weeks (Goertz, Thorson et al. 2012). This classification has been useful for establishing clinical guidelines and recommendations for research purposes (e.g. eligibility for trials, inclusion criteria for systematic reviews) (Van der Windt and Dunn 2013), and is adopted in this thesis.

In addition, the International Classification of Diseases (ICD-11) has recently defined chronic (primary) pain as "pain in one or more anatomic regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or significant functional disability (interference with activities of daily life and participation in social roles) and that cannot be better explained by another chronic pain condition" (Treede, Rief et al. 2015). This definition highlights the multifactorial nature of the pain experience.

1.1.2 The biopsychosocial model of low back pain

Almost three decades ago, it was recognised that progress in the clinical management of low back pain, when based on a purely biomedical perspective, was very limited. As a result, low back pain has since been reconceptualised from a biopsychosocial perspective, where not only biological factors, but psychological and social influences, and their interactions, are recognised to play a significant role in the low back pain experience. Since then, there has been a keen interest in the investigation of psychosocial factors as contributors towards low back pain chronicity (Pincus, Burton et al. 2002, Chou and Shekelle 2010). Consequently, a number of clinical tools to identify psychological and environmental features of low back pain have been developed (Linton and Boersma 2003, Hill, Dunn et al. 2008). This knowledge has been incorporated in clinical practice guidelines for low back pain which recommend screening for psychosocial indicators (also known as yellow flags) associated with prolonged or delayed recovery (Van Tulder and Koes 2012).

1.1.3 Factors associated with poor outcomes in low back pain

Most systematic reviews report inconclusive results regarding which prognostic factors are important in low back pain (Hayden, Chou et al. 2009). Nonetheless, psychosocial factors remain the most investigated prognostic indicators in low back pain (Kent and Keating 2008). For example, the presence of non-organic signs, a high level of functional impairment, a high level of maladaptive pain-coping behaviours, and psychiatric comorbidities have been shown to be significantly associated with poor outcomes in low back pain at 1 year (Chou and Shekelle 2010). However, psychosocial factors together with relevant pain-related features, such as leg pain and higher pain intensity, still only explain a limited proportion (up to 46%) of the variance in low back pain outcomes (Kent and Keating 2008). While methodological issues in prognostic studies hamper advances in this field, it is possible that additional factors need to be considered in the prognosis of low back pain, including the biological contributors using validated neurophysiological techniques.

An area of growing interest is the role of pain-related somatosensory changes, measured using QST, which have promise to predict outcomes in various clinical conditions such as whiplash injury (Sterling, Jull et al. 2005, Walton, MacDermid et al. 2011), epicondylalgia (Coombes, Bisset et al. 2015), and post-surgical pain (Werner, Mjöbo et

al. 2010). The prognostic utility of QST responses in low back pain will be explored in Chapter 5.

1.2 Somatosensory function in normal and pathological states

The somatosensory nervous system processes information about several modalities of somatic sensation, i.e. pain, touch, temperature and proprioception. Pain is the main focus of this thesis. In this section a brief introduction is provided to the peripheral and central mechanisms of nociceptive processing under normal and pathological states, followed by a review of the current evidence available on altered nociceptive processing in low back pain.

1.2.1 Nociception and pain

The following definitions of nociception and pain are endorsed by the International Association for the Study of Pain (IASP): nociception is defined as "the neural process of encoding noxious stimuli"; whereas pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Nociception can occur in peripheral tissues and structures and yet not be experienced as pain; similarly, pain is a central nervous system phenomenon and can be perceived in the absence of any peripheral inputs (Willard 2008).

1.2.2 Acute pain and chronic pain

From a neurophysiological point of view, acute pain that arises from a musculoskeletal injury, commonly referred to as nociceptive pain, is the physiological perception that is generated from a normally functioning nervous system exposed to tissue damage and inflammation (Kettner 2008). Acute pain is adaptive and protective in nature and has the biological role of facilitating behaviours that promote tissue healing and prevent further injury (Latremoliere and Woolf 2009).

In contrast, pain that persists beyond the expected healing time course is often maladaptive and does not have any apparent defensive or helpful functions (Latremoliere and Woolf 2009). The interplay between peripheral and central changes in the somatosensory nervous system, and psychological and environmental factors (Kendall 1999, Siddall and Cousins 2004), together with genetic influences (Hudspith, Siddall et al. 2006), seem to be important contributors to pain persistence. Further, with

non-specific low back pain, subclinical dysfunction of vertebral nerve roots may also contribute to this interplay (Hush and Marcuzzi 2012).

1.2.3 Neurophysiological mechanisms of pain

Almost all structures in the lumbosacral spine are innervated by primary afferent nerve fibres (Bogduk 1983). Sensory afferent fibres can be categorised into three subtypes: large myelinated *A-beta fibres* which normally transmit non-noxious signals such as light touch and vibration, but are involved in some aspects of nociceptive modulation; and thinly myelinated *A-delta fibres* and unmyelinated *C fibres* which are mostly involved in initiating nociceptive processing. When activated by nociceptive stimuli, A-delta fibres are responsible for brief, acute, pinprick-like, and well-localised pain sensations ("first pain"), while C fibres transmit slower, dull, more diffuse, and poorly localised pain ("second pain") (Marchand 2008). Under normal conditions, receptors on nociceptive neurons respond with a high threshold to chemical, mechanical and thermal noxious stimuli (Woolf and Ma 2007), and then transmit this information to the spinal cord.

Primary afferent nociceptors terminate primarily in lamina I, II, and V of the dorsal horn of the spinal cord where they make synaptic contact with spinal cord neurons. Two classes of neurons that transmit the nociceptive signal to supraspinal structures (projection neurons) can be distinguished: *nociceptive specific* projection neurons which are located in the superficial layer of the dorsal horn and appear to respond preferentially to noxious stimuli; and *wide dynamic range* projection neurons which are located in the deeper layers of the dorsal horn and respond to noxious and non-noxious stimuli (Marchand 2008).

Wide dynamic range neurons can exhibit a phenomenon called *wind up*, which is an activity dependent form of synaptic plasticity (adaptation) (D'Mello and Dickenson 2008) resulting in an increase in evoked response and post-discharge with each stimulus which may contribute to the amplification of pain (see section 1.2.4). Synaptic transmission may also be influenced by excitatory and inhibitory interneurons within the spinal cord which modulate nociceptive signals by either enhancing or diminishing responsiveness to sensory input from the periphery (Siddall and Cousins 1997). Further, non-neuronal cells such as astrocytes and microglia in the spinal cord can influence nociceptive transmission (D'Mello and Dickenson 2008).

Projection neurons from the spinal cord transmit nociceptive signals to higher supraspinal structures through several tracts including the spinothalamic, spinoreticular and spinomesencephalic tracts. A large proportion of neurons terminate in the lateral and medial nuclei of the thalamus (involved in the sensory-discriminative and affective-motivational components of pain, respectively) which then project to multiple cortical and sub-cortical structures (Almeida, Roizenblatt et al. 2004). The widespread supraspinal processing of nociceptive signals is relatively new knowledge (Coghill, Talbot et al. 1994), and it is the integration of activity in these cortical and sub-cortical structures that results in the multidimentional nature of the pain experience.

Some ascending nociceptive neurons (mainly of the spinomesencephalic tract) terminate in brain stem regions (periaqueductal grey or PAG) which provide links with the descending (endogenous) pain modulation systems (Marchand 2008). PAG neurons project to the rostroventral medulla (RVM), the final relay of descending pain modulation, from which two classes of neurons, excitatory (on-cells) and inhibitory (off-cells), send projections to the spinal cord to influence the defensive reflex arcs and pathways ascending to the brain (Fields and Heinricher 1985).

Ascending nociceptive transmission can also be inhibited by *noxious* stimuli at body areas outside their excitatory receptive field, a phenomenon called diffuse noxious inhibitory controls (DNIC), which was first identified in animal studies. DNIC is a spinal-bulbo-spinal pathway triggered specifically by activation of A-delta and C fibres and involves the activity of brain structures located in the caudal medulla including the subnucleus reticularis dorsalis (SDR) with descending projections terminating in the dorsal horn at all levels of the spinal cord (Le Bars 2002). In humans the phenomenon of inhibition of pain by a second painful stimulus has been extensively studied using a technique referred to as conditioned pain modulation (CPM) (Yarnitsky, Arendt-Nielsen et al. 2010), which is described further in section 1.3.3. Other descending pain pathways also exist, involving connectivity with other brain centres involved in emotion regulation, motivation, attention and cognition, which in combination influence pain perception (Bushnell, Čeko et al. 2013).

To summarise, pain is a dynamic phenomenon resulting from processing and modulation of nociceptive signals at all levels of the central nervous system. In the next

section, both peripheral and central nervous system changes relevant to low back pain are explored.

1.2.4 Mechanisms of pain in pathological states

Peripheral mechanisms

A host of molecular events takes place immediately after an injury to lumbosacral structures, which have an impact on the transmission of nociceptive signals at multiple levels of the nervous system. At the periphery, tissue damage produces an inflammatory reaction that modifies the response of the nociceptors to subsequent stimulation. The release of inflammatory mediators such as extracellular protons, prostaglandins, bradykinin, and substance P from damaged cells can activate and sensitise primary afferent nociceptors so that lower intensity stimuli that would not normally cause pain are perceived as painful. The activation of nociceptors can in turn release pro-inflammatory peptides and neurotransmitters, a phenomenon called neurogenic inflammation, which serves to protect surrounding tissue by promoting further release of inflammatory mediators (Siddall and Cousins 1997). Inflammation can also activate another group of C fibre nociceptors called "silent" nociceptors that are normally insensitive to regular noxious stimuli (Schmidt, Schmelz et al. 1995), but, when activated, can discharge vigorously even during activation in the physiological (non-noxious) range. This enhanced responsiveness to noxious (and non-noxious) peripheral inputs within the injured area is called peripheral sensitisation (Siddall and Cousins 1997).

Spinal cord plasticity

Peripheral sensitisation results in an increase of nociceptive inputs to the spinal cord, which can in turn change the response properties of dorsal horn (projection) neurons. High frequency C fibre stimulation generates a progressive increase in the activity of dorsal horn neurons due to the activation of N-methyl-d-aspartate (NMDA) receptors, the phenomenon referred to above as wind up, which results in pain amplification (D'Mello and Dickenson 2008). While under normal conditions wind up is reversed within seconds once the initiating peripheral stimulus has ended, in pathological states enhanced dorsal horn spinal cord neuronal output can persist (Salter 2014). The increase in the excitability of the dorsal horn neurons is known as *central sensitisation* (Latremoliere and Woolf 2009), which results in increased discharges to inputs from

primary afferents, expansion of receptive field sizes and discharges in response to stimuli that were previously subthreshold or would not normally evoke a response (e.g. innocuous inputs from A-beta fibres). These alterations can be responsible for signs and symptoms such as the spread of pain sensitivity beyond the site of tissue damage (*secondary hyperalgesia*), aftersensations, enhanced temporal summation, allodynia and spontaneous pain (Woolf 2011).

Other modifications of the nociceptive system can occur following prolonged nociceptive stimulation, including: a phenotypic shift of A-beta fibres such that they express substance P (normally only found in C fibres); and the loss of inhibitory interneurons in the spinal dorsal horn, which further contribute to central amplification (Woolf and Salter 2000).

Supraspinal mechanisms

Multiple changes can occur in the structure (e.g. (Apkarian, Sosa et al. 2004, Ung, Brown et al. 2012), function (e.g. (Flor, Braun et al. 1997, Giesecke, Gracely et al. 2004, Jiang, Oathes et al. 2016)) and neurochemistry (e.g. (Siddall, Stanwell et al. 2006)) of the brain in people with chronic pain including low back pain. Brain regions commonly altered in chronic pain include the prefrontal cortex (PFC), anterior cingulate cortex (ACC), amygdala and the insula, which are involved in cognitive and emotional processing (Bushnell, Čeko et al. 2013). This knowledge helps our understanding of how thoughts and mood (e.g. depression) may influence pain perception (Wiech and Tracey 2009). One system which mediates these effects is the descending modulatory pathway (section 1.2.3). Descending pathways impact on the levels of spinal cord sensitisation (Zusman 2002), even in the absence of pathology (Rhudy, Williams et al. 2006). Of interest, reduced neuronal function, identified by functional magnetic resonance imaging (fMRI) in brain areas involved in descending pain modulation (i.e. PAG) has been reported in chronic low back pain (Giesecke, Gracely et al. 2006). Furthermore, dysfunction of descending pain inhibition has been noted in a range of chronic pain conditions (Lewis, Rice et al. 2012). These supraspinal changes illustrate how widespread neuroplastic changes can occur in pathological pain states.

1.2.5 Psychophysical evidence for altered somatosensory function in low back pain

The majority of psychophysical research investigating somatosensory function has been conducted in the chronic stage, and this is particularly the case for low back pain. There is robust evidence demonstrating that, at the group level, people with chronic low back pain display higher sensitivity to experimental noxious stimulation when compared with individuals without pain. For example, lower mechanical pain thresholds have been found at the lumbar spine (Giesbrecht and Battié 2005, Kobayashi, Kurata et al. 2009, O'Neill, Kjær et al. 2011) and also in areas unrelated to the back (Giesecke, Gracely et al. 2004, Laursen, Bajaj et al. 2005, O'Neill, Manniche et al. 2007, O'Neill, Kjær et al. 2011). People with chronic low back pain have been shown to perceive noxious heat stimuli delivered at the hand as more painful compared with controls (Derbyshire, Jones et al. 2002). Widespread pain hypersensitivity to cold stimuli has also been reported in chronic low back pain (Hübscher, Moloney et al. 2014). In addition, a more intense, widespread and longer lasting pain has been reported after hypertonic saline injection in the shoulder muscle in people with chronic low back pain compared to controls (O'Neill, Manniche et al. 2007).

Other abnormalities of somatosensory processing have been documented in chronic low back pain which include enhanced temporal summation to repetitive noxious stimuli (Peters, Schmidt et al. 1989, Flor, Knost et al. 2002, Manresa, Neziri et al. 2013), lowered nociceptive withdrawal reflex (NWR) threshold and expansion of reflex receptive fields (RRF) (Manresa, Neziri et al. 2013) using electrophysiological tests, reduced tactile acuity (Wand, Di Pietro et al. 2010, Luomajoki and Moseley 2011) and less efficient CPM (Corrêa, Costa et al. 2015, Rabey, Poon et al. 2015).

Taken together, this body of evidence shows that chronic low back pain is characterised by generalised changes in somatosensory processing suggesting alterations at multiple levels of the nervous system. Such changes are thought to be an important determinant in the development and/or maintenance of chronic pain (Woolf 2011). It remains largely unknown whether changes in somatosensory function precede the onset of chronic pain. Therefore the aim of this thesis is to investigate changes in somatosensory function in people with low back pain from an early time point (acute: <3 weeks from onset), and to examine the time course of such changes until low back pain is considered chronic (> 3 months).

1.3 Assessment of somatosensory function

Direct recordings of the neural activity in the spinal cord or in the brain cannot be made in humans (Curatolo 2011). However, somatosensory function can indirectly be investigated by using QST. While QST is the focus of this thesis, other approaches including electrophysiological (e.g. pain-related somatosensory evoked potential) or imaging techniques (e.g. fMRI) may also be used to assess somatosensory function; however there latter techniques are beyond the scope of this thesis. This section provides background knowledge and clinical relevance of QST assessment. Current methodological issues with QST testing are also discussed.

1.3.1 Overview of QST assessment

QST encompasses a set of psychophysical tests of the skin, mucosa and muscle tissues to assess the function of small (A-delta, C) and large (A-beta) fibres of the somatosensory nervous system and their pathways in the central nervous system (Backonja, Attal et al. 2013). QST involves the delivery of standardised calibrated stimuli according to specific algorithms, using standardised instructions and quantification of the evoked responses (Backonja, Attal et al. 2013). Depending on the set of endpoints used, QST can include *static* tests, which include threshold determination (stimuli detection and tolerance thresholds), and evoked-pain magnitude rating (using a pain intensity scale) for suprathreshold stimuli, providing an insight into the basal state of the nociceptive system; and *dynamic* tests which include tests of central integration (e.g. temporal summation) and descending controls (e.g. conditioned pain modulation) to provide insight into mechanisms of pain processing (Arendt-Nielsen and Yarnitsky 2009).

QST can inform about the presence of sensory loss (e.g. hypoesthesia, hypoalgesia) and sensory gain (e.g. allodynia, hyperalgesia) (Backonja, Attal et al. 2013) but lacks the specificity to determine the location or underlying mechanisms of such dysfunction (Curatolo 2011). Nonetheless, it is commonly accepted that sensory abnormalities detected in areas not affected by tissue injury are the result of central rather than peripheral phenomena (Curatolo, Arendt-Nielsen et al. 2006).

1.3.2 Clinical relevance of QST findings

While some controversy exists about the extent to which QST findings relate to the clinical experience of pain (Hübscher, Moloney et al. 2013), the widespread reporting of

QST research during the last decades has provided important evidence regarding its clinical relevance. Indeed, QST responses have contributed to the characterisation of somatosensory disturbances in neuropathic syndromes and in idiopathic painful conditions (Backonja, Attal et al. 2013) as well as to phenotype subgroups of patients (Scott, Jull et al. 2005, Freynhagen, Rolke et al. 2008, Blumenstiel, Gerhardt et al. 2011, Tampin, Slater et al. 2012, Moloney, Hall et al. 2013). This increasing knowledge is contributing to better understanding of the pathophysiology underlying various clinical populations. More recently, QST has shown promise as a prognostic tool. For example, QST responses were found to be predictive of the risk of developing persistent pain in musculoskeletal conditions (Sterling, Jull et al. 2005, Coombes, Bisset et al. 2015), and in the context of surgical procedures (Bisgaard, Klarskov et al. 2001, Granot, Lowenstein et al. 2003, Yarnitsky, Crispel et al. 2008) and predictive of some treatment outcomes for chronic pain (Attal, Rouaud et al. 2004, Yarnitsky, Granot et al. 2012).

1.3.3 Methodological considerations of QST assessment

As a psychophysical method, QST is a subjective measure; while the stimulus delivered is controlled, the response depends on the active participation of the subject. Therefore, factors such as attention, motivation, and boredom can influence QST results. Further, environmental influences (e.g. room temperature, noise) and technical features (e.g. type of stimulus, area stimulated, stimulus duration, interstimulus interval, instructions to the subject) are known to be important variables influencing QST results (Backonja, Walk et al. 2009). In order to minimise such variability and facilitate comparability of QST results, a comprehensive standardised QST protocol has been developed and published by the German Research Network of Neuropathic Pain (DFNS) (Rolke, Magerl et al. 2006). This QST battery encompasses seven tests measuring 13 parameters including thermal and mechanical test stimuli primarily designed for characterisation of sensory profiles in neuropathic pain. Of the seven tests from the DFNS protocol, four were selected to use in this thesis (i.e. cold and heat pain threshold, wind up ratio, pressure pain threshold). Additional QST measures adopted in this thesis were two-point discrimination (TPD) and CPM, which are not part of the DFNS protocol. The selection of testing was based on a literature search of existing psychophysical evidence about sensory dysfunction in painful musculoskeletal conditions, which were likely to be relevant for the population investigated in this thesis.

Dynamic tests, in particular CPM, have been introduced more recently in psychophysical investigations. In a typical CPM testing protocol, a noxious test stimulus is delivered before and during (or after) delivery of a noxious conditioning stimulus (Yarnitsky 2015). However, one major issue with CPM assessment is the lack of standardised protocols. As such, considerable methodological variability of protocols exists, including stimulus modalities (e.g. thermal, mechanical or electrical), intensity and duration of stimuli, measurement endpoints (e.g. pain threshold, suprathreshold pain rating and neurophysiological waveform analysis), timing of test stimulus delivery (e.g. parallel or sequential to the conditioning stimulus), and assessment sites (within or distant to an area of pain) (Pud, Granovsky et al. 2009, Yarnitsky 2015). This lack of protocol standardisation limits the comparability of CPM data. To aid identification of the optimal CPM protocol, consensus-based recommendations have been recently published (Yarnitsky, Bouhassira et al. 2015). The two key recommendations were: to use two types of test stimuli (thermal and mechanical) and to employ well defined endpoints. These consensus recommendations were implemented and assessed in this thesis. Specifically, the effects of CPM testing using two test stimuli were evaluated, as reported in Chapter 4.

An essential requirement for a measure to use in clinical and research settings is adequate reliability. When repeated measures are taken on the same subject under identical conditions over short retest periods, the repeatability of the measure is tested. This allows identification of the variability of the measure that is mainly owed to the measurement bias. When measures are taken on a subject over long retest periods, the reproducibility of the measure is tested (Bartlett and Frost 2008). In this context, previous research has shown acceptable repeatability for static QST (Chong and Cros 2004) and for the DFNS protocol in particular (Geber, Klein et al. 2011) however, dynamic tests showed more variability (Kennedy, Kemp et al. 2016). Importantly, the reproducibility of QST is largely unknown. This knowledge is important when QST is used to monitor longitudinal changes or responses to interventions. This topic is investigated in Chapter 6.

1.4 Aims of the thesis

The overall aims of the thesis are to investigate changes in somatosensory function from the acute stage of low back pain, to explore the prognostic utility of QST responses in low back pain and to evaluate the temporal stability of QST responses in pain-free individuals. The specific aims are:

1. To establish whether, and to what extent, somatosensory changes are features of acute and subacute low back pain (Chapter 2);

2. To assess whether somatosensory changes can be detected soon after onset of low back pain compared to pain-free controls using a comprehensive QST protocol (Chapter 3);

3. To assess whether CPM is impaired in acute low back pain compared to pain-free controls and to evaluate methodological aspects of CPM testing (Chapter 4);

4. To explore whether QST responses are of prognostic value in low back pain (Chapter 5);

5. To assess the long-term reliability of QST in pain-free individuals (Chapter 6);

6. To explore the temporal development of somatosensory changes soon after the onset of low back pain (Chapter 7).

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Chapter 2

Early changes in somatosensory function in low back pain

2.1 Preface

In Chapter 1, it was recognised that somatosensory function has mostly been investigated in chronic low back pain. In Chapter 2, the first study of this thesis is reported. A systematic review was conducted to address the first aim of the thesis; to establish whether and what type of somatosensory changes can be detected in acute and subacute low back pain. Meta-analyses were performed, where possible, to quantify the extent of somatosensory changes in people with low back pain compared to healthy controls.

This chapter consists of two publications, the first of which is a protocol paper:

Marcuzzi A., Dean C.M., Hush J.M. (2013) "Early changes in somatosensory function in spinal pain: protocol for a systematic review." *Systematic Reviews* 2(1): 90.

Marcuzzi A., Dean C.M., Wrigley P.J., Hush J.M. (2015) "Early changes in somatosensory function in spinal pain: a systematic review and meta-analysis" *Pain* 156(2): 203-21

2.2 Co-authors' statements

As co-authors of the paper, "Early changes in somatosensory function in spinal pain: protocol for a systematic review", we confirm that Anna Marcuzzi has made the following contributions to this study:

- Conception and design of the research
- Drafting and revising of the manuscript
- Critical appraisal of the content

Associate Professor Julia Hush _____ Date 5 Dec 2016

Professor Catherine Dean _____ Date 5 Dec 2016

SYSTEMATIC REVIEWS

PROTOCOL Open Access

Early changes in somatosensory function in spinal pain: protocol for a systematic review

Anna Marcuzzi, Catherine M Dean and Julia M Hush*

Abstract

Background: Back and neck pain are common conditions that have a high burden of disease. Changes in somatosensory function in the periphery, the spinal cord and the brain have been well documented at the time when these conditions have become chronic. It is unknown, however, how early these changes occur, what the timecourse is of sensory dysfunction and what the specific nature of these changes are in the first 12 weeks after onset of pain. In this paper, we describe the protocol for a systematic review of the literature on somatosensory dysfunction in the first 12 weeks after pain onset.

Methods and design: We will conduct a comprehensive search for articles indexed in the databases Ovid MEDLINE, Ovid Embase, Ovid PsycINFO and Cochrane Central Register of Controlled Trial (CENTRAL) from their inception to August 2013 that report on any aspect of somatosensory function in acute or subacute neck or back pain. Two independent reviewers will screen studies for eligibility, assess risk of bias and extract relevant data. Results will be tabulated and a narrative synthesis of the results conducted.

Discussion: Currently, there is a gap in our knowledge about the timing of somatosensory changes in back and neck pain. The systematic review outlined in this protocol aims to address this knowledge gap and inform developments in diagnostic tools and pain mechanism based treatments.

Trial Registration: Our protocol has been registered on PROSPERO, CRD42013005113.

Keywords: Pain, Back pain, Neck pain, Acute pain, Subacute pain, Somatosensory function, Sensitization, Sensory testing

Background

Back and neck pain are acknowledged as common health problems affecting nearly everyone at some point in their life [1]. Although pain reduces rapidly in the first 1 to 2 months for some individuals after an acute onset, approximately two-thirds of people do not recover [2]. For those who develop disabling chronic pain, the associated personal and societal burden is high [3].

Current treatments for back and neck pain do not result in outcomes that are much better than the natural course of the condition [2]. Over the last few decades, there has been an emphasis on research to unravel the mechanisms that contribute to the pathogenesis of chronic pain to inform the development of more effective treatments [4,5]. There is now a great deal of evidence that multiple changes in the somatosensory nervous system characterize chronic spinal pain (for a review, see [6]). For example, recent studies have shown that positive and negative sensory phenomena such as increased pain sensitivity [7-9], allodynia or hypoesthesia [10] as well as alterations in body perception [11,12] are commonly encountered in chronic back and neck pain patients, reflecting functional and structural changes at different levels along the neuraxis. In addition, functional imaging studies provide evidence of central pain amplification and cortical reorganization in low back pain, which correlate with clinical manifestations observed in these patients [13,14]. These changes in somatosensory function impact on, and are affected by, cognitive and behavioral factors such as catastrophizing, fear, and anxiety, which dynamically interact to modulate and facilitate the experience of pain.

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It is therefore well documented that somatosensory dysfunction characterizes chronic spinal pain conditions; however, it is not fully elucidated how early these changes occur in back and neck pain. The review outlined in this protocol will explore changes in somatosensory function in acute and subacute spinal pain populations in order to address this gap in current knowledge.

Research questions

This literature review aims to answer the following research questions: (1) Have changes in somatosensory function been detected in the first 12 weeks of spinal pain? (2) How early has somatosensory dysfunction been detected in spinal pain? And (3) What type of somatosensory changes have been detected in spinal pain?

Methods and design

Study registration

The protocol of this systematic review has been registered on PROSPERO 2013 [15] (registration number: CRD42013005113).

The systematic review protocol has been conducted and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [16].

Search strategy for identification of relevant studies

To identify the relevant literature, electronic searches will be conducted in the following databases: Ovid MEDLINE, Ovid Embase, Ovid PsycINFO and Cochrane Central Register of Controlled Trial (CENTRAL) from their inception to August 2013. A comprehensive search strategy has been designed with the assistance of an experienced research librarian and adjusted to account for differences in indexing across databases. The updated search strategy of the Cochrane Back Review Group 2013 [17] was used to identify spinal pain terms, which were combined with relevant keywords for the somatosensory function domain (Appendix 1). Articles identified through reference lists of included studies and relevant systematic reviews will be considered for inclusion based on their title. Non-English language studies will be included, where a translation can be made available.

Eligibility criteria

Participants

We will include studies of adults (18 years or older) with acute or subacute (up to and including 12 weeks) spinal pain (back or neck pain). Studies will be excluded if the participants have spinal pain due to serious pathologies (for example, fracture, neoplasm, infection, failed back surgery syndrome) or specific conditions (for example, rheumatoid arthritis, fibromyalgia, spondylolisthesis, pregnancy and postpartum) or who have had spinal surgery. Studies will also not be included if they report on a mixed population of chronic and acute or subacute spinal pain where the results for acute or subacute participants cannot be extracted separately.

Outcome measures

The outcomes of interest are any measure of somatosensory dysfunction (for example, hyperalgesia, allodynia, dysaesthesia, neuropathic pain) assessed by any experimental or clinical examination, by quantitative sensory testing or by any relevant questionnaire, reported within the first 12 weeks of onset of back or neck pain.

Types of study

We will include relevant study designs such as cross-sectional studies, surveys, case-control studies, randomized controlled trials and observational studies. Qualitative studies and retrospective studies will be excluded. We will exclude intervention studies if assessment of somatosensory function is only reported after treatment (for example, drug administration, surgical techniques). Reference lists of relevant systematic reviews will be checked in order to identify relevant primary studies, but systematic reviews will otherwise be excluded.

Screening of studies

After removal of duplicate papers, identification of studies that meet the inclusion criteria will be independently conducted by two reviewers based on the title and then abstract. Reasons for exclusion of papers will be recorded when screening full papers. Papers of the resulting studies will be reviewed independently by two reviewers for their eligibility using a standardized eligibility sheet. Any disagreement arising between the reviewers will be resolved by discussion and consensus and with the assistance of a third reviewer at all stages of screening.

Data extraction

Data from included studies will be extracted independently by two reviewers using a standardized data extraction form. Differences in data extraction will be resolved by consensus and the assistance of a third reviewer. Authors of studies will be contacted if data are incomplete or clarification is required. The following data will be extracted from each included study. General study information: authors, year of publication, language; study design: cross-sectional, survey, case-control, observational study or clinical trial; clinical setting: primary care, specialist clinic, hospital outpatient department; population characteristics: demographic information (age, gender); case definition and description: classification or

diagnostic criteria used, region of pain (lumbar, cervical, mixed), duration of pain, severity of pain, functional status, comorbidities, medications; somatosensory function: data from psychophysical measures, clinical assessment or description, questionnaire at specified time points from onset of spinal pain for spinal pain and control cohorts (where described).

Risk of bias assessment

We were unable to identify an existing instrument suitable to assess the risk of bias for the different study types eligible for this review. Therefore, study quality will be assessed using a system adapted from Lewis *et al*. [18] and Tesarz *et al*. [19], designed to evaluate study features most relevant to the current review. These features are: (1) that the sample was clearly described; (2) that the sample was representative of the target population; (3) that the somatosensory assessment method used was standardized, validated and fully described; (4) that there was blinding of those assessing somatosensory function to group allocation (where relevant); and (5) that factors known to influence pain assessment were evaluated or controlled for in the analysis (for psychophysical studies). For this last item, known confounders include medication use, caffeine intake prior to testing, comorbid pain condition, different testing times during the day and phase of menstrual cycle (females) [18]. Each risk of bias item will be evaluated as outlined in Table 1, by two reviewers and any disagreement discussed with a third reviewer to reach consensus. Studies will be considered to have high risk of bias if the majority of relevant criteria are not satisfied.

Data analysis

It is anticipated that the studies will be too heterogeneous in multiple domains to allow any data pooling or

Table 1 Risk of bias assessment

Category	Criteria	Judgment
Defined sample	Inclusion/exclusion criteria were clearly specified	Yes
	Comment:	No
		Unsure
		N/A
Representative sample	Clinical and demographic characteristics were well described	Yes
	Comment:	No
		Unsure
		N/A
	Recruitment procedure was specified (including source population) and appropriate	Yes
	Comment:	No
		Unsure
		N/A
Somatosensory assessment	Somatosensory assessment method was standardized or validated	Yes
	Comment:	No
		Unsure
		N/A
	Method of somatosensory assessment was fully described	Yes
	Comment:	No
		Unsure
		N/A
Blinding of assessment	Assessment of somatosensory function was blinded to participant group or condition	Yes
	Comment:	No
		Unsure
		N/A
Controlled risk of known confounders	Factors known to influence pain assessment were evaluated or controlled for	Yes
	Comment:	No
		Unsure
		N/A

quantitative synthesis. Data will be therefore gathered and presented in a table and a narrative synthesis of the findings will be conducted. Where possible, an indication of the timeline of changes in somatosensory function will be presented. Because of the anticipated heterogeneity of studies, it is unlikely that quantitative analyses based on study quality will be possible. Therefore, the risk of bias assessment of included studies will be summarized in a table and results and implications will be critically discussed.

Discussion

This systematic review will fill an important gap in our current knowledge about the timecourse and nature of changes in somatosensory function that occur in the early stages of back and neck pain, which may be instrumental in the development of disabling chronic pain. An improved understanding of the timing and onset of sensory dysfunction will enable clinicians and researchers to develop more effective diagnostic tools and mechanism-based treatments to prevent the development of chronic back and neck pain.

Appendix 1: Ovid MEDLINE search strategy

1. back pain/
2. low back pain/
3. back disorder*.mp.
4. (lumbar adj pain).ti,ab.
5. sciatica/
6. sciatic neuropathy/
7. Intervertebral Disc Degeneration/
8. (disc adj prolapse).ti,ab.
9. (disc adj herniation).ti,ab.
10. (facet adj joint*).ti,ab.
11. backache.ti,ab.
12. dorsalgia.mp.
13. or/1-12
14. Neck Pain/
15. whiplash injur*.mp.
16. exp Neck Injuries/
17. Neck Muscles/
18. neck.ti,ab.
19. or/14-18
20. (femur or humerus).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
21. 19 not 20
22. exp Pain Perception/
23. pain, referred/
24. sensory profile*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
25. Analgesia.ti,ab.
26. allodynia.ti,ab.
27. neuralgia/
28. sensory hypersensitivity.ti,ab.
29. hyperpathia.ti,ab.
30. exp somatosensory disorders/
31. hyp?algesia.ti,ab.
32. peripheral sensit*.ti,ab.
33. central pain.ti,ab.
34. quantitative sensory test*.mp.
35. experim* pain.mp.
36. (pain adj test*).mp.
37. bedside exam*.mp.
38. psychophysic*.mp.
39. (neuropathic pain questionnaire or painDETECT or DN4 or NPSI or PQAS or ID-pain or LANSS).ti,ab. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
40. temporal summation.ti,ab.
41. wind up.ti,ab.
42. two-point discrimination.ti,ab.
43. (second adj pain).ti,ab.
44. tactile acuity.ti,ab.
45. diffuse noxious inhibitory control.mp.
46. conditioned pain modulation.mp.
47. pain threshold/
48. central sensit*.ti,ab.
49. Nociceptors/
50. ((pressure or thermal or cold or heat or eletrical or mechanical) adj pain).ti,ab. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
51. ((cold or warm) adj detection).ti,ab.
52. (pain adj tolerance).ti,ab.
53. (detection adj threshold).ti,ab.
54. 13 or 21
55. or/22-53
56. 54 and 55
57. 56 not surg*.mp.
58. qualitative research/
59. retrospective studies/
60. 58 or 59
61. 57 not 60
62. limit 61 to humans

Abbreviations

CENTRAL: Cochrane Central Register of Controlled Trials; PROSPERO: Prospective Registering of Systematic Reviews; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta analyses.

Competing interests
The authors declare they have no competing interests.

Authors' contributions
AM is the lead researcher of this project, supported by doctoral supervisors JMH and CMD. AM, JMH and CMD all contributed to the development of the protocol. AM and JMH led the writing of the protocol manuscript. All authors critically revised the protocol and read and approved the final version.

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2.4 Co-authors' statements

As co-authors of the paper, "Early changes in somatosensory function in spinal pain: a systematic review and meta-analysis", we confirm that Anna Marcuzzi has made the following contributions to this study:

- Conception and design of the research
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript
- Critical appraisal of the content

Associate Professor Julia Hush _____ Date 5 Dec 2016

Dr Paul Wrigley_____ Date 5 Dec 2016

Professor Catherine Dean _____ Date 5 Dec 2016

Comprehensive Review

PAIN

Early changes in somatosensory function in spinal pain: a systematic review and meta-analysis

Anna Marcuzzi[a,b,*], Catherine M. Dean[a,b], Paul J. Wrigley[c,d], Julia M. Hush[a,b]

Abstract

Alterations in sensory processing have been demonstrated in chronic low back and neck pain. However, it has not been yet systematically summarized how early these changes occur in spinal pain. This systematic review examines the available literature measuring somatosensory function in acute (<6 weeks) and subacute (6-12 weeks) spinal pain. The protocol for this review has been registered on the International Prospective Register of Systematic Reviews (PROSPERO). An electronic search of 4 databases was conducted to retrieve studies assessing somatosensory function by quantitative sensory testing in adults with spinal pain of up to 12 weeks duration. Two reviewers independently screened the studies and assessed the risk of bias. Studies were grouped according to spinal pain condition (whiplash injury, idiopathic neck pain, and nonspecific low back pain), and, where possible, meta-analyses were performed for comparable results. Fifteen studies were included. Sources of bias included lack of assessor blinding, unclear sampling methods, and lack of control for confounders. We found that: (1) there is consistent evidence for thermal and widespread mechanical pain hypersensitivity in the acute stage of whiplash, (2) there is no evidence for pain hypersensitivity in the acute and subacute stage of idiopathic neck pain, although the body of evidence is small, and (3) hyperalgesia and spinal cord hyperexcitability have been detected in early stages of nonspecific low back pain, although evidence about widespread effects are conflicting. Future longitudinal research using multiple sensory modalities and standardized testing may reveal the involvement of somatosensory changes in the development and maintenance of chronic pain.

Keywords: Spinal pain, Back pain, Neck pain, Whiplash, Sensitization, Acute pain, Sensory testing, Somatosensory function

1. Introduction

Acute spinal pain has traditionally been characterized as self-limiting with only a small percentage that persists as chronic neck or back pain.[63,65] This view has been challenged by more recent research indicating that between one-third and two-thirds of people do not recover after an acute episode of spinal pain and develop chronic pain.[26,27,64] Despite an extensive international research effort during the past 30 years, it has become apparent that current treatments do not significantly change the natural course of spinal pain[1,61] and, importantly, do not prevent the development of chronic pain.[64]

In recent decades, research has focussed on better understanding the neurophysiological mechanisms underlying chronic pain conditions. It is now established that people with chronic low back and neck pain exhibit exaggerated pain responses to different experimental noxious stimulations applied to the area of injury, as well as to areas unrelated to the site of injury.[14,18,21,32,48,53] This widespread pain hypersensitivity is thought to reflect changes in somatosensory function such as central sensitization.[12] Other somatosensory abnormalities have been documented in chronic spinal pain including lowered nociceptive withdrawal reflex (NWR) thresholds,[2,56] temporal summation of pain,[14,46] higher thresholds in response to innocuous stimuli (ie, hypesthesia),[7,49] and reduced tactile acuity,[38,41] suggesting higher order plasticity of the nociceptive processing system.

Although the growing body of evidence of altered somatosensory function in chronic musculoskeletal conditions has been extensively reviewed over the last decade,[13,51,62,68] the available literature investigating somatosensory function in acute stages of spinal pain has not yet been systematically summarized. Acquiring insight into early somatosensory abnormalities may help direct future research to better understand mechanisms underlying the development of chronic spinal pain.

The aim of this review was to critically evaluate the available literature measuring somatosensory function in acute (<6 weeks) and subacute (6-12 weeks) spinal pain and to analyze which somatosensory abnormalities can be detected in these time frames.

2. Method

2.1. Procedure

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines[36] and the Cochrane Back Review Group guidelines,[19] where applicable. The protocol for this systematic review was prospectively registered on PROSPERO 2013 (registration

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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number: CRD42013005113) and published.[39] Electronic searches for articles were conducted using the following databases from inception to August 2013: Ovid MEDLINE, Ovid EMBASE, Ovid PsychINFO, and Cochrane Central Register of Controlled Trial (CENTRAL). A comprehensive search strategy was developed with the assistance of an experienced research librarian and adjusted for each database (see Appendix A for MEDLINE search strategy, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A10). Additionally, the reference lists of included studies and reviews were screened to identify additional relevant articles. There were no restrictions on the publication type and status nor on the language of the articles.

2.2. Study selection

We included any relevant study reporting on measures of somatosensory function assessed by quantitative sensory testing (QST), questionnaires, or clinical/bedside examination based on the following criteria: adults who are at least 18 years or older with acute (<6 weeks) and subacute (6-12 weeks) spinal pain and who had nonspecific low back pain (LBP), idiopathic (non-traumatic) cervical pain, or thoracic pain, defined as pain with or without radiating pain for which a specific underlying pathology could not been detected,[4,33] or whiplash-associated disorder.[5] We excluded spinal pain due to serious pathology or a specific spinal condition (eg, fracture, spondylolisthesis, osteoporosis, fibromyalgia after surgery), or where there was a mixed duration of pain and results for acute or subacute participants who were not reported separately, and studies that did not include any control group for comparison.

2.3. Study inclusion

Articles were first screened for eligibility independently by 2 reviewers based on title. Abstracts of selected references were then assessed independently by 3 reviewers. Reference lists of review articles were screened to locate other relevant articles. Finally, full-text articles were assessed for inclusion independently by 2 reviewers using a piloted standardized eligibility sheet, and any disagreements were resolved by discussion and consensus. Authors were contacted where further information to clarify eligibility was needed.

2.4. Risk of bias assessment

The risk of bias was assessed independently by 2 reviewers for the following categories adapted from Tesarz et al.[59] and Lewis et al.[35]: (1) clarity of sample description (ie, defined inclusion/exclusion criteria, completeness of clinical and demographic characteristics, defined source population and sampling method), (2) quality of somatosensory assessment (ie, standardized testing methods, comprehensiveness of procedure description), (3) blinding of assessments, and (4) whether factors known to influence pain perception (eg, medication intake, comorbid pain condition, psychological factors, age and gender) were evaluated and controlled. Each category was scored as satisfied (yes), not satisfied (no), partially satisfied (unclear), or not applicable. The "yes" score was given only if the majority of items within each category were fulfilled (see Appendix B for the risk of bias assessment tool used, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A11). Individual studies were judged as low, moderate, or high risk of bias based on the proportion of criteria met as follows: studies in which at least 6 of 7 criteria were met were classified as low risk; studies in which 5 of 7 criteria were met were classified as moderate risk; and studies in which less than 5 criteria were met were classified as high risk. Any disagreement was resolved by discussion and consensus with a third person if required.

2.5. Data extraction

Data from included studies were extracted independently by 2 reviewers using a piloted standardized data extraction sheet.-Data extracted included information about study design, clinical setting, sample size, demographics, diagnosis, duration and severity of pain, type and sites of assessments, sensory outcome measures, and QST findings. Any disagreement was resolved by discussion and consensus of the 2 reviewers. Authors were contacted where required for clarification or further data.

2.6. Data synthesis and analysis

Results of comparisons of patients and controls were tabulated for each outcome measure grouped according to the following features:

(1) Spinal pain condition, ie, whiplash injury, idiopathic neck pain, nonspecific LBP
(2) Sensory parameter (eg, pain detection threshold, pain tolerance threshold)
(3) Stimulation modality (eg, pressure, cold)
(4) Duration of pain, ie, acute or subacute
(5) Assessment site, ie, local, anatomically remote (based on Hubscher et al.[25] definition), or over peripheral nerves.

Separate, post hoc meta-analyses were performed for distinct QST outcome measures, where data were available for at least 2 studies. This was possible for 2 QST assessments, namely pressure and cold pain detection thresholds. Where possible, the standardized mean difference was calculated for these QST outcomes from reported means and SDs of patient and control groups. Statistical pooling of data was performed using a random effects model. We excluded from quantitative analyses data that could not be accurately extracted (eg, when reported only in figures) or that could not be obtained from the study authors. Effect size estimates were interpreted as small (≤0.2), moderate (0.5), or large (≥0.8).[11] Statistically significant heterogeneity was considered using the χ^2 test when $P > 0.10$, and substantial heterogeneity was considered present when $I^2 > 60\%$.[24] The Comprehensive Meta-Analysis software (Version 2.0, Biostat, Englewood, NJ) was used to perform statistical analyses.

The following rules were applied when conducting meta-analyses: (1) in cases where outcomes were reported separately for different patient subgroups (eg, recovered, mild pain, severe pain for whiplash), the data were combined to obtain a single comparison (patients vs controls), (2) if more than 1 measurement at a local site was performed in the same study, we used the one that was most commonly reported across studies. If this was not possible, we used the site that showed the greatest mean difference from controls, and (3) when follow-up measures were reported at multiple time points in the same time frame (acute or subacute), we used the most extreme temporal measures as representative of each stage. For example, the earliest (eg, baseline) measure was used for the acute stage, and the latest measure was used for the subacute stage.

Quantitative sensory testing findings of each individual study are reported in detail as Appendices C, D, and E for whiplash injury, idiopathic neck pain, and nonspecific LBP, respectively.

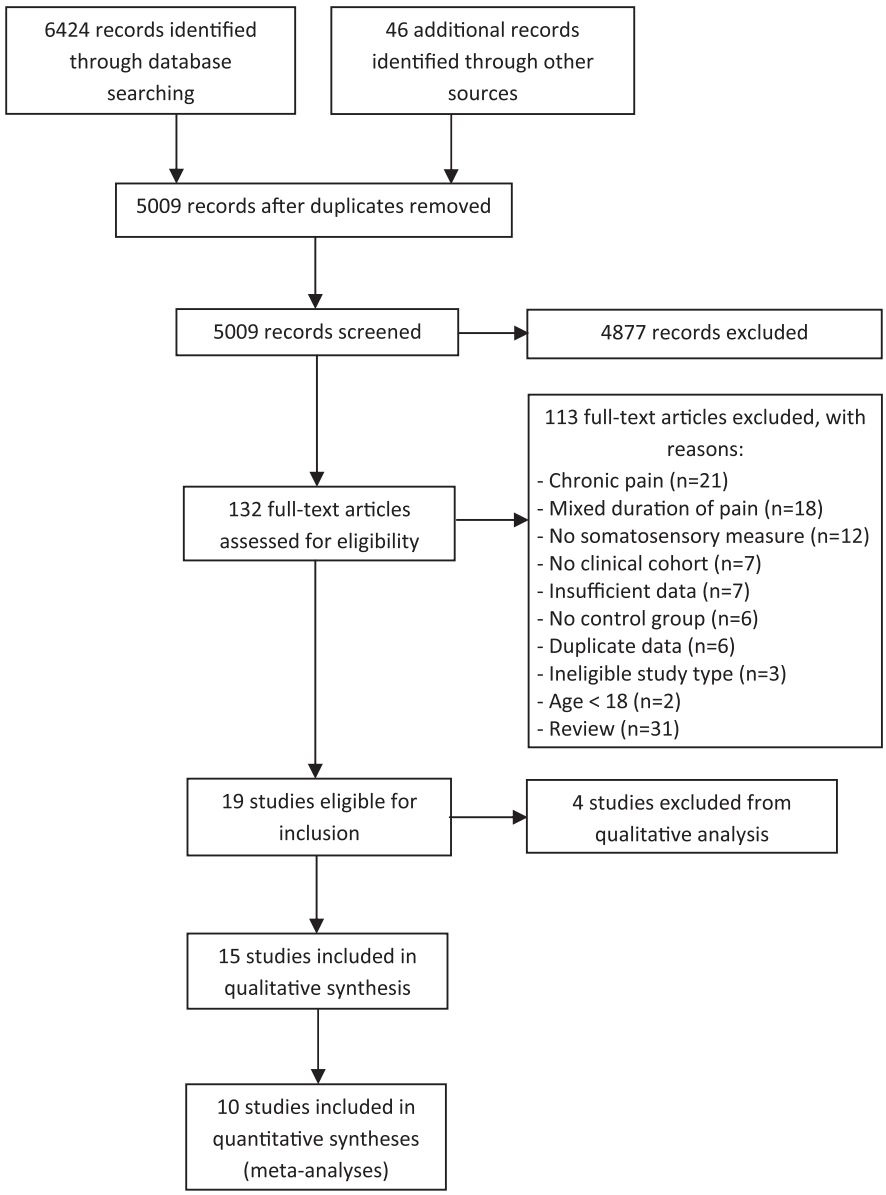

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta Analyses study selection flow chart.

3. Results

The search strategy retrieved 6470 articles from which 132 articles remained after initial screening of titles and abstracts. Full-text copies were then examined for eligibility (**Fig. 1**). The most common reason for exclusion was duration of pain beyond 12 weeks or mixed duration, followed by inadequate somatosensory measures (eg, changes in visual analog scale score after intervention). At this stage, 14 authors (of 15 articles) were contacted to clarify eligibility. Of these authors, 9 provided additional information for 10 articles (9 excluded and 1 included), 3 were unable to provide the requested information, and 2 did not reply after 2 attempts and were therefore excluded. Of the 19 studies that met the eligibility criteria, we excluded 4 studies that reported only questionnaire and clinical examination data[20,37,54,60], as these outcome measures were not relevant to the main focus of the review. Finally, 15 studies providing data from QST on 12 cohorts of participants with acute or subacute spinal pain were included in this review. Meta-analyses were performed for data from 10 studies that provided 24 comparisons. The main findings for each spinal pain condition are summarized in **Table 4**.

3.1. Description of included studies

A summary of the characteristics of the 15 included studies is provided in **Table 1**. Eight studies were cross-sectional in design, 6 were longitudinal, and 1 was a clinical trial. Whiplash injury was the most commonly assessed spinal condition (9 studies), followed by nonspecific LBP (4 studies) and idiopathic neck pain (2 studies).

3.2. Risk of bias assessment

Data were not available from 1 study (Neziri et al.,[44] abstract only) to assess risk of bias. Of the remaining 14 studies, the overall risk of bias was moderate (**Table 2**); 11 studies satisfied 5 to 6 of the 7 criteria, indicating low-to-moderate risk of bias, and the other 3

Table 1

Summary of study characteristics.

Study	Study design	Condition	Duration of pain at baseline	Intensity of pain at baseline (0-10 score)	Patients			Controls		
					Age, y	Gender (F), %	N*	Age, y	Gender (F), %	N*
Biurrun Manresa et al.[3]	Cross sectional	Nonspecific LBP	1 (1 2.5)† wk	5 (4 6)†	39 (30 57)†	N/R	23	49 (34 65)†	N/R	300
Chien et al.[6]	Cross sectional	Whiplash	3.44 (1.7) wk	N/R	36.3 (13.1)	62	52	31.4 (8.9)	81	31
Chien and Sterling[9]	Longitudinal	Whiplash	3.44 (1.7) wk	N/R	36.3 (13.1)	62	52	32.6 (8.7)	74	38
Farasyn and Meeusen[15]	Cross sectional	Nonspecific LBP	>3 wk, <3 mo‡	N/R	43 (13)	55	87	40 (11)	63	64
Farasyn and Meeusen[16]	RCT	Nonspecific LBP	>3 wk, <3 mo‡	54 (24)§	45 (13)	43	58	40 (11)	60	64
Fernández Pérez et al.[17]	Cross sectional	Whiplash	26.6 (3.8) d	6.2 (2.6)	28.7 (12.4)	50	20	29.1 (12.2)	50	20
Javanshir et al.[28]	Cross sectional	Idiopathic neck pain	1.7 (1.1) mo	4.7 (1.7)	33 (9)	60	5	33 (8)	50	6
Kasch et al.[31]	Longitudinal	Whiplash	0 1 wk‡	N/R	35.6 (10.7)	53	141	34.8 (12)	53	40
Kasch et al.[30]	Longitudinal	Whiplash	11 (7.8 16.3)† d	N/R	35.6 (10.7)	53	141	34.8 (12)	53	40
Nebel et al.[42]	Longitudinal	Whiplash	7 (2.9) d	N/R	28.75 (12.1)	55	20	28.8 (10.4)	48	23
Neziri et al.[44]	Cross sectional	LBP	1.8 ± 1.0 wk	5.2 ± 1.5	41.4 (12.5)	N/R	40	37.4 (10.9)	N/R	30
Sterling et al.[56]	Longitudinal	Whiplash	0 30 d‡	2.3 (0.9) recovered 3.2 (1.2) mild pain 3.2 (1.3) severe pain	36.27 (12.7)	70	80	40.1 (13.6)	60	20
Sterling[55]	Longitudinal	Whiplash	14 (6) d	3.6 (1.9)	36.1 (13.1)	58	62	40.1 (13.6)	64	22
Stude et al.[58]	Cross sectional	Whiplash	7 (2.9) d	N/R	28.9 (12.1)	57	23	28.8 (10.2)	46	24
Walton et al.[67]	Cross sectional	Idiopathic neck pain (33% WAD)	38 (7 90)‖ d	4 (0 8)‖	40.4 (20 68)‖	66	40	25.4 (22 55)‖	65	60

All values are expressed as mean (SD), unless otherwise specified.
* Sample size at baseline assessment.
† Median (25% quartile 75% quartile).
‡ Mean value not provided.
§ Zero to 100 mm pain visual analog scale score.
‖ Mean (range).
LBP, low back pain; N/R, not reported; RCT, randomized controlled trial; WAD, whiplash associated disorders.

studies had higher risk of bias, as they satisfied only 4 of the 7 criteria. There was a lack of assessor blinding in 71% of included studies, and the sampling methods were unclear or not reported in 57% of studies. Potential confounders were addressed in 57% of studies where, most commonly, the effect of variables such as age, gender, and psychological factors on QST results was analyzed. All studies used standardized or validated QST assessments and were therefore deemed to have low performance bias.

3.3. Somatosensory assessment

Somatosensory assessments using 5 stimulation modalities were reported in included studies (**Table 3**): pressure (81%), cold (37%), heat (25%), electrical (25%), and vibration (12%). The majority of studies reported results for more than 1 sensory parameter. Pain sensitivity was assessed using pain detection and tolerance thresholds in most studies. Only 2 studies examining whiplash injury[6,8] used innocuous stimuli to investigate abnormal sensation (ie, hypesthesia). Other QST modalities included conditioned pain modulation (CPM)[30,44] and electrophysiological measures, such as NWR threshold,[3,55] reflex receptive field (RRF), and temporal summation of pain.[3]

Regarding the inception time frames, 12 of 16 studies performed QST assessments in the acute phase (<6 weeks). Among them, 2 studies assessed participants within 1 week from onset of pain,[30,31] 3 studies within 2 weeks,[42,44,58] 1 study within 3 weeks,[55] and the remaining 5 studies within 4 weeks.[3,6,8,17,57]

3.4. Whiplash injury results

Nine studies (6 distinct cohorts) provided QST findings for 12 sensory parameters in whiplash injury (Appendix C, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A12). Meta-analyses were performed for pressure pain detection threshold (PPT) measured at 3 sites (local, remote, and nerve) in acute and subacute stages and for cold pain detection threshold (CPT) measured in the acute stage.

3.4.1. Psychophysical assessment of noxious stimuli

3.4.1.1. Pressure stimulation

Pressure pain detection threshold was reported in 6 studies[6,17,31,55,57,58] in the acute stage and in 3 studies[31,55,57] in the subacute stage for at least 1 site. One study (Sterling et al.[57]) could not be included in these meta-analyses because the standardized mean difference for PPT measures could not be calculated (published results were in figures from which accurate data could not be extracted). The main finding from this longitudinal study was that a subgroup of patients with whiplash with greater pain and disability levels had widespread pain

Table 2

Risk of bias assessment.

Study	Sample description and representativeness			Assessment quality		Blinding	Confounders
	Inclusion and exclusion criteria were specified	Clinical and demographic features were fully described	Recruitment procedure was fully described	Somatosensory assessment was standardized or validated	Somatosensory assessment was fully described	Assessors were blinded to participant group or condition	Confounders were evaluated and controlled for
Biurrun Manresa et al.[3]	Y	Y	Y	Y	Y	N	Y
Chien et al.[6]	Y	Y	?	Y	Y	Y	Y
Chien et al.[8]	Y	Y	?	Y	Y	Y	Y
Farasyn and Meeusen[15]	Y	Y	?	Y	Y	N	Y
Farasyn and Meeusen[16]	Y	Y	Y	Y	Y	N	Y
Fernández Pérez et al.[17]	Y	Y	?	Y	Y	Y	?
Javanshir et al.[28]	Y	Y	Y	Y	Y	Y	?
Kasch et al.[31]	Y	?	Y	Y	Y	N	Y
Kasch et al.[30]	Y	?	Y	Y	Y	N	?
Nebel et al.[42]	Y	Y	N	Y	Y	N	?
Neziri et al.[44]*	NA	NA	NA	NA	NA	NA	NA
Sterling et al.[56]	Y	Y	?	Y	Y	N	Y
Sterling[55]	Y	Y	?	Y	Y	N	Y
Stude et al.[58]	Y	Y	N	Y	Y	N	N
Walton et al.[67]	Y	Y	Y	Y	Y	N	N

* Abstract only available.
NA, not available; ?, unclear.

hypersensitivity at all time points assessed (1, 2, and 3 months), whereas patients with milder symptoms and those who recovered had pain hypersensitivity localized at the spine at early stage (ie, 1 month), which resolved after 2 months. In acute whiplash (**Fig. 2**), pooled results from 4 comparisons (n = 246 patients and n = 106 controls) and 3 comparisons (n = 223 patients and n = 82 controls) at local and remote sites, respectively, showed a moderate effect size estimate of −0.57 (95% confidence interval [CI], −0.84 to −0.31] and −0.47 (95% CI, −0.85 to −0.08). At the median nerve, pooled results from 2 comparisons (n = 114 patients and n = 53 controls) showed a large effect estimate of −1.01 (95% CI, −1.67 to −0.36), where a negative value indicates a lower threshold for patients compared with controls. At all sites, in acute stage, patients with whiplash had lower PPTs than healthy controls, indicating widespread pain hypersensitivity. In subacute whiplash (**Fig. 3**), pooled results from 2 comparisons (n = 203 patients and n = 62 controls) at local sites showed a moderate effect estimate of −0.46 (95% CI, −0.78 to −0.14), whereas at remote sites, the same 2 studies (n = 203 patients and n = 62 controls) showed a non-significant effect estimate of −0.30 (95% CI, −0.66 to 0.06). These results indicate that pain hypersensitivity to pressure stimuli may persist in subacute stage, although only detected at the spine sites.

Pressure pain tolerance threshold was measured in 2 studies[30,58] at the spine at 2 different time points: after 15 days and at 3 months after whiplash injury. The authors reported significantly lower tolerance threshold in patients with whiplash compared with controls. Another 2 studies[42,58] measured pain magnitude rating for a suprathreshold pressure stimulus at spinal sites in the same cohort of patients with whiplash. They reported higher pain sensitivity (assessed by area under the pain intensity–time curve) between 0 and 3 weeks after injury, but no difference when assessed at 4 and 6 weeks. Overall, these results indicate that hypersensitivity to suprathreshold pressure stimuli also occurs in acute and subacute whiplash, although there is some inconsistency between studies reporting measures taken during the late acute to subacute stage.

3.4.1.2. Cold and heat stimulation

Cold pain detection threshold was reported in 3 studies[6,55,57] (n = 194 patients and n = 73 controls) in the acute stage (**Fig. 4**). The forest plot showed a pooled effect estimate of 1.07 (95% CI, 0.40-1.74), where a positive value indicates higher threshold for patients compared with controls. This result shows that patients with acute whiplash have hypersensitivity to painful cold stimuli. However, it should be noted that there was significant heterogeneity for this pooled estimate ($P = 0.04$, $I^2 = 69\%$). In subacute whiplash, 2 studies[55,57] found that cold pain hypersensitivity only persisted in the subgroup of patients with greater pain and disability levels, whereas patients with milder symptoms or those who recovered were no different from controls.

One study[30] investigated cold pain tolerance threshold in whiplash. They used the cold pressor test (immersion of the hand

Table 3

Summary of somatosensory assessment performed in the included studies.

Sensory parameter	Stimulation modality	Studies
Pain detection threshold: The minimum intensity of a stimulus that is perceived as painful	Pressure	Whiplash: Chien et al.,[6] Fernández Pérez et al.,[17] Kasch et al.,[31] Sterling et al.,[57] Sterling,[55] Stude et al.[58] NP: Javanshir et al.,[28] Walton et al.[67] LBP: Farasyn and Meeusen,[16] Farasyn and Meeusen[15]
	Cold	Whiplash: Chien et al.,[6] Sterling et al.,[57] Sterling[55] NP: Javanshir et al.[28]
	Heat	Whiplash: Sterling et al.[57] NP: Javanshir et al.[28]
	Electrical	LBP: Biurrun Manresa et al.[3]
Pain tolerance threshold: The maximum intensity of a stimulus that can be tolerated	Pressure	Whiplash: Kasch et al.,[30] Stude et al.[58] LBP: Neziri et al.[44]
	Cold	Whiplash: Kasch et al.[30]
Pain magnitude rating: Pain intensity rating for a standardized subthreshold, threshold, or suprathreshold stimulus	Pressure	Whiplash: Nebel et al.,[42] Stude et al.[58]
Detection threshold: The minimum intensity of a non noxious stimulus that can be perceived by a subject	Cold Vibration	Whiplash: Kasch et al.[30]
	Thermal Electrical	Whiplash: Chien et al.,[6] Chien et al.[8]
NWR threshold: The minimum current of an electrical stimulus that can evoke a flexion reflex	Electrical	Whiplash: Sterling[55] LBP: Biurrun Manresa et al.[3]
Temporal summation: Increase in perceived intensity to repetitive stimulations of the same intensity	Electrical	LBP: Biurrun Manresa et al.[3]
RRF: Area from which a NWR can be elicited	Electrical	LBP: Biurrun Manresa et al.[3]
CPM: Evaluation of a painful stimulus in the absence and presence of a second painful (conditioning) stimulus applied to a remote region of the body	Cold bath + pressure	Whiplash: Kasch et al.[30] LBP: Neziri et al.[44]

CPM, conditioned pain modulation; LBP, nonspecific low back pain; NP, idiopathic neck pain; NWR, nociceptive withdrawal reflex; RRF, reflex receptive field.

in cold water) to measure the time to withdrawal and the area under the pain intensity–time curve. They reported no significant difference between patients and controls when measured in the acute stage (7 days) and the subacute stage (3 months). However, subgroup analysis revealed that patients who did not recover after 6 months had significantly higher cold pain sensitivity at both time points (7 days and 3 months) compared with the subgroup that recovered.

Sterling et al.[57] measured heat pain detection threshold at the cervical spine in patients with whiplash. When assessed at 1, 2, and 3 months, they found significantly lower threshold for the subgroup of patients with more severe pain and disability compared with controls at all time points. However, no difference was found between controls and the subgroups of patients who had recovered or who had milder symptoms. These results suggest that there is evidence for higher thermal pain sensitivity both in the acute and subacute stages of whiplash, and that this may be specific to subgroups with more severe symptoms.

3.4.1.3. Conditioned pain modulation

Kasch et al.[30] assessed CPM in patients with whiplash 3 months after injury by measuring the pressure pain tolerance as pain test stimulus at the masseter muscle during the immersion of the hand in cold water (conditioning stimulus). The authors reported no significant difference in the CPM response between patients and controls.

3.4.2. Psychophysical assessment of non-noxious stimuli

Two studies[6,8] reported detection thresholds for innocuous cold and warm (CDT and WDT), vibration (VDT), and electrical (EDT) stimuli at the hand (C6 and C7 dermatomes) in a whiplash cohort measured at 1 month[6] and 3 months.[8] There was evidence of sensory hypesthesia to vibration, cold, and electrical stimuli in whiplash compared with controls at 1 month at the hand. These sensory changes persisted at 3 months, but only in the subgroup of patients at high risk of poor recovery. Sensory hypesthesia to electrical stimulation was reported at a remote site (tibialis anterior) in acute whiplash but not at 3 months. These results indicate that changes in sensory responses to different innocuous stimulus modalities occur in the very early stage of whiplash but that this sensory hypesthesia persists only in patients with whiplash who are at risk of nonrecovery.

3.4.3. Electrophysiological assessment

One study[55] measured the NWR threshold at the biceps femoris muscle in patients with whiplash. When assessed at 3 weeks after injury, the NWR threshold was significantly lower in patients compared with controls. However, when measured at 3 months,

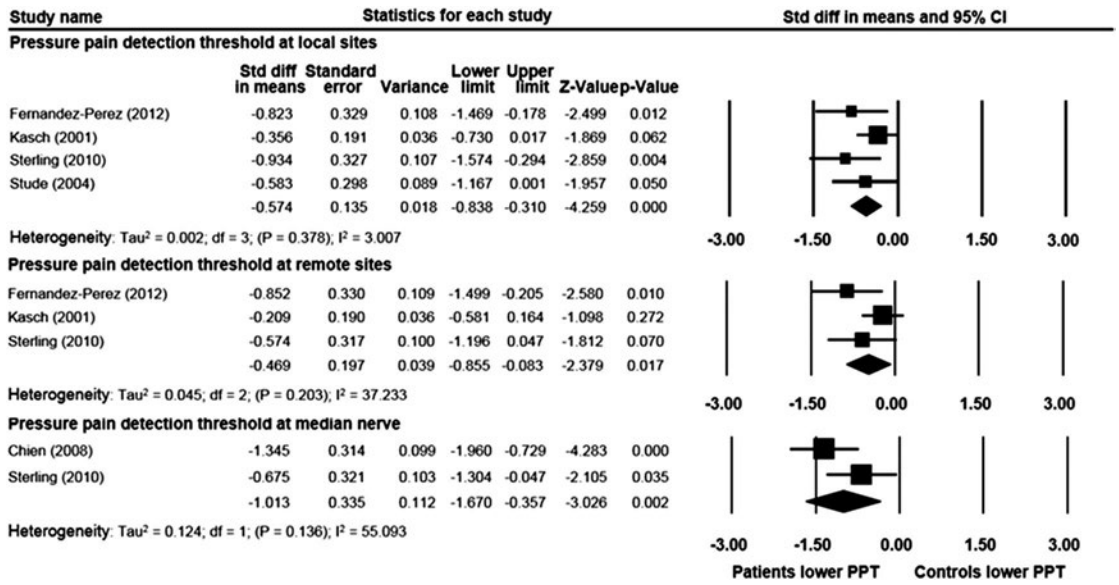

Figure 2. Forest plots of pressure pain detection threshold at local, remote, and median nerve sites assessed in the acute stage in whiplash injury.

only the subgroup of patients with more severe pain and disability had lower threshold compared with controls, whereas patients with milder symptoms or those who recovered were no different from controls.

3.5. Idiopathic neck pain results

Two studies provided QST findings for 3 sensory parameters in idiopathic neck pain (Appendix D, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A13). Meta-analyses were performed for PPT at local and remote sites in the subacute stage.

3.5.1. Psychophysical assessment of noxious stimuli

3.5.1.1. Pressure stimulation

Two studies[28,67] including 45 patients and 66 controls reported comparisons between people with neck pain and controls for PPT at local and remote sites, in the subacute stage. The forest plot (**Fig. 5**) shows a pooled effect estimate at the local site of 0.18 (95% CI, 0.56 to 0.21) and at the remote site of 0.29 (95% CI, 0.09 to 0.68), indicating that patients with idiopathic neck pain were not significantly different from controls at both assessment sites.

3.5.1.2. Cold and heat stimulation

One study[28] assessed cold and heat pain detection threshold, reporting no significant difference between patients and controls at both local and remote sites.

Taken together, these studies suggest that pain sensitivity to either pressure or thermal stimuli in the early stages of idiopathic neck pain is unaltered.

3.6. Nonspecific low back pain results

Four studies provided QST findings for 7 sensory parameters in nonspecific LBP (Appendix E, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A14). Meta-analyses were performed for PPT at local and remote sites in the subacute stage.

3.6.1. Psychophysical assessment of noxious stimuli

3.6.1.1. Pressure stimulation

Two studies[15,16] of 145 patients and 128 controls measured PPTs at local and remote sites in subacute LBP (**Fig. 6**). The pooled effect estimate for the local sites was 1.7 (95% CI, 2.05 to 1.49),

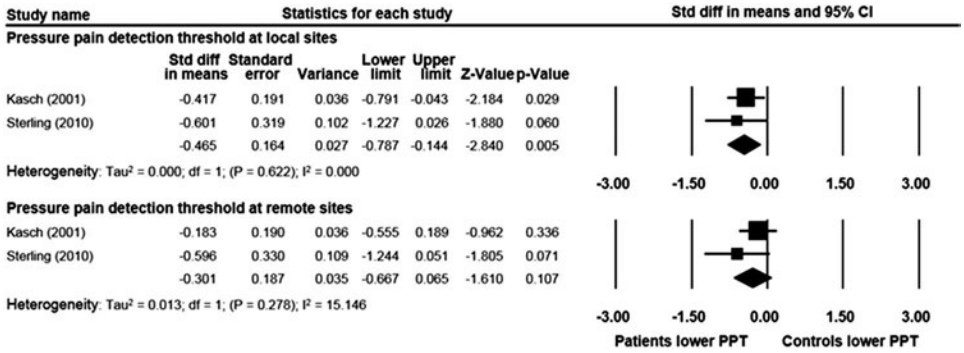

Figure 3. Forest plots of pressure pain detection threshold at local and remote sites assessed in the subacute stage in whiplash injury.

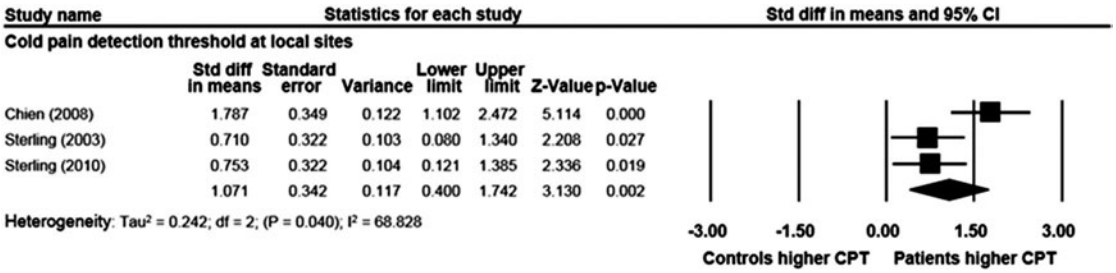

Figure 4. Forest plot of cold pain detection threshold at local sites assessed in the acute stage in whiplash injury.

where a negative value indicates a lower threshold for patients compared with controls. However, the estimate for the remote sites at triceps brachii (0.18 [95% CI, 0.42 to 0.06]) indicates that there was no difference between LBP and controls. In contrast, Neziri et al.[44] reported a significantly lower threshold to pressure pain tolerance at a different remote site (the second toe) in patients with LBP compared with controls. These results provide preliminary evidence for mechanical pain hypersensitivity in the early stages of LBP, although widespread effects may only occur in response to suprathreshold stimuli.

3.6.1.2. Electrical stimulation

Biurrun Manresa et al.[3] measured the electrical pain detection threshold at the sural nerve in the lower limb in patients with nonspecific acute LBP. They found that the patient group had a significantly lower threshold compared with controls, indicating pain hypersensitivity.

3.6.1.3. Conditioned pain modulation

Neziri et al.[44] assessed CPM in acute LBP by measuring pressure pain tolerance threshold at the foot as pain test stimulus while the hand was immersed in cold water (conditioning stimulus). They found no significant difference between patients and controls.

3.6.2. Electrophysiological assessment

Biurrun Manresa et al.[3] used 3 tests to evaluate spinal cord hyperexcitability in patients with acute nonspecific LBP: NWR threshold, RRF area, and temporal summation. Testing revealed a lower NWR current threshold, enlarged RRF, and temporal summation to repeated electrical stimulation, indicating the presence of central pain amplification.

4. Discussion

This is the first systematic review to report on early changes in somatosensory function in acute and subacute spinal pain. Studies included in this review provide QST measures from as early as 7 days from whiplash injury; however, the bulk of studies measured somatosensory function within 4 weeks from injury. In nonspecific LBP, QST measures were reported as early as 4 weeks from onset, whereas in idiopathic neck pain, only QST measures for the late acute/subacute time frame were available. The main findings from the 15 studies included (**Table 4**) are that: (1) there is consistent evidence for thermal and widespread mechanical pain hypersensitivity in the acute stage, whereas mechanical widespread effects cannot be demonstrated in the subacute stage of whiplash, (2) idiopathic neck pain is not characterized by pain hypersensitivity in the acute or subacute stage, although the body of evidence is small, and (3) hyperalgesia and spinal cord hyperexcitability can be detected in the early stages of nonspecific LBP, although there is conflicting evidence about widespread effects.

4.1. Whiplash injury

Quantitative sensory testing data analyzed in this review demonstrate that mechanical and thermal pain hypersensitivity occurs early after whiplash injury and that these changes in somatosensory function persist in subgroups of patients who do not recover. Previous research has shown that widespread cold and heat pain hypersensitivity persists in chronic whiplash[52,66] and is strongly associated with pain catastrophizing, anxiety, and depression,[66] emphasizing the link between maladaptive beliefs, mood, and pain in whiplash-associated disorders. The fact that NWR thresholds are lowered early after injury provides further

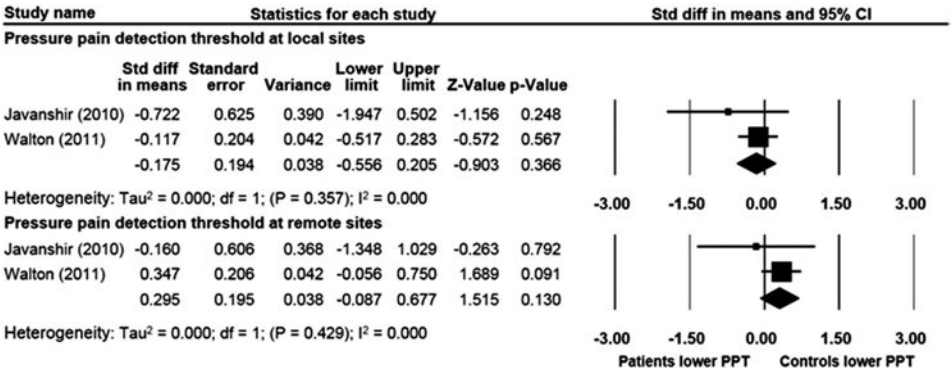

Figure 5. Forest plots of pressure pain detection threshold at local and remote sites in subacute stage in idiopathic neck pain.

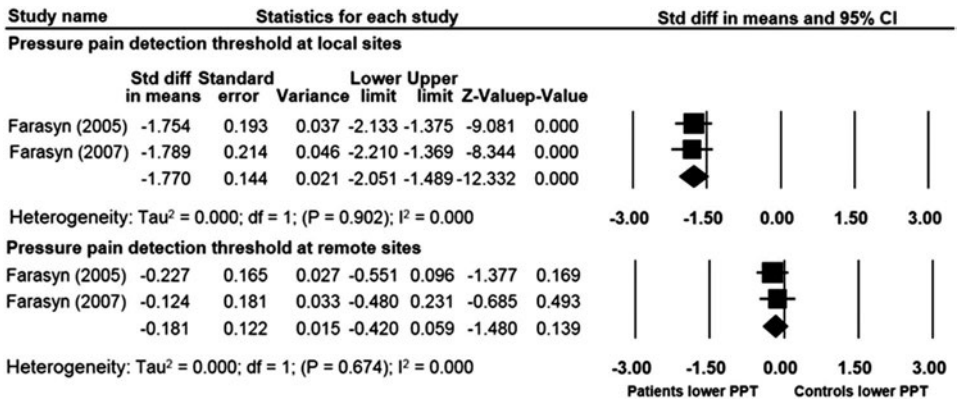

Figure 6. Forest plots of pressure pain detection threshold at local and remote sites in subacute stage in nonspecific LBP. LBP, low back pain.

evidence for the involvement of central sensitization in whiplash.[55] This evidence from longitudinal studies that spinal cord hyperexcitability occurs in acute whiplash and persists in the subgroup of patients who do not recover suggests that these early central changes may be involved in the development of chronic pain in whiplash.

In addition to pain hypersensitivity, the literature demonstrates evidence for sensory loss (hypesthesia) to non-noxious electrical, vibration, and thermal stimuli delivered to the hand in acute whiplash.[6] As with sensory gain, these changes often persist only in patients at high risk of nonrecovery after 3 and 6 months.[8] The hypesthesia to vibration is of particular interest as it indicates dysfunction of large myelinated fibers (Aβ) and their lemniscal pathways, which has been noted in other musculoskeletal conditions and is thought to be an early indicator of neural dysfunction.[23] These results reveal evidence of widespread somatosensory changes occurring in the early stages of whiplash, including pain hypersensitivity at distal sites, spinal cord hyperexcitability, and hypesthesia.

4.2. Idiopathic neck pain

In contrast to whiplash, there is no suggestion from the evidence found in this review that increased pain sensitivity occurs in acute or subacute idiopathic neck pain when compared with healthy subjects. Both mechanical and thermal pain sensitivity tests revealed no significant differences between patient groups and controls. While further research using larger samples of people with acute neck pain is needed, the available evidence suggests that whiplash and idiopathic neck pain are mechanistically distinct conditions. This hypothesis is supported by studies comparing whiplash injury with idiopathic neck pain. For example, while widespread pressure pain hypersensitivity occurs in acute and chronic whiplash injury,[29,50,55,56] pressure algometry testing at remote sites reveals no differences between patients with idiopathic neck pain and healthy controls.[52] Similarly, vibration detection thresholds are unaltered in chronic idiopathic neck pain, while hypesthesia to vibration is a feature in both acute and chronic whiplash.[9] These observations suggest that different mechanisms underpin the development of chronic pain in whiplash and idiopathic neck pain. This finding has important implications for how patients are assessed to predict recovery or nonrecovery and the development of treatments that target specific mechanisms in the development of chronic pain.[9,52]

4.3. Nonspecific low back pain

Our review provides evidence for hyperalgesia to mechanical and electrical stimuli in the early stages of LBP. Pressure pain hypersensitivity occurs in subacute LBP locally at the spine and at remote sites with suprathreshold stimuli. This finding supports previous research showing that widespread pain hypersensitivity exists in chronic LBP and is associated with augmented central pain processing,[10,21,34,45] as demonstrated by widespread activation of pain-related regions in the brain.[22] In support of the evidence for early dysfunction of central nociceptive processing in LBP are the findings from Biurrun Manresa et al.[3] that demonstrated spinal cord hyperexcitability in acute LBP using electrophysiological tests (eg, NWR threshold and RRF area) that are more objective than psychophysical QST measures.

Although there is a great deal of evidence for other somatosensory changes that occur in chronic LBP,[49] there are currently no published data about responses to noxious or non-noxious mechanical or thermal stimuli in acute LBP. An exception is a study investigating CPM in acute LBP. As with early stage whiplash, no difference in the CPM response was found in acute LBP patients compared with controls, suggesting that descending inhibitory control may not be affected in the early stages of these conditions. However, several methodological limitations of CPM testing have been recognized by other researchers.[47] For example, the magnitude of the CPM effect can be influenced by factors such as the duration and strength of stimulation, the body region stimulated, and the modality of stimulation.[47] Because there is no standardized approach to evaluate the CPM response, it is possible that the CPM testing was unable to detect these changes if they exist. Impaired pain modulation has been demonstrated by CPM in many other chronic conditions[35] including LBP in a subgroup of patients.[40]

4.4. Risk of bias

Several risk of bias issues were identified that need to be taken into consideration when interpreting these results. There was no blinding of QST assessors in the majority of studies (10 of 14), increasing the risk of reporting and outcome bias. Sampling methods were not reported in most studies assessing whiplash injury; indeed, only 2 studies[30,31] clearly reported consecutive sampling, and 2 other studies[42,58] did not specify the source of healthy controls recruitment. Therefore, selection bias may have

Table 4

Summary of results for each spinal pain condition.

Sensory parameter	Stimulation modality	Duration of pain	Assessment site	Findings (patients group compared with controls group)
Whiplash injury				
Pain detection threshold	Pressure	Acute and subacute	Local, remote, and median nerve	Pain hypersensitivity (acute)[6,17,31,55,56,58]; pain hypersensitivity at local site (subacute)[31,55,56]; pain hypersensitivity in severe pain/disability subgroup at remote site and median nerve (subacute)[55,56]
	Cold	Acute and subacute	Local	Pain hypersensitivity (acute)[6,55,56]; pain hypersensitivity in severe pain/disability subgroup (subacute)[55,56]
	Heat	Acute and subacute	Local	Pain hypersensitivity in severe pain/disability subgroup[56]
Pain tolerance threshold	Pressure	Acute and subacute	Local	Pain hypersensitivity[30,58]
	Cold	Acute and subacute	Remote	Pain hypersensitivity in nonrecovered subgroup[30]
Pain magnitude rating	Pressure	Acute	Local	Pain hypersensitivity (2, 3 wk)[42,58]; no significant difference (4, 6 wk)[42]
NWR threshold	Electrical	Acute and subacute	Remote	Spinal cord hyperexcitability (acute); spinal cord hyperexcitability in severe pain/disability subgroup (subacute)[55]
Detection threshold	Cold	Acute and subacute	Remote	Hypesthesia[6,8]
	Warm	Acute and subacute	Remote	No significant difference (acute)[6]; hypesthesia in high risk of nonrecovery whiplash subgroup (subacute)[8]
	Vibration	Acute and subacute	Remote	Hypesthesia in high risk of nonrecovery subgroup[6,8]
	Electrical	Acute and subacute	Remote (hand and leg)	Hypesthesia (acute)[6]; hypesthesia in high risk of nonrecovery subgroup at the hand (subacute); no significant difference at the leg (subacute)[8]
CPM	Cold bath and pressure	Subacute	Local	No significant difference in CPM response[30]
Idiopathic neck pain				
Pain detection threshold	Pressure	Acute and subacute	Local and remote	No significant difference[28,67]
	Cold	Acute and subacute	Local and remote	No significant difference[28]
	Heat	Acute and subacute	Local and remote	No significant difference[28]
Nonspecific LBP				
Pain detection threshold	Pressure	Subacute	Local and remote	Pain hypersensitivity (local); no significant difference (remote)[15,16]
	Electrical	Acute	Remote	Pain hypersensitivity[3]
Pain tolerance threshold	Pressure	Acute	Remote	Pain hypersensitivity[44]
NWR threshold	Electrical	Acute	Remote	Spinal cord hyperexcitability[3]
RRF area	Electrical	Acute	Remote	Spinal cord hyperexcitability[3]
Temporal summation	Electrical	Acute	Remote	Spinal cord hyperexcitability[3]
CPM	Cold bath and pressure	Acute	Remote	No significant difference in CPM response[44]

CPM, conditioned pain modulation; LBP, low back pain; NWR, nociceptive withdrawal reflex; RRF, reflex receptive field.

inflated effect sizes for whiplash. Factors that can confound QST results were controlled for in 53% of studies. Most commonly, studies adjusted statistical analysis for age, gender, and psychological variables; more stringent criteria were applied in studies on nonspecific LBP, where participants who took medications such as opioids or antidepressants were excluded in 3 of 4 studies. Other relevant factors such as exclusion of conditions known to influence pain threshold (eg, diabetes mellitus) or concomitant pain conditions were rarely reported. This is important because, if these conditions coexist, they could have contributed to sensory alterations attributed to the spinal condition. Finally, although QST protocols were satisfactorily described across studies, indicating a low risk of performance bias, different protocols were used between studies. The effect of such differences in QST techniques on the resulting data is unknown.

4.5. Strengths and limitations

In this systematic review, we carefully adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,[36] including prospective registration of the protocol, development of a thorough search strategy, and formal assessment of the risk of bias. However, we acknowledge some limitations. First, meta-analyses were not planned a priori because we anticipated high heterogeneity of outcome measures. However, we found sufficient availability of comparable data that enabled meta-analyses to be performed. Second, the majority of included studies were conducted on whiplash, and therefore less evidence was available for idiopathic neck pain and nonspecific LBP for which only cross-sectional studies were found. Furthermore, sample sizes were small (<50 participants) for 7 studies, and the other 8 had sample sizes between 50 and 141. It is noted that only 4 studies provided a priori sample size calculations to demonstrate sufficient power to detect statistically significant differences between patient groups and healthy controls.

4.6. Future perspectives

Assessment using multiple sensory modalities[43] should be considered particularly for future LBP and idiopathic neck pain

research, where knowledge gaps persist. To improve the value of somatosensory assessment in future studies, researchers should adopt standardized protocols, blinding of assessors, and better control for variables that are known to influence pain perception. A consensus statement to standardize the physical and psychological measures used would assist progress in this area of research.

5. Conclusions

This systematic review has revealed that pain hypersensitivity potentially involving both peripheral and central mechanisms occurs in the acute stage of whiplash injury and in nonspecific LBP, whereas no alterations in sensory function have been reported in the early stages of idiopathic neck pain. Further longitudinal studies are needed to determine whether early somatosensory changes are mechanistically involved in the development and maintenance of chronic pain.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendices. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A10, http://links.lww.com/PAIN/A11, http://links.lww.com/PAIN/A12, http://links.lww.com/PAIN/A13, and http://links.lww.com/PAIN/A14.

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Chapter 3

A comparison of somatosensory function between acute low back pain and pain-free controls

3.1 Preface

In Chapter 2, it was recognised that the literature investigating somatosensory function in acute and subacute low back pain is sparse, that only limited sensory modalities have been assessed, and that the evidence regarding early somatosensory changes is somewhat conflicting. In Chapter 3, the second aim of the thesis is addressed; a cross-sectional analysis of baseline data from a clinical study was performed to investigate whether somatosensory changes can be detected soon after onset of low back pain compared to pain-free controls using a comprehensive QST protocol.

A paper based on this Chapter is in the final stage of preparation for submission in a journal in the field of pain:

Marcuzzi A., Wrigley P.J., Dean C.M., Graham P.L., Hush J.M. (2016) (in preparation) "Quantitative sensory test responses are similar in acute back pain and pain-free groups, but cold pain sensitivity distinguishes individuals with different pain severity".

3.2 Co-authors' statement

As co-authors of the paper, "Quantitative sensory test responses are similar in acute back pain and pain-free groups, but cold pain sensitivity distinguishes individuals with different pain severity", we confirm that Anna Marcuzzi has made the following contributions to this study:

- Conception and design of the research
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript
- Critical appraisal of the content

Associate Professor Julia Hush _____ Date 5 Dec 2016

Dr Paul Wrigley_____ Date 5 Dec 2016

Professor Catherine Dean _____ Date 5 Dec 2016

Dr Petra Graham _____ Date 5 Dec 2016

3.3 Quantitative sensory test responses are similar in acute back pain and pain-free groups, but cold pain sensitivity distinguishes individuals with different pain severity

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Keywords

Quantitative sensory testing, low back pain, acute pain, cold pain testing, sensory testing

Disclosure

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The authors have no conflicts of interest to declare.

3.3.1 Abstract

Objectives: The aim of this study was to compare QST responses in people with acute LBP and pain-free controls and to investigate whether QST profiles are different between people classified with high versus low back pain intensity. Methods: Twenty-five people with acute LBP (mean: 12 days from onset) and 47 pain-free controls were enrolled in the study. Demographic, clinical and psychological variables were recorded. QST variables measured were: cold and heat pain threshold, wind up ratio, pressure pain threshold, two-point discrimination and cold pressor test responses. Non-parametric Mann-Whitney U tests were used to compare QST responses between the two groups. People with LBP were then stratified based on pain severity into low/moderate and high pain and these subgroups were compared. Results: There were no statistically significant differences in QST responses between acute LBP and pain-free controls groups. People in the high pain subgroup (NRS≥5/10) had a significantly lower cold pain threshold recorded at the hand and higher pain ratings for the cold pressor test compared with the low/moderate pain subgroup. Conclusions: This study suggests that differences in pain sensitivity measured by a wide range of QST variables are not evident at a group level in acute LBP. People with high LBP severity were characterised by higher cold pain sensitivity compared to those with lower LBP. Since abnormal responses to a range of sensory tests are consistently reported in chronic LBP, future longitudinal studies are warranted to further understand the time course of QST responses in LBP.

3.3.2 Introduction

Low back pain (LBP) continues to be the leading cause of global disability (Vos, Flaxman et al. 2013) and remains a significant challenge in clinical management (Machado, Kamper et al. 2009). A better understanding of the mechanisms underpinning the development of persisting pain is advocated, so that targeted treatments can be developed (Woolf, Bennett et al. 1998). During recent decades, quantitative sensory testing (QST) techniques have been employed to provide insight into nociceptive processing in painful conditions (Arendt-Nielsen and Yarnitsky 2009). In chronic LBP, QST studies have demonstrated generalised pain hypersensitivity to various noxious stimuli in people with pain compared with pain-free controls (Flor, Diers et al. 2004, Giesecke, Gracely et al. 2004, O'Neill, Manniche et al. 2007, Corrêa, Costa et al. 2015). Such exaggerated responses in areas unrelated to the site of injury are thought to reflect central sensitisation and/or changes in pain modulation in the central nervous system and may have clinical relevance (Curatolo 2011).

However, there is comparatively little known about the timing of onset of such changes in LBP. Early dysfunction of nociceptive processing has been demonstrated using QST in some cases, although the evidence is sparse and somewhat inconsistent (Marcuzzi, Dean et al. 2015). For example, hyperalgesic responses for pressure pain stimuli have been reported in acute and subacute LBP compared with controls, although the evidence about widespread effects is conflicting (Farasyn and Meeusen 2005, Mlekusch, Neziri et al. 2016). Enlargement of the reflex receptive field (RRF) and reduced nociceptive withdrawal reflex (NWR) thresholds have also been reported using electrophysiological measures that indicate hyperexcitability at the spinal cord in acute LBP (Manresa, Neziri et al. 2013). Others have found no differences in responses to noxious mechanical and thermal stimuli between people with acute LBP and healthy controls (O'Neill, Kjær et al. 2011, Hübscher, Moloney et al. 2014, O'Neill, Manniche et al. 2014).

Therefore, it is still unclear whether changes in pain sensitivity that can be detected with QST are a feature of LBP in the very early stage of the condition when compared with healthy controls. Given the heterogeneity of LBP without specific cause (Artus, van der Windt et al. 2010), it is possible that such changes only occur in particular subgroups of patients. Differential development of pain hypersensitivity in acute pain states has been shown in people with whiplash injury reporting higher levels of pain and disability

(Sterling, Jull et al. 2004). Such knowledge has provided useful clinical tools to estimate individual patient prognosis in whiplash associated disorders (Sterling 2014). Therefore, it is worthwhile investigating whether pain sensitivity can distinguish individuals with different levels of symptom severity in LBP.

The primary aim of this study was to investigate whether changes in pain sensitivity can be identified in the early stages of LBP, by comparing QST responses in people with acute LBP with a pain-free group. A secondary exploratory subgroup analysis was performed to investigate whether QST profiles are different in people with LBP when stratified by pain severity.

3.3.3 Materials and Methods

Study design

This study reports the analysis of baseline data collected for a longitudinal study investigating the time course of somatosensory changes in acute LBP compared with pain-free controls.

Study participants

Twenty-five people with acute LBP and 47 pain-free controls were enrolled in the study. People with LBP were recruited from primary care practices (medical, physiotherapy, chiropractic clinics) and from the local community via advertisements, in the Sydney metropolitan area and were enrolled consecutively. The following inclusion criteria were applied: (1) adults (≥ 18 years old); (2) LBP duration ≤ 3 weeks; (3) average pain intensity during the last week of ≥ 3 on an 11-point numeric rating scale (NRS), with 0 indicating no pain and 10 the worst pain imaginable. Acute LBP was defined as pain and discomfort in the spine, localised below the costal margin and above the inferior gluteal folds with or without leg pain (Van Tulder, Becker et al. 2006). Symptoms were required to last more than 24 hours but less than 3 weeks and be preceded by a pain-free period of at least 1 month. Participants were excluded if they had possible serious spinal pathology (i.e. spinal fracture or malignancy) based on the presence of red flags (Downie, Williams et al. 2013), previous back surgery, pregnancy, any pain condition that has lasted for longer than one month over the last year affecting daily function and work ability, diabetes mellitus, diagnosed co-morbid pain syndrome (e.g. fibromyalgia, osteoarthritis, irritable bowel syndrome), diagnosed neurological disease, unstable psychiatric disorder or psychosis, severe cognitive impairment (arising

from head injury or other comorbidities), substance abuse problem in the past 24 months, long term use of medications that may impact on cognitive or sensory function (e.g. opiates intake greater than daily morphine equivalent 40mg), unable to read, write and understand English. Participants were allowed to continue their usual care for LBP and medications and/or treatments received were recorded. Pain-free participants were recruited from the local community via advertisements. The recruitment of pain-free participants was conducted to match the age and gender of acute LBP cohort, where possible. The exclusion criteria for the control group were the same as the LBP group plus any pain at time of testing. The study protocol was approved by the Human Research Ethics Committee at Macquarie University (Approval Reference No. 5201400840) and all participants gave written informed consent.

Descriptive variables

Demographic information collected included gender, age, body mass index (BMI), ethnicity and work status. People with LBP provided the following clinical information: LBP duration, LBP distribution, pain intensity at time of testing, average pain intensity and worst level of pain over the last week (or few days) scored from 0 (no pain) to 10 (the worst possible pain) on an 11 point Numeric Rating Scale (NRS11), level of function measured by the Functional Rating Index (FRI) scored from 0 (high functional level) to 40 (low functional level) (Feise and Menke 2001), disability level measured by the Roland Morris Disability Questionnaire (RMDQ) scored from 0 (no disability) to 24 (high disability) (Roland and Morris 1983) and the extent of self-rated recovery measured with the Back Pain Recovery Scale (BPRS), scored on a Likert scale from -5 (very much worse) to +5 (completely recovered) (Hush, Kamper et al. 2012).

All participants completed the following questionnaires: Depression, Anxiety and Stress Scale (DASS-21) scored from 0 (not at all) to 42 (extremely) (Lovibond and Lovibond 1995), Pain Catastrophizing Scale (PCS) scored from 0 (not at all) to 52 (all the time) (Sullivan, Bishop et al. 1995). Participants with LBP also completed the Pain Self-Efficacy Questionnaire (PSEQ) scored from 0 (not at all confident) to 60 (completely confident) (Nicholas 2007), the Short-form McGill Pain questionnaire (SF-MPQ) to measure the sensory and emotional/affective dimensions of pain (Melzack 1987) and the PainDETECT questionnaire to screen for neuropathic features of LBP (Freynhagen, Baron et al. 2006).

Quantitative sensory testing (QST) protocol

A rigorous protocol was followed for all QST testing. Participants were asked to limit the intake of caffeinated drinks and alcohol beverages as well as refrain from taking sleeping medications 24 hours before testing. Tests were conducted in a quiet room maintained at a constant temperature (23±1°C) in the following order: cold and heat pain thresholds (CPT, HPT), mechanical wind up ratio (WUR), pressure pain threshold (PPT) two-point discrimination (TPD) and the cold pressor test. All participants initially underwent a training session to be familiarised with the testing procedure. CPT, HPT, WUR, PPT were performed according to the QST protocol of the German Research Network on Neuropathic Pain (DFNS) (Rolke, Magerl et al. 2006). Measurements were taken at 3 body sites: bilaterally at the back and at the dorsum of the left hand (except for PPT, which was tested at the thenar eminence). For people with LBP, the testing site at the back was in the area of maximal pain, nominated by participants and the level confirmed through palpation by an experienced physiotherapist. A random level at the back (from T12 to S1) was chosen for pain-free controls. Previous investigations have shown no significant differences in QST responses at different levels of the spine in healthy controls subjects (Pfau, Krumova et al. 2014). A DFNS-certified researcher (AM) performed all tests blinded to participants' LBP or pain-free control status.

Thermal pain thresholds

Cold and heat pain thresholds (CPT, HPT) were measured using a 30x30mm ATS thermode (PATHWAY, MEDOC, Ramat Yishai, Israel). The temperature was decreased or increased at a ramp rate of 1°C/s starting at a baseline temperature of 32°C until participants pressed a button to indicate detection of the threshold. The final threshold was calculated as the mean value of 3 consecutive measurements.

Wind up ratio

Wind up ratio (WUR) was measured by comparing the perceived pain severity from a single pinprick stimulus (256 mN, MRC System GmbH, Heidelberg, Germany) with that of a series of 10 pinprick stimuli of the same force, delivered at 1/s rate within an area of 1 cm^2. The subject was instructed to give a pain rating for the single stimulus and at the end of the 10 stimulus series using a 101 point Numeric Rating Scale (NRS101). This procedure was repeated 5 times at different skin sites within the testing area. If a pain rating of 0 was reported more than 3 times for the single stimulus the WUR could not be calculated and these results were reported as missing values. The

final WUR was calculated as the mean pain rating of 5 series of repeated pinprick stimulation divided by the mean pain rating of 5 single stimuli.

Pressure pain threshold

The pressure pain threshold (PPT) was measured using a pressure algometer (FDK40, Wagner Instrument, Greenwich, CT, USA) with a probe area of 1 cm^2. The pressure was gradually increased at a ramp rate of 50 kPa/s and the participants were instructed to verbally stop the test when the sensation of pressure alone changed to one of pressure and pain. The final threshold was calculated as the mean value of 3 consecutive measurements.

Two-point discrimination threshold

The two-point discrimination threshold (TPD) was measured according to established protocol (Moberg 1990) using a stainless steel digital calliper ruler (150 mm Vernier Calliper, Kincrome). The calliper was applied at the L3 level for all participants, perpendicular to the back surface, until the first blanching of the skin. An ascending series was performed starting from 0 mm distance between the two tips and increasing the distance by 2 mm until the participant was able to perceive two points instead of one. Similarly, a descending series was applied where the distance was decreased by 2 mm until one point instead of two was felt. The participants were asked to report that they felt one point if there were unsure. A conservative approach was used whereby the TPD value of each run (ascending or descending) was recorded only when a consistent response was obtained for three consecutive stimuli. For example, if in the ascending series two points were first felt at 40 mm, then the distance was increased by 2 mm up to 44 mm and the threshold recorded as 40 mm only if successive trials were confirmed as two points. Otherwise, the stimulus was repeated starting from 40 mm until consistency was obtained. The final threshold was calculated as the mean value of two ascending and two descending runs.

Cold pressor test

The cold pressor test consisted of immersion of the non-dominant foot in a cold water bath maintained at 10.5±1 °C for 90 seconds. The bath consisted of a container divided into two by a perforated perspex sheet. One chamber was filled with ice and water that was stirred to maintain the other chamber at a constant temperature and continuously monitored by a thermometer with a digital display. Participants were instructed to

immerse their foot in the water up to the ankle without touching the sides or bottom of the bath. They could withdraw the foot from the cold bath if the pain became intolerable. The time the foot was kept in the water was recorded. The pain rating from the cold water stimulus was recorded at 30, 60 and 90 seconds using the NRS101 scale. If the foot was withdrawn from the water before 90 seconds, a pain rating of 100 on the NRS101 scale was assigned to subsequent ratings.

Data analysis

Sample size calculation

The sample size calculation for this cross-sectional analysis was based on the expected difference in conditioned pain modulation (CPM) responses between acute LBP and pain-free controls. CPM results have been reported separately (Marcuzzi A, Wrigley PJ, Dean CM et al., unpublished data, 2016). The CPM measure was considered to have the highest variability among the QST variables assessed (Olesen, van Goor et al. 2012, Nahman-Averbuch, Yarnitsky et al. 2013, Pfau, Krumova et al. 2014). This calculation was based on previous published research on CPM (using PPT as test stimulus) in LBP (Corrêa, Costa et al. 2015, Mlekusch, Neziri et al. 2016) indicating that a minimum of 25 people per group (acute LBP and pain-free controls) would achieve 80% power using a 5% significance level to find a CPM between-group difference of 130 kPa with a standard deviation of 150 kPa.

Statistical analysis

Data were analysed using SPSS statistics 22.0 software. Between groups differences in demographic, psychological and QST variables were compared using the Mann-Whitney U Test. Categorical variables were compared using chi-squared tests of association. For the QST variables tested at the back, it was decided *a priori* that only the values of the affected side of people reporting unilateral LBP would be used in the analysis while for people with bilateral (or central) LBP and for pain-free controls the average values of the left and right sides would be used. For the cold pressor test, group comparisons were made using repeated measure analysis of variance (ANOVA) with a within group factor of Time (3 levels: 30, 60 and 90 sec) and a between group factor of Condition (2 levels: LBP, controls). The LBP group was then stratified into two groups based on the average pain severity score (NRS11), where ≥5/10 NRS was classified as high pain and <5/10 NRS was classified as low/moderate pain. Previous research has

identified the cut point of 5/10 NRS as clinically relevant in LBP (Jensen, Smith et al. 2001). Group differences between demographic/clinical and QST variables between LBP subgroups were further analysed as described above. Due to the exploratory nature of this analysis a significance level of α=0.05 was chosen.

3.3.4 Results

A total of 246 individuals were screened for the study. Of 98 potentially eligible participants (41 with LBP and 57 controls), 73 (25 with LBP and 48 controls) provided consent to participate and were enrolled in the study. One pain-free participant withdrew during testing and was therefore excluded from this analysis. Despite all efforts to maintain blinding, this was not possible for 17 of the 72 participants (7 LBP and 10 pain-free controls) due to scheduling issues. The majority (88%) of LBP participants were enrolled from the community. Eight participants (32%) with LBP received treatments such as physiotherapy, massage and chiropractic for their LBP and four (16%) took simple non-opioid analgesics during the 24 hours prior to testing.

Summary statistics for both groups are reported in Table 1. Demographic variables did not differ between groups with the exception of BMI, which was significantly higher in the LBP group ($p=0.011$). The proportion of people who had previous LBP episodes differed significantly between the two groups ($p<0.001$), being nearly 90% for the LBP group and 40% for the pain-free controls. Although people with LBP reported significantly higher levels of anxiety compared with pain-free controls ($p=0.008$), psychological profiles were in the normal range in both groups.

Table 1 Demographic and psychological characteristics of low back pain and pain-free control groups

	Low back pain N=25	**Pain free controls** N=47
Female, n (%)	13 (52.0)	24 (51.1)
Age, years	30.6 (11.9)	30.0 (9.8)
BMI, Kg/m^2	24.3 (2.7)*	23.2 (5.9)*
Smoking, n (%)	1 (4.0)	2 (4.2)
Race, n (%)		
White/Caucasian	15 (60.0)	27 (57.4)
Asian	6 (24.0)	15 (31.3)
Other	4 (16.0)	5 (10.4)
Current work status, n (%)		
Student	15 (60.0)	28 (60.0)
Employed	9 (36.0)	17 (35.4)
Other	1 (4.0)	2 (4.2)
Previous LBP episodes, n (%)	22 (88.0)*	18 (38.3)*
Stress, DASS-21 (0-42 score)	10.6 (9.0)	6.6 (5.8)
Anxiety, DASS-21 (0-42 score)	6.6 (7.0)*	2.9 (3.6)*
Depression, DASS-21 (0-42 score)	6.7 (8.4)	3.0 (3.6)
Pain catastrophizing, PCS (0-52 score)	11.3 (8.9)	8.7 (7.7)
Pain self-efficacy, PSEQ (0-60 score)	45.3 (15.3)	NA

All values are presented as mean (SD), unless otherwise specified. BMI: body mass index; DASS-21: Depression, Anxiety and Stress scale; PCS: Pain Catastrophizing Scale; PSEQ: Pain Self-Efficacy Questionnaire. *$p<0.01$

Clinical characteristics of the LBP group are reported in Table 2. On average, people with LBP were assessed as early as 12 days from the onset of LBP. The FRI and RMDQ scores revealed that, overall, people with LBP were a high functioning group with a low level of disability. None of the LBP participants had a pain distribution consistent with nerve root compromise or sciatica.

Table 2 Clinical and pain-related characteristics of the LBP group

Characteristics	
Pain duration, days	11.7 (6.2)
Pain distribution, n (%)	
Unilateral	12 (48)
Bilateral	8 (32)
Central	5 (20)
Medication intake, n (%)	4 (16)
Current pain intensity, NRS (0-10 score)	4.0 (1.8)
Highest pain intensity, NRS (0-10 score)	7.3 (1.7)
Average pain intensity, NRS (0-10 score)	4.4 (1.5)
Function, FRI (0-40 score)	14.4 (6.4)
Disability, RMDQ (0-24 score)	5.9 (4.4)
Recovery, BPRS (-5-+5 score)	0.7 (2.1)
Pain Descriptors, SF-MPQ	
Sensory (0-33 score)	8.8 (4.6)
Affective/emotional (0-12 score)	1.7 (1.8)
Neuropathic screening, PainDETECT, n (%)	
Nociceptive (0-12 score)	21 (84)
Unclear (13-18 score)	3 (12)
Neuropathic (19-38 score)	1 (4)

All values are presented as mean (SD), unless otherwise specified. NRS: Numeric Rating Scale; FRI: Functional Rating Index; RMDQ: Roland Morris Disability Questionnaire; BPRS: Back Pain Recovery Scale; SF-MPQ: Short-Form McGill Pain Questionnaire.

Regarding the QST responses, none of the variables assessed were significantly different between people with acute LBP and pain-free controls (all $p>0.05$) including thermal and mechanical pain threshold, wind up ratio and two-point discrimination (Table 3).

Table 3 Comparisons of QST variables between low back pain and pain-free controls groups

	Low back pain N=25	**Pain-free controls** N=47	**P value**
CPT hand, °C	9.2 (3.2-18.5)	9.2 (1.0-18.8)	0.882
CPT back, °C	20.0 (0.1-24.9)	11.6 (0.0-21.7)	0.176
HPT hand, °C	43.4 (41.2-44.1)	43.9 (40.0-45.9)	0.425
HPT back, °C	42.6 (39.7-43.8)	43.4 (40.3-45.2)	0.421
WUR hand, ratio	1.6 (1.3-2.0)	1.4 (1.2-1.8)	0.313
WUR back, ratio	1.9 (1.4-2.5)	1.8 (1.3-2.5)	0.814
PPT hand, kPa	400.0 (325.0-505.0)	393.3 (316.7-503.3)	0.636
PPT back, kPa	518.3 (375.0-716.7)	480.0 (413.3-595.0)	0.813
TPD back, mm	62.7 (55.0-70.3)	60.0 (53.0-71.0)	0.414

All values are presented as median (lower quartile, upper quartile). CPT: cold pain threshold; HPT: heat pain threshold; WUR: wind up ratio; PPT: pressure pain threshold; TPD: two-point discrimination.

For the cold pressor test, the ANOVA analysis showed a significant effect for Time ($p<0.001$) indicating that the pain rating for the cold stimulus increased over time, but there was no significant effects for Condition (LBP or pain-free controls) ($p=0.65$) or for the interaction between Time and Condition ($p=0.33$) (Table 4).

Table 4 Repeated measure analysis of variance (RM-ANOVA) for cold pressor pain between low back pain and pain-free controls

Cold pressor pain (NRS101)	**Low back pain** N=25	**Pain-free controls** N=47	Main effects		Interaction
			Time	Condition	Time*Condition
30 seconds	51.4 (42.6-60.2)	50.0 (42.2-57.7)			
60 seconds	65.8 (56.5-70.0)	60.7 (53.0-68.3)	P<0.001‡	P=0.65	P=0.33
90 seconds	67.2 (57.1-77.3)	65.7 (58.4-73.0)			

Values are reported as mean (95% CI) unless otherwise specified. NRS: Numeric Rating Scale. ‡p<0.01

When the acute LBP group was stratified according to pain severity, some differences in QST responses were identified (Table 5). The high pain subgroup (n=10, mean age (SD): 27 (9) years; females (%): 5 (50%)) had significantly higher CPT at the hand ($p=0.048$) compared with the low/moderate pain subgroup (n=15, mean age (SD): 33 (13) years; females (%): 8 (53%)), but no significant difference was found at the back ($p=0.495$). There were no significant differences between subgroup for HPT at either site (all $p>0.846$). Regarding the mechanical QST variables, no significant differences were found between LBP subgroups for WUR and PPT at either site (all $p>0.06$) (Table 5).

Table 5 Comparisons of QST variables between LBP subgroups

	High pain N=10	**Low/moderate pain** N=15	**P value**
CPT hand, °C	16.1 (9.5-19.1)	6.5 (1.0-10.8)	0.048*
CPT back, °C	20.4 (10.2-24.7)	15.0 (0.0-25.5)	0.468
HPT hand, °C	43.2 (41.4-44.3)	43.4 (41.2-44.1)	0.846
HPT back, °C	42.2 (39.8-43.7)	43.2 (39.5-44.0)	0.890
WUR hand, ratio	1.3 (1.2-1.8)	1.7 (1.3-2.1)	0.221
WUR back, ratio	1.9 (1.6-2.2)	2.0 (1.3-3.3)	0.815
PPT hand, kPa	370.0 (188.3-577.5)	416.7 (336.7-483.3)	0.375
PPT back, kPa	396.7 (284.6-562.1)	588.3 (416.7-760)	0.059
TPD back, mm	58.1 (52.2-77.6)	65.0 (59.0-69.0)	0.331

All values are presented as median (lower quartile, upper quartile). High pain: individuals with LBP presenting with average pain intensity ≥5/10 NRS; Low/moderate pain: individuals with LBP presenting with average pain intensity <5/10 NRS; CPT: cold pain threshold; HPT: heat pain threshold; WUR: wind up ratio; PPT: pressure pain threshold; TPD: two-point discrimination. *p<0.05

For the cold pressor test, the ANOVA analysis showed a significant effect for Time ($p<0.001$) indicating that the pain rating for the cold stimulus increased over time and a significant effect for Condition (high pain or low/moderate pain) ($p=0.02$), but no significant effect for the interaction between Time and Condition ($p=0.64$). The high pain subgroup reported significantly higher pain severity rating during the cold pressor test compared to the low/moderate subgroup (Table 6 and Figure 1).

Table 6 Repeated measure analysis of variance (RM-ANOVA) for cold pressor pain between LBP subgroups

Cold pressor pain (NRS101)	**High pain** N=10	**Low/moderate pain** N=15	Main effects		Interaction
			Time	Condition	Time*Condition
30 seconds	62.5 (46.3-78.7)	44.0 (34.3-53.7)			
60 seconds	76.5 (63.1-90.0)	58.6 (46.1-71.2)	P<0.001‡	P=0.02*	P=0.64
90 seconds	80.5 (68.7-92.3)	58.3 (44.4-72.3)			

Values are reported as mean (95% CI) unless otherwise specified. NRS: Numeric Rating Scale. *p<0.05; ‡p<0.01

Demographic features of the two LBP subgroups were similar, although participants in the "high pain" subgroup had a significantly higher level of pain catastrophizing ($p=0.004$) and a lower level of pain self-efficacy ($p=0.010$) compared with the low/moderate pain subgroup.

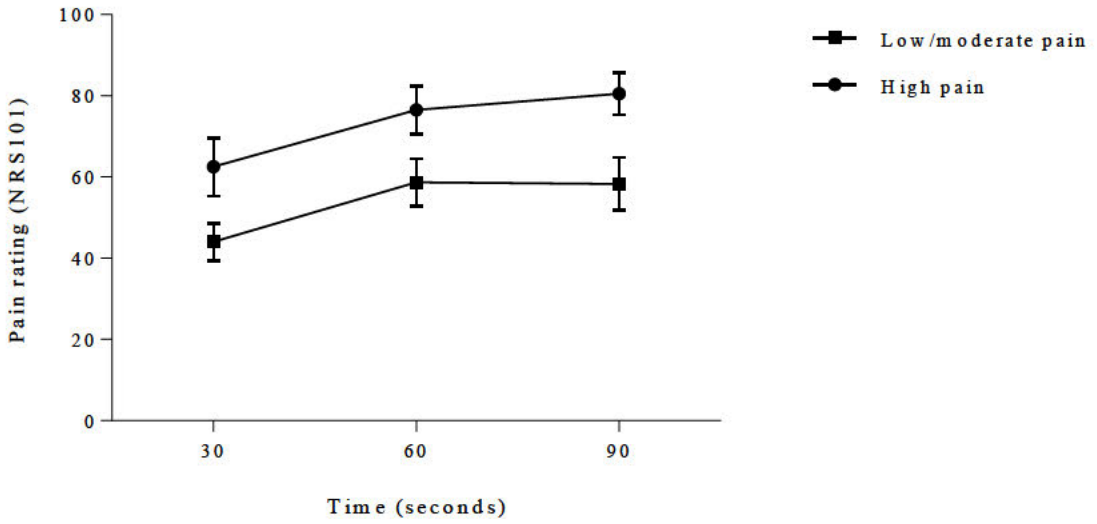

Figure 1 Pain rating for the cold pressor test (mean ±SE) at 30, 60 and 90 seconds in high pain and low/moderate pain groups

3.3.5 Discussion

Summary of main findings

This study investigated a wide range of QST variables in people with LBP as early as 3 weeks from onset and compared their responses to pain-free controls. At the group level, there were no differences in the QST responses between acute LBP and pain-free controls. When stratifying LBP participants according to their pain severity, people with higher levels of LBP symptoms were associated with significantly higher cold pain sensitivity compared to those reporting lower LBP.

Comparisons with other studies assessing QST in acute LBP and healthy controls

This is the first study to use a comprehensive QST protocol that encompasses both static and dynamic tests to evaluate somatosensory changes in acute LBP. A small number of previous studies have reported selected QST responses in people with recent onset of LBP, but the results have been inconsistent (Marcuzzi, Dean et al. 2015). Pressure pain testing was found to be unchanged at the back (O'Neill, Manniche et al. 2014) and at an unrelated site (O'Neill, Kjær et al. 2011) in acute LBP compared to healthy controls, which aligns with our results. Interestingly, localised, but not widespread, pressure pain hypersensitivity has been shown at the later subacute stage of LBP (Farasyn and Meeusen 2005, Farasyn and Meeusen 2007) which may reflect changes in pain processing that develop over time. However, responses to *suprathreshold* pressure pain stimuli might be able to better discriminate between acute LBP and pain-free controls as has been reported elsewhere (O'Neill, Manniche et al. 2014, Mlekusch, Neziri et al. 2016). Our results confirm two previous reports of unchanged cold and heat pain threshold and suprathreshold responses in acute LBP (Hübscher, Moloney et al. 2014, O'Neill, Manniche et al. 2014). These latter studies both found evidence of enhanced generalised cold pain sensitivity in subsamples of chronic LBP, compared with healthy controls. Taken together, this evidence suggests that localised pain hypersensitivity at a group level may be detected at the subacute stage of LBP but widespread effects become evident in people with longer LBP duration (Giesecke, Gracely et al. 2004, Giesbrecht and Battié 2005, O'Neill, Manniche et al. 2007, Blumenstiel, Gerhardt et al. 2011, Corrêa, Costa et al. 2015).

Dynamic QST measures of temporal summation and conditioned pain modulation (CPM) provide insight into pain modulation processing and are thought to better relate

to the clinical experience of pain, than pain thresholds testing (Yarnitsky, Granot et al. 2014). Enhanced temporal summation (Peters, Schmidt et al. 1989, Kleinböhl, Hölzl et al. 1999) as well as reduced CPM efficiency (Corrêa, Costa et al. 2015, Rabey, Poon et al. 2015) have been reported in chronic LBP. In a previous analysis we showed that the CPM effect is preserved in acute LBP (Marcuzzi A, Wrigley PJ, Dean CM et al., unpublished data, 2016), confirming previous reports on LBP at this early stage (O'Neill, Manniche et al. 2014, Vlckova, Srotova et al. 2014, Mlekusch, Neziri et al. 2016). As with the pressure pain threshold results, it may be that central pain modulation becomes less efficient as pain persists; however, longitudinal studies are required to test this hypothesis. Regarding temporal summation our finding of no difference between acute LBP and controls, supports the previous study by Hübscher et al. even though different test stimulus modalities (mechanical and thermal respectively), were used (Hübscher, Moloney et al. 2014). In contrast, Manresa et al. showed significantly higher temporal summation in people with acute LBP compared to controls as well as enlarged reflex receptive fields (RRF) using electrophysiological pain tests, which suggests an augmented spinal excitability in this early time frame (Manresa, Neziri et al. 2013). It is unclear whether these conflicting findings are due to different test stimulus modalities (Neziri, Curatolo et al. 2012), differences in samples or the fact that different mechanisms are tested (for example, the spinal reflex arc in the latter study) (Neziri, Curatolo et al. 2011). In this respect, agreeing upon standards for the multiple stimuli used will be important to compare findings and improve our understanding of the changes occurring in the somatosensory nervous system over time in this condition.

QST findings in LBP subgroups

Our exploratory secondary analysis in which people with acute LBP were stratified according to their pain severity, showed that those reporting higher pain severity were associated with significantly higher cold pain sensitivity measured by CPT at the hand and by the cold pressor test at the foot, compared with those reporting mild pain. Surprisingly, differences in CPT were not detected locally at the back. One possible explanation of this might be the higher variability of CPT measurements when performed at the back (Marcuzzi A, Wrigley PJ, Dean CM et al., unpublished data, 2016, Pfau, Krumova et al. 2014) as indicated by wider interquartile ranges in Table 3. Hubscher et al found a trend towards increased CPT at the forearm in acute LBP

compared to controls, although the difference was not statistically significant at a whole group comparison level, and subgroup analyses were not performed (Hübscher, Moloney et al. 2014). If confirmed, differences in cold pain sensitivity between LBP subgroups could be of prognostic utility. Indeed, cold pain hypersensitivity has been shown to be associated with poor prognosis in other musculoskeletal conditions (Kasch, Qerama et al. 2005, Sterling, Jull et al. 2005, Coombes, Bisset et al. 2015). In 157 people with acute LBP, QST responses including cold pressor test were not found to be significant predictors of persistent pain at 4 months (LeResche, Turner et al. 2013). However, CPT was not tested in this latter study.

In the current study, people in the high pain subgroup also reported significantly higher level of pain catastrophizing compared to the low/moderate pain subgroup. It is known that catastrophic thinking contributes to clinical pain and it has shown to be associated with persistent pain (Sullivan, Bishop et al. 1995). Further, a positive correlation between pain catastrophizing scores and cold pain sensitivity has been reported in whiplash injury (Sterling, Hodkinson et al. 2008, Rivest, Côté et al. 2010, Wallin, Liedberg et al. 2012). Therefore, it cannot be excluded that the differences we found in cold pain testing could be related to differences in psychological profiles between subgroups. Nonetheless, in the Hubscher et al. study, CPT at the forearm was a significant independent predictor that explained 8% of the variance for membership of the chronic LBP group after controlling for DASS-21 and PCS scores (Hübscher, Moloney et al. 2014). Notably, the PCS scores of those in the high pain subgroup in this study, are similar to the scores reported in the chronic LBP sample of Hubscher et al. (mean and SD: 17.0 (7.7) and 15.6 (9.9), respectively). Ongoing examination of psychological features is therefore warranted in future psychophysical studies to better understand their contribution to pain sensitisation in this condition.

Strengths and limitations

The first strength of this study is that we applied a protocol encompassing a wide range of QST variables, using established protocols. The second design strength was that we addressed a common limitation of QST studies: the lack of assessor blinding (Marcuzzi, Dean et al. 2015). We limited this bias by blinding the assessor (A.M.) to participant group. Further, in order to minimise variability, the same rigorous protocol was used for assessment of all participants (i.e. positioning, testing sites, room temperature, standardised instructions).

The following limitations need to be taken into consideration when interpreting these results. Firstly, we included people with acute LBP (≤ 3 weeks) preceded by a pain-free period of at least one month (De Vet, Heymans et al. 2002). Since LBP is understood to be a recurrent condition (Stanton, Henschke et al. 2008), those with previous episodes of LBP were not excluded to ensure generalisability of results. Indeed around 90% of people with LBP reported previous episodes. However, to minimise confounding by existing changes in somatosensory function from long-standing previous LBP, we excluded those who had a significant pain condition (including LBP) lasting for at least one month during the past year. Further, we did not apply any restriction regarding having had previous episodes of LBP in pain-free controls. Indeed, 40% of controls reported previous LBP, although more than a year ago for approximately half of this group. It is unclear whether more stringent criteria regarding previous LBP would have led to different results in particular for QST measured at the back. Secondly, pain severity levels reported in our LBP sample, together with the low disability and the normal psychological profiles, reflect a high functioning group more representative of a community sample (Vasseljen, Woodhouse et al. 2013). Therefore, these findings might be more generalisable to people not seeking care for their LBP. Thirdly, we based our sample size on the expected group difference of the CPM test, and therefore may be underpowered to detect differences between the two groups for other QST variables. Lastly, because multiple comparisons were made, caution should be taken when interpreting the subgroup analyses which, as stated, were exploratory.

3.3.6 Conclusion

This study shows that changes in pain sensitivity measured by a wide range of QST variables are not evident at a group level in LBP within the first 3 weeks of onset. However, those with high LBP severity were characterised by higher cold pain sensitivity compared to those with lower pain severity. Further investigation of the value of identifying cold pain sensitisation in this population is warranted. Finally, since abnormal responses to a range of sensory tests are consistently reported in chronic LBP, future longitudinal studies will be useful to further understand the time course of such changes in LBP.

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Chapter 4

Conditioned pain modulation in acute low back pain and pain-free controls: a comparison using two test paradigms

4.1 Preface

The cross-sectional analysis reported in Chapter 3 is extended in Chapter 4 to address the third aim of the thesis: to assess whether CPM is impaired in acute low back pain compared to pain-free individuals, and to address methodological issues regarding CPM testing.

A paper based on this Chapter is in the final stage of preparation for submission in a journal in the field of pain:

Marcuzzi A., Wrigley P.J., Dean C.M., Graham P.L., Hush J.M. (2016) (in preparation) "Conditioned pain modulation is preserved in acute low back pain: a cross-sectional analysis using two test paradigms".

4.2 Co-authors' statement

As co-authors of the paper, "Conditioned pain modulation is preserved in acute low back pain: a cross-sectional analysis using two test paradigms", we confirm that Anna Marcuzzi has made the following contributions to this study:

- Conception and design of the research
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript
- Critical appraisal of the content

Associate Professor Julia Hush _____ Date 5 Dec 2016

Dr Paul Wrigley_____ Date 5 Dec 2016

Professor Catherine Dean _____ Date 5 Dec 2016

Dr Petra Graham _____ Date 5 Dec 2016

4.3 Conditioned pain modulation efficiency is preserved in acute low back pain: a cross-sectional analysis using two test paradigms

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Keywords

Conditioned pain modulation; pain inhibition; sensory testing; acute pain; low back pain

Disclosure

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Conflict of interest: the authors have no conflicts of interest to declare.

4.3.1 Abstract

Objective: Endogenous pain inhibition can be measured experimentally using the conditioned pain modulation (CPM) test paradigm. Less efficient CPM has been shown in many chronic pain conditions. In low back pain (LBP) there are conflicting reports about dysfunction of CPM and little is known about how early changes in CPM might occur. Methodological issues might also contribute to the variability in CPM results. The aim of this study was to compare the CPM effect using two different test stimuli in people with acute LBP and pain-free controls. Design: Twenty-five people with acute LBP and 37 pain-free controls who were recruited consecutively underwent CPM testing. The test stimuli used were suprathreshold heat pain and pressure pain threshold (PPT) while the conditioning stimulus was a cold bath. Results: People with LBP displayed a significant CPM effect that was no different from the control group. No correlation was observed between CPM responses for the two test stimuli used. Conclusions: This study shows that endogenous pain modulation is not impaired in the acute stage of LBP. The lack of correlation between results using the two test stimuli further emphasises that methodological differences in CPM protocols are important and reinforces the use of multiple test stimuli to improve our understanding of CPM responses.

4.3.2 Introduction

The conditioned pain modulation (CPM) test paradigm is used experimentally to assess the efficacy of the endogenous pain modulatory system. CPM occurs when the nociceptive response of a test stimulus is inhibited by a painful conditioning stimulus applied remotely. Less efficient CPM has been demonstrated in various chronic pain conditions (see Lewis et al (Lewis, Rice et al. 2012) for review) including musculoskeletal conditions such as whiplash injury (Daenen, Nijs et al. 2013) and knee pain (Rathleff, Petersen et al. 2016), suggesting that altered function of endogenous pain inhibition might be relevant in the pathogenesis of these conditions. CPM has more recently been investigated in low back pain (LBP) but the results are conflicting: CPM efficiency has been reported as reduced in two studies (Correa, Costa et al. 2015, Rabey, Poon et al. 2015), but unchanged in others (Julien, Goffaux et al. 2005, Vlckova, Srotova et al. 2014, Mlekusch, Neziri et al. 2016). In addition, there is limited information on how early deficiencies in CPM are detectable. One study assessing CPM in acute LBP (< 4 weeks) (Mlekusch, Neziri et al. 2016) demonstrated longer lasting pain inhibition from the conditioning stimulus in healthy controls compared with those in the back pain group. However, further research is required to definitively establish the characteristics of changes in the CPM response in this early time frame.

One major challenge in this area of research is the methodological variability of CPM protocols reported in the literature. A wide range of stimuli (thermal, mechanical and electrical), measurement endpoints (e.g. perception thresholds, suprathreshold pain ratings), duration of stimuli, temporal sequences (parallel vs sequential), assessment sites and measures (neurophysiological vs perceptual) have been described (Pud, Granovsky et al. 2009). In response, consensus recommendations have recently been made regarding CPM testing, with the aim of improving standardisation of CPM protocols (Yarnitsky, Bouhassira et al. 2015). Two key recommendations were to use more than one test stimulus, and to employ well defined endpoints (Yarnitsky, Bouhassira et al. 2015).

The aims of this study were: 1) to quantify and compare the CPM effect using two different test paradigms in people with acute LBP and pain-free controls and 2) to analyse the relationship between CPM responses for the two test paradigms used.

4.3.3 Methods

Study design

This was a cross-sectional analysis of CPM responses comparing two samples: acute LBP and pain-free controls.

Participants

Twenty-five patients with acute LBP were recruited consecutively from primary care practices (medical, physiotherapy, chiropractic clinics) and from the local community via advertisements in the Sydney metropolitan area between February 2015 and March 2016. An *acute* episode of LBP was defined as pain and discomfort, localised below the costal margin and above the inferior gluteal folds with or without leg pain (Van Tulder, Becker et al. 2006) lasting more than 24 hours but less than 3 weeks preceded by a pain-free period of at least 1 month. The inclusion criteria were: 1) adults ≥ 18 years old; 2) LBP duration less than 3 weeks; 3) average pain intensity over the last week of at least 3 on an 11-point numeric rating scale (NRS11, where 0 indicates no pain and 10 the worst pain imaginable). Subjects were excluded if they: 1) had possible serious spinal pathology (i.e. spinal fracture or malignancy) based on the presence of red flags; (Downie, Williams et al. 2013) 2) previous back surgery; 3) pregnancy; 4) any pain condition that had lasted for longer than one month over the last year affecting daily function and work ability; 5) diabetes mellitus; 6) diagnosed co-morbid pain syndrome (e.g. fibromyalgia, osteoarthritis, irritable bowel syndrome); 7) diagnosed neurological disease; 8) unstable psychiatric disorder or psychosis or severe cognitive impairment (arising from head injury or other comorbidities); 9) substance abuse problem in the past 24 months or long term use of medications that may impact on cognitive or sensory function (e.g. opiates intake greater than daily oral morphine equivalent 40mg); or 10) if they were unable to read, write and understand English. Participants were allowed to continue their usual care for LBP and medications and/or treatments received were recorded. The control group consisted of 47 pain-free participants recruited consecutively from the local community via advertisements. The recruitment of pain-free participants was conducted to match the age and gender of acute LBP cohort, where possible. The exclusion criteria for control subjects were the same as the LBP group plus any pain at time of testing. The study protocol was approved by the Human Research Ethics Committee at Macquarie University (Approval Reference No. 5201400840). All participants gave written informed consent.

Descriptive variables

Demographic and clinical variables measured were: age, gender, BMI, LBP duration, pain intensity at time of testing and average pain intensity over the last week scored from 0 (no pain) to 10 (the worst possible pain) on an 11 point Numeric Rating Scale (NRS11). Participants also completed the following questionnaires: 24 point Roland Morris Disability Questionnaire (RMDQ, (Roland and Morris 1983)) scored from 0 (no disability) to 24 (high disability), Depression, Anxiety and Stress Subscales (DASS-21,(Lovibond and Lovibond 1995)) scored from 0 (not at all) to 42 (extremely), Pain Catastrophizing Scale (PCS, (Sullivan, Bishop et al. 1995)) scored from 0 (not at all) to 52 (all the time), and the PainDETECT questionnaire to screen for neuropathic features of LBP including potential nerve root compromise (Freynhagen, Baron et al. 2006). Demographic and clinical information as well as questionnaires responses were collected by a trained research assistant.

CPM protocol

Another researcher (AM) performed CPM testing blinded to participants' LBP or pain-free control status. Despite all efforts to maintain blinding, this was not possible for 17 of the 72 participants (7 LBP and 10 pain-free controls) due to scheduling issues. Tests were conducted using a standardised protocol in a room maintained at a constant temperature. Participants were asked to limit the intake of caffeinated drinks and alcohol beverages as well as refrain from taking sleeping medications 24 hours before testing. Standardised instructions were used throughout CPM assessment.

Conditioned pain modulation (CPM) was performed using two test stimuli (TS): one thermal and one mechanical. The thermal test stimulus involved 30-seconds of heat (ATS thermode 30x30 mm PATHWAY, MEDOC, Israel) delivered to the volar aspect of the non-dominant forearm. The intensity of the heat stimulus was determined individually based on the temperature that induced a pain score of 60 (*pain60*) on a 0-100 numeric rating scale (NRS101). *Pain60* was determined from a series of increasing or decreasing 30 second heat stimuli starting at a temperature of 45°C (Granot, Weissman-Fogel et al. 2008) with an inter-stimulus interval of 30 seconds. When *pain60* could not be identified, a pain rating ranging between 50 and 65 was accepted. The thermode was slightly moved around in between subsequent stimuli to avoid sensitisation of the skin. The mechanical test stimulus used was the pressure pain threshold (PPT) measured at the upper trapezius muscle. Measurement was made one

third proximally between the spinal process of C7 and the acromion using a pressure algometer (FDK40, Wagner Instrument, Greenwich, CT, USA) with a probe area of 1 cm^2 and application rate of 50 kPa/s. The participant was instructed to verbally stop the test when the sensation of pressure alone changed to one of pressure and pain. In 44% of participants a single PPT measurement was taken before and after the conditioning stimulus (CS) and in the other 56% the average of three PPT measurements was used in the analysis. The proportion of people who had a single or three PPT measures was equally distributed across the LBP and control groups. Additional analysis showed there were no meaningful differences in the results whether a single PPT measure or the average of three was used.

The conditioning stimulus (CS) was immersion of the contralateral foot in a cold water bath maintained at 10.5±1°C for 2 minutes. The bath consisted of a container divided into two by a perforated perspex sheet. One chamber was filled with ice and water that was stirred to maintain the other chamber at a constant temperature and continuously monitored by a thermometer with a digital display. Participants were instructed to immerse their foot in the water up to the ankle without touching the sides or bottom of the bath. They could withdraw the foot from the cold bath if the pain became intolerable. The time the foot was kept in the water was recorded. If the foot was withdrawn from the water, the thermal test stimulus was applied immediately after, followed by the PPT.

Participants were asked to rate pain intensity of the foot while in the cold bath at 30, 60 and 90 seconds on the NRS101 scale. A second assessment of the heat stimulus was performed during the last 30 seconds of CS, and finally the PPT testing was performed immediately after CS (Figure 1).

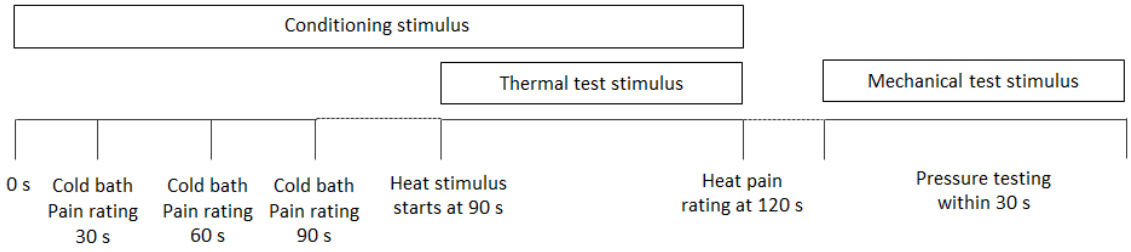

Figure 1 Procedure for inducing CPM

Data analysis

Sample size considerations

Sample size calculations suggested that sample size of 25 for each group (acute LBP and pain-free controls) would achieve 80% power based on previously published research in LBP (Correa, Costa et al. 2015, Mlekusch, Neziri et al. 2016) using a 5% significance level, CPM PPT between group effect size of 130kPa and a standard deviation of 150kPa. We aimed to recruit a minimum of 25 in each group to account for possible drop out.

Statistical analysis

Analyses were conducted using IBM SPSS statistics 22.0 software. Between group differences in demographic and psychological variables were compared using the Mann-Whitney U Test. Categorical variables were compared using chi-squared tests of association. Between group differences in pain rating from the CS were investigated using repeated measure ANOVA with within group factor of Time (3 levels: 30, 60 and 90 seconds) and within group factor of Group (2 levels: LBP and pain-free controls). CPM effect was calculated as the change between the baseline scores of the test stimuli (i.e. heat pain and PPT) and the scores during (for heat pain) or after (for PPT) the CS, where a negative value indicated pain inhibition (Yarnitsky, Bouhassira et al. 2015). CPM effect was also reported as percentage change for both test stimuli in each group, as recommended in the current guidelines (Yarnitsky, Bouhassira et al. 2015). Within and between group differences in CPM effect were analysed using paired and independent t-tests, respectively. The magnitude of the between-group difference in CPM effect for both test stimuli was calculated by the standardised effect size (Hedge's g). Participants were further categorized based on individual CPM responses. For the heat stimulus, we used the O'Neill et al (O'Neill, Manniche et al. 2014) classification where: inhibitory or facilitatory CPM was defined as a decrease or increase in the heat pain score during CS of ≥5/100 NRS, respectively; and a CPM non-responder was defined as a change in the heat pain score during CS of <5/100 NRS. For the PPT, a value of 50kPa was used as the minimal detectable change as reported in Walton et al (Walton, MacDermid et al. 2011) and was confirmed from the PPT data from our pain-free controls. Inhibitory or facilitatory CPM was defined as an increase or decrease in the PPT after CS of ≥50kPa, respectively; and a CPM non-responder was defined as a change in the PPT after CS of <50kPa. Fisher's exact test was used to determine

whether responder category was independent of LBP or control group. The correlation between the change score for heat pain and PPT was analysed using the Spearman's rank correlation since the two variables were not linearly related.

4.3.4 Results

Participants details

Twenty-five participants with acute LBP (13 females, mean age 30.6 ± 11.9) and 47 pain-free controls (24 females, mean age 30.0 ± 9.8) completed the study. The mean (SD) duration of LBP was 12 ± 6 days and the mean (SD) pain intensity at time of testing, and the average during the last week, was 4.0 (1.8) and 4.3 (1.6), respectively. Four people with LBP took simple (non-opioid, non-psychotropic) analgesic medications 24 hours prior to testing. The disability level measured by the RMDQ was 5.7 (4.5). Although there were statistically significant differences in stress and anxiety scores between participants with LBP and controls, the psychological profiles were in the normal range in both groups (Table 1). One of the LBP participants had a pain distribution that could be consistent with nerve root compromise and scored in the likely neuropathic pain range on the painDETECT questionnaire (20 out of 38).

Table 1 Demographics and psychological variables

	Low back pain N=25	**Pain free controls** N=47	**P-value**
Female, n (%)	13 (52)	24 (51)	0.995
Age, years	30.6 (11.9)	30.0 (9.8)	0.825
BMI, Kg/m^2	24.3 (2.7)	22.3 (2.6)	0.016*
Stress, DASS-21 (0-42 score)	10.6 (9.0)	6.0 (5.8)	0.026*
Anxiety, DASS-21 (0-42 score)	6.6 (7.0)	2.6 (3.5)	0.020*
Depression, DASS-21 (0-42 score)	6.7 (8.4)	3.2 (3.8)	0.052
Pain catastrophizing, PCS (0-52 score)	11.3 (8.9)	9.2 (8.1)	0.279

All values are presented as mean (SD), unless otherwise specified. BMI: body mass index; DASS-21: Depression, Anxiety and Stress scale; PCS: Pain Catastrophizing Scale. *p<0.05

CPM effect and individual CPM responses

A statistically significant (p<0.001) reduction in heat pain rating (NRS101) was observed in both the LBP and control groups when tested during the conditioning stimulus. The percentage change was 38% (95%CI 26 to 49%) for the LBP group and 36% (95%CI 28 to 44%) for pain-free controls. Similarly, a statistically significant increase in PPT after the conditioning stimulus was found in people with LBP (p=0.021) and pain-free controls (p<0.001). The percentage change was 24% (95%CI

10 to 38%) for the LBP group and 22% (95%CI 15 to 29%) for pain-free controls. There was no significant difference in the CPM effect for the heat stimulus (p=0.92) and the PPT (p=0.89) between LBP and control groups (Table 2). The effect sizes of between-group differences in CPM magnitude measured by Hedge's g were 0.02 for the heat stimulus and 0.04 for the PPT.

Table 2 Within and between group differences in the CPM effect for heat pain and PPT stimuli

	Low back pain Mean (SD)		**Pain-free controls** Mean (SD)		**CPM effect** Mean (95% CI)		
Test stimulus	Baseline	During or after CS	Baseline	During or after CS	Within group difference: Low back pain	Within group difference: Pain-free controls	Between group difference
Heat, NRS101	54.6 (6.3)	34.7 (17.2)	55.7 (9.1)	35.4 (16.0)	-19.9 (-26.0 to -13.8)	-20.3 (-24.8 to -15.7)	-0.3 (-7.9 to 7.1)
PPT, kPa	430.4 (244.9)	513.2 (270.2)	378.3 (133.6)	456.4 (174.7)	-82.8 (-151.8 to -13.8)	-78.1 (-99.7 to -56.4)	4.7 (-67.1 to 76.5)

CS: conditioning stimulus; NRS: Numeric Rating Scale; PPT: pressure pain threshold

Regarding individual CPM responses, the proportion of those with an inhibitory CPM effect for the heat pain (i.e. reduction of ≥5/100 NRS during the conditioning stimulus) was 76% in the LBP group and 85% in the pain-free controls. For the PPT, an inhibitory CPM effect (i.e. increase in ≥50kPa after the conditioning stimulus) occurred in 52% of people with LBP and 56% of pain-free controls (Table 3). There were no statistically significant between group differences in the proportion of people classified based on their CPM responses (i.e. inhibitory, facilitatory, non-responders) for the heat stimulus (p=0.55) and the PPT (p=0.86) (Table 3).

Table 3 Individual CPM responses for heat pain and PPT stimuli in low back pain and pain-free controls

	Low back pain N (%)	**Pain-free controls** N (%)	**P-value**
Heat Pain			
Inhibitory	19 (76%)	40 (85%)	
Non-responder	5 (20%)	5 (11%)	0.550
Facilitatory	1 (4%)	2 (4%)	
PPT			
Inhibitory	13 (52%)	27 (56%)	
Non-responder	11 (44%)	20 (42%)	0.863
Facilitatory	1 (4%)	1 (2%)	

PPT: pressure pain threshold

During the cold water bath test (CS) there were no statistically significant differences in the proportion of people who withdrew before 120 seconds (12% in LBP and 9% in controls, p=0.885). The pain rating from the CS was not significantly different between groups (p=0.652).

Comparison of the two CPM test paradigms

There was no correlation between group CPM responses for heat pain and PPT in people with LBP (r=-0.02, p=0.94) and pain-free controls (r=0.03, p=0.84). Individual CPM responses using heat pain and PPT were in agreement (i.e. both inhibitory, facilitatory or non-responders) in 52% (n=13) of people with LBP and in 57% (n=27) of pain-free controls (Table 4).

Table 4 Agreement of CPM responses between heat pain and PPT stimuli in low back pain and pain-free controls

	PPT inhibitory N (%)	PPT non-responder N (%)	PPT facilitatory N (%)
Heat inhibitory	10 (40%) LBP 24 (51%) Controls	8 (32%) LBP 16 (34%) Controls	1 (4%) LBP 0 (0%) Controls
Heat non-responder	2 (8%) LBP 2 (4%) Controls	3 (12%) LBP 3 (6%) Controls	0 (0%) LBP 0 (0%) Controls
Heat facilitatory	1 (4%) LBP 1 (2%) Controls	0 (0%) LBP 1 (2%) Controls	0 (0%) LBP 0 (0%) Controls

Shaded areas represent agreement of CPM responses between PPT and heat test stimuli. PPT: pressure pain threshold; LBP: low back pain.

4.3.5 Discussion

In this study we have demonstrated that a significant CPM effect occurred in an acute LBP sample, regardless of the test stimulus used (i.e. thermal heat or mechanical PPT),

and this was similar in pain-free controls. These findings suggest that endogenous pain modulation is normally functioning at this early stage of acute LBP. However, no correlation was found in the group CPM responses *between* the two test stimuli; furthermore, there was low percentage agreement in the individual CPM responses between the thermal and mechanical stimuli.

Our result that there are no group differences in the CPM effect between acute LBP and pain-free controls is consistent with the only other study that has assessed CPM in acute LBP, that we are aware of (Mlekusch, Neziri et al. 2016). One difference between the two groups reported in the Mlekusch study (Mlekusch, Neziri et al. 2016) was that the inhibitory response lasted significantly longer in the healthy controls compared to people with LBP. This was not investigated in the current study. We are not aware of other studies that have assessed CPM in acute clinical settings. In chronic LBP, there are conflicting reports in the literature, with some studies reporting an impaired CPM response (Correa, Costa et al. 2015, Rabey, Poon et al. 2015), while others report no difference in CPM compared with healthy controls (Julien, Goffaux et al. 2005, Vlckova, Srotova et al. 2014, Mlekusch, Neziri et al. 2016).

When investigating individual CPM responses, we found no significant difference in the proportion of people who had an inhibitory, facilitatory or neutral CPM response between acute LBP and pain-free controls. The majority of people were in the inhibitory range in both groups for the heat pain stimulus (76% in LBP and 85% in controls) and PPT (52% in LBP and 56% in controls). These results are consistent with those from O'Neill et al (O'Neill, Manniche et al. 2014) who reported a greater percentage (47%) of people with acute LBP showing an inhibitory CPM response, compared with 39% who had no change and 11% with a facilitatory response. These proportions were not significantly different from those of the healthy controls.

In chronic LBP, differing individual CPM responses have also been reported. O'Neill et al (O'Neill, Manniche et al. 2014) showed similar results to those in acute LBP, with a greater proportion of people in the inhibitory range (46% inhibitory, 35% no change, 18% facilitatory). However, Rabey et al (Rabey, Poon et al. 2015) reported that CPM responses in a chronic LBP sample were: 11% inhibitory, 16% no change and 73% facilitatory, all of which were significantly different from healthy controls. As outlined by Rabey et al (Rabey, Poon et al. 2015) it remains unclear whether the testing site, i.e.

the painful area versus an area unrelated to pain (in O'Neill et al (O'Neill, Manniche et al. 2014)), may have played a role in these differences. It is intruiging that there are differences in CPM responses reported across the various healthy control groups in the studies referred to above. Besides methodological factors related to CPM testing, it is possible that variable inclusion and exclusion criteria between studies increased the heterogeneity of samples.

Because there is currently no single standardised protocol for CPM testing we examined two test stimuli (one thermal and one mechanical) consistent with recent consensus-based recommendations (Yarnitsky, Bouhassira et al. 2015). Interestingly, no correlation was found between the two test stimuli used. This is in agreement with other studies also showing weak or no correlation between different test stimuli for CPM testing in both healthy controls and patients (Nahman-Averbuch, Yarnitsky et al. 2013, Schliessbach, Siegenthaler et al. 2014). We also found low agreement in the individual CPM responses between the thermal and mechanical stimuli (52% LBP and 57% in pain-free controls). In Schliessback study (Schliessbach, Siegenthaler et al. 2014) comparing PPT with suprathreshold electrical stimuli to assess the CPM effect in chronic LBP (n=68) an 84% agreement between individual CPM responses using the two stimuli was found, which is higher than the agreement found in our study. It is important to note however, that in the Schliessback study (Schliessbach, Siegenthaler et al. 2014) only two categories (inhibition and facilitation) were used, while we calculated a third category of CPM non-responders, determined by change scores within the minimal detectable change of the measurement (Walton, MacDermid et al. 2011, O'Neill, Manniche et al. 2014). In line with current literature (O'Neill, Manniche et al. 2014, Rabey, Poon et al. 2015), we decided that the use of a non-responder category was important to avoid categorising less than minimal change scores as inhibitory or facilitatory. It will be valuable for consensus recommendations to address this issue in the future, to aid comparability between studies. Schliessback et al (Schliessbach, Siegenthaler et al. 2014) concluded that the weak correlation and the disagreement found in 16% of the sample between the two paradigms may represent a specific chronic pain phenotype. Our results do not support this hypothesis, as a high proportion of discordant responses was also found in pain-free subjects. Our results would suggest that the discrepancy observed between stimuli is more likely due to the complex methodological differences between the CPM paradigms used (e.g. heat vs pressure

modalities, parallel vs sequential application, suprathreshold vs threshold endpoints and forearm vs trapezius test sites). Others have suggested that different test stimuli may invoke different inhibitory mechanisms (Nahman-Averbuch, Nir et al. 2016), however this was beyond the scope of our study to assess. These considerations reinforce the current recommendations to use two test stimuli for CPM testing, so that further optimisation of CPM protocols can be achieved.

Interpretation of these results should take into consideration the following methodological limitations. First, the heat test stimulus was applied in parallel to the conditioning stimulus while the PPT was applied sequentially. Parallel application of test stimulus with the conditioning stimulus has been shown to yield to a greater CPM effect (Pud, Granovsky et al. 2009). Secondly, it cannot be excluded that the heat stimulus acted as a second conditioning stimulus, thereby impacting the inhibitory capacity for the subsequent PPT test. This hypothesis has been tested by Arendt-Nielsen and colleagues showing that a concurrent application of two conditioning stimuli reduced the CPM effect compared with separately applied conditioning stimuli (Arendt-Nielsen, Sluka et al. 2008). Further, the higher variability of CPM using thresholding testing (Pud, Granovsky et al. 2009) might have accounted for the smaller CPM magnitude found for the pressure testing. This cross-sectional analysis is part of a cohort study investigating a wider array of QST measures. In order to minimise variability the same rigorous approach was employed for all tests in all participants (i.e. positioning, testing sites, room temperature). However, it is unknown whether the order of testing may have influenced CPM results. A systematic difference in sensory test results due to order effects has been reported in the literature (Gröne, Crispin et al. 2012). It is possible that other variables such as pain medications might have affected the CPM effect. However, only four people of the LBP group had taken simple non-opioid analgesic medications in the 24 hours prior testing. Finally, the within-group CPM variability in our study was greater than that in studies we used to calculate our sample size, which may suggest underpowering. However, the confidence intervals of between group differences together with the small effect sizes suggest our sample is adequate to rule out any clinically important differences in CPM effect in those with or without LBP.

A final point to note is that the LBP sample reported a low disability score and had a psychological profile in the normal range reflecting a high functioning group more

representative of a community sample (Williams, Maher et al. 2014), and so the results are more likely to be generalisable to people not seeking care for their LBP. It will be valuable in future research to investigate whether the CPM profile is different for people receiving treatment for acute LBP.

4.3.6 Conclusion

This study shows that endogenous pain modulation is not impaired in the acute stage of LBP. The variation in CPM responses using two different test paradigms further emphasises that methodological differences in CPM testing are important and highlights the need for standardisation of CPM protocols to move this field of research forward.

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Chapter 5

The prognostic value of Quantitative Sensory Testing in low back pain

5.1 Preface

Over recent years, QST tests have shown promising ability to predict outcomes in various clinical conditions, including musculoskeletal pain. In Chapter 5, a systematic review of the literature was performed to address the fourth aim of the thesis; to establish whether QST responses have prognostic value in low back pain.

This chapter is presented as the manuscript published in the *Journal of Pain Research*:

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5.2 Co-authors' statement

As co-authors of the paper, "Prognostic value of quantitative sensory testing in low back pain: a systematic review of the literature", we confirm that Anna Marcuzzi has made the following contributions to this study:

- Conception and design of the research:
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript
- Critical appraisal of the content

Associate Professor Julia Hush _____ Date 5 Dec 2016

Dr Paul Wrigley_____ Date 5 Dec 2016

Professor Catherine Dean _____ Date 5 Dec 2016

Ms Rosemary Chakiath _____ Date 5 Dec 2016

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REVIEW

Prognostic value of quantitative sensory testing in low back pain: a systematic review of the literature

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Abstract: Quantitative sensory testing (QST) measures have recently been shown to predict outcomes in various musculoskeletal and pain conditions. The aim of this systematic review was to summarize the emerging body of evidence investigating the prognostic value of QST measures in people with low back pain (LBP). The protocol for this review was prospectively registered on the International Prospective Register of Systematic Reviews. An electronic search of six databases was conducted from inception to October 2015. Experts in the field were contacted to retrieve additional unpublished data. Studies were included if they were prospective longitudinal in design, assessed at least one QST measure in people with LBP, assessed LBP status at follow-up, and reported the association of QST data with LBP status at follow-up. Statistical pooling of results was not possible due to heterogeneity between studies. Of 6,408 references screened after duplicates removed, three studies were finally included. None of them reported a significant association between the QST measures assessed and the LBP outcome. Three areas at high risk of bias were identified which potentially compromise the validity of these results. Due to the paucity of available studies and the methodological shortcomings identified, it remains unknown whether QST measures are predictive of outcome in LBP.

Keywords: prognosis, quantitative sensory testing, low back pain, cohort studies, pain, sensory testing

Introduction

The course of low back pain (LBP) is typically characterized by symptoms subsiding quickly within the first 4–6 weeks, but for some people there is little improvement thereafter.[1] It has been estimated that up to 65% of people presenting to primary care for treatment of an episode of LBP still experience pain after 1 year.[2] Persistent LBP has been identified as the world's leading cause of disability[3] and remains a challenge in clinical management.[4] Determining which factors predict outcomes in LBP would allow the identification of people at high risk of poor outcomes for whom early, targeted interventions could be beneficial. Several studies have evaluated the contribution of clinical, demographic, and psychosocial factors on functional recovery after LBP,[5–8] but previous attempts to synthesize this body of research have led to inconsistent conclusions about which set of factors are useful for prognosis of LBP.[9] Reasons for this uncertainty may include methodological limitations of the study design.[10] However, another reason might be that we lack knowledge about potential factors that can provide useful prognostic information for LBP.

The prognostic value of quantitative sensory testing (QST) measures has more recently been investigated in musculoskeletal pain conditions. For example, cold and

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mechanical pain hypersensitivity (pressure pain) have been shown to predict those at risk of poor outcome in both whiplash injury[11–13] and lateral epicondylalgia.[14] Evidence from cross-sectional studies has shown that specific QST measures can discriminate between people with chronic LBP and healthy controls.[15–18] Further, we know that some abnormal QST findings can be detected soon after the onset of LBP.[19] However, to date, there has been no review of the literature investigating the prognostic value of QST measures in LBP.

The aim of this systematic review is to identify, evaluate, and summarize the emerging body of literature investigating the prognostic ability of QST responses in LBP.

Methods

Procedure

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.[20] The protocol for this systematic review was prospectively registered on International Prospective Register of Systematic Reviews 2015 (registration number: CRD42015027228). Electronic searches for articles were conducted using the following databases from inception to October 2015: Ovid Medline, Ovid EMBASE, Ovid PsycINFO, Ovid Mantis, and Scopus. The PubMed database was also searched from January 2015 to October 2015 to retrieve recent literature not yet indexed in other databases. A comprehensive search strategy was designed with the assistance of an experienced research librarian and adjusted to account for differences in indexing across databases (Ovid Medline search is presented in Table S1). The search encompassed terms for the three domains of interest: LBP, QST, and prognosis. Terms for each domain were combined using the "AND" operator. The updated search strategy of the Cochrane Back Review Group 2013[21] was used to identify back pain terms, while relevant terms for prognosis were based on those suggested by Altman[10] and Hayden.[22] Reference lists of the included studies were screened to track other relevant literature. In addition, 21 experts in the field were contacted to identify any studies we had missed or to retrieve additional results from unpublished data. Non-English language studies, where a translation could be made available, were included.

Study selection

We included prospective longitudinal studies based on the following criteria: adults at least 18 years or older with acute (<6 weeks), subacute (6–12 weeks), or chronic (>12 weeks) nonspecific LBP with or without leg pain;[23] participants had been assessed by at least one QST measure; LBP status at follow-up was reported; the association between QST responses at baseline and LBP outcomes at follow-up was reported; and the follow-up duration was a minimum of 1 week. No restrictions were placed on the setting or recruitment source of participants. We excluded LBP due to serious pathology (eg, fracture, neoplasm, and infection) or a specific condition (eg, rheumatoid arthritis, failed back surgery syndrome, pregnancy, postpartum back pain, and chronic widespread pain such as in fibromyalgia, irritable bowel syndrome) or after back surgery. Studies that investigated LBP together with other musculoskeletal pain disorders (eg, neck pain and thoracic pain) were also included if at least >75% of the sample had LBP, or if data for LBP could be extracted separately.

The prognostic factors of interest were QST responses. The term QST was broadly used in this review to include psychophysical as well as specific electrophysiological tests. Psychophysical tests included "static" measures (eg, threshold determination to noxious and non-noxious stimuli and pain magnitude rating to suprathreshold stimuli) as well as "dynamic" measures (eg, temporal summation, conditioned pain modulation [CPM], and offset analgesia).[24] Specific electrophysiological tests included assessment of nociceptive reflexes (eg, nociceptive withdrawal reflex).

The outcomes of interest were measures of LBP status at follow-up, including pain intensity, functional status or disability, work status, health-related quality of life, and global perceived effect/recovery.

Study inclusion

After removal of duplicate papers, studies that met the inclusion criteria were independently screened by two reviewers based on the title and then abstract. Finally, full-text articles were assessed for inclusion independently by two reviewers using a piloted standardized eligibility sheet, and any disagreements were resolved by discussion and consensus, and with the assistance of a third reviewer at all stages of screening. Reference lists of the included papers were screened to locate other relevant articles. Further, 21 experts in the field were contacted by email to retrieve any additional published or unpublished data.

Risk of bias assessment

The risk of bias was assessed independently by two reviewers using the Quality in Prognostic Studies tool developed by Hayden et al[25] which was adapted for the needs of this systematic review, and incorporated additional criteria for assessment of bias in prognostic studies from other

sources.[10,26,27] Each of the six domains comprised multiple items that were individually scored as "yes", "no", "unclear", or "not applicable" and comments to support judgment were provided. The "yes" score within each domain was given only if the majority of items were fulfilled and indicated low risk of bias. Results of risk of bias assessment were summarized for each domain across studies. An overall risk of bias in each study (eg, summary score) was not provided in accordance with the current recommendations.[28]

Data extraction and analysis

Data from included studies were extracted independently by two reviewers using a piloted standardized data extraction sheet. Data extracted included information about study design, sample size, study population (eg, participant demographics and LBP features), recruitment source, inception time, follow-up duration, prognostic variables analyzed, outcome measures adopted, statistical analysis performed, and key findings. Any disagreement was resolved by discussion and consensus among the two reviewers.

Due to heterogeneity between studies with respect to LBP duration, clinical outcomes, follow-up duration, and statistical methods, it was not possible to statistically pool the results. Instead, findings were reported descriptively.

Results

The search strategy retrieved 8,628 articles from which 6,422 articles remained after duplicates were removed and 30 after screening by titles and abstracts. Full-text copies were then examined for eligibility (Figure 1). The reasons for exclusion at the full-text stage were: ineligible study design, QST assessment not performed, outcomes of LBP status at follow-up not reported, and ineligible participants. Three studies met the eligibility criteria and were therefore included.

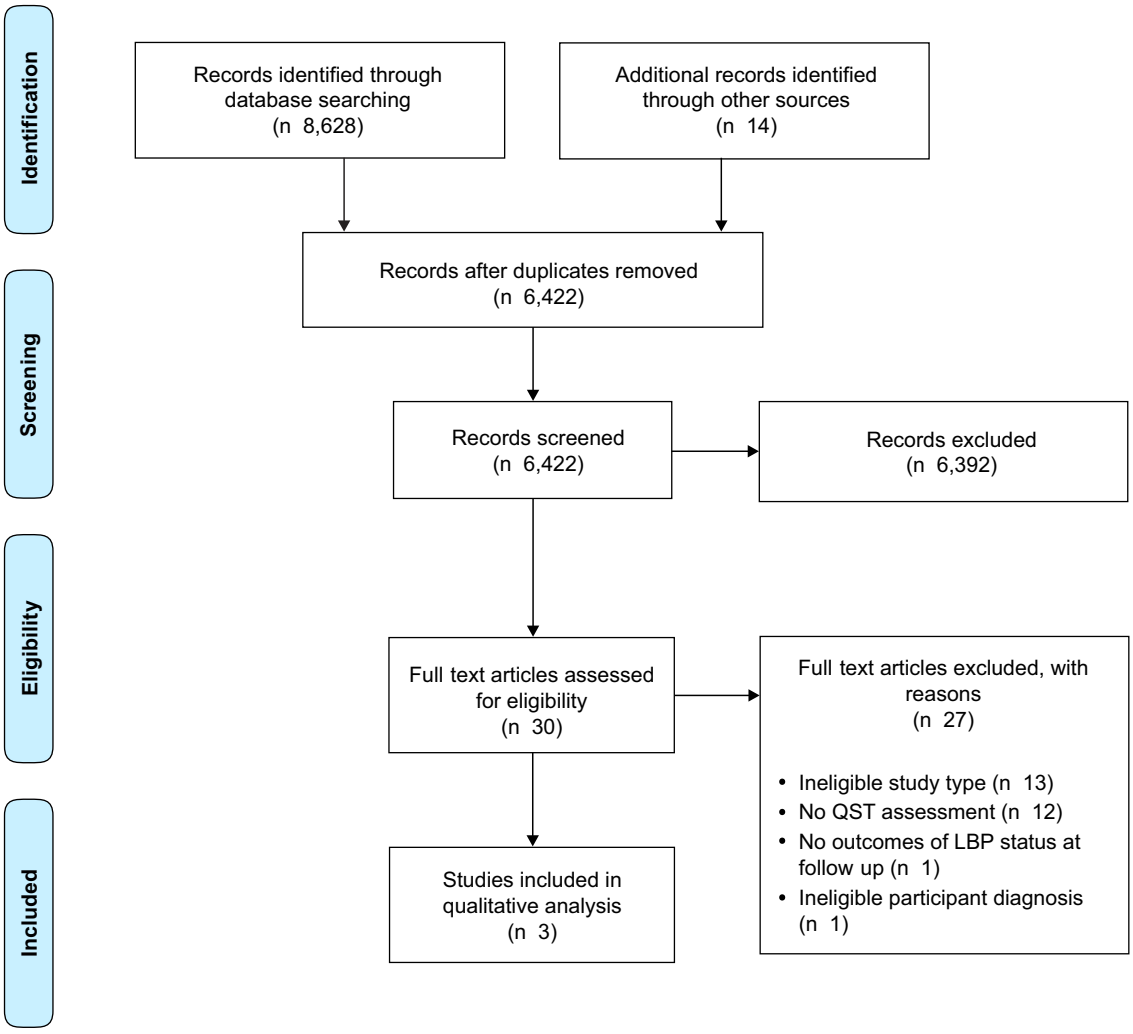

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.
Abbreviations: LBP, low back pain; QST, quantitative sensory testing.

An additional 14 studies from the reference lists of included studies were screened, but none were eligible for inclusion. None of the experts in the field who were contacted by the review team had data that fulfilled our criteria or were able to provide results from current prospective studies.

Characteristics of samples in the included studies

A description of the samples from the included studies is provided in Table 1. Two studies recruited patients with LBP from primary care practices[29,30] and one study from tertiary care.[31] LeResche et al[29] assessed 157 patients who made their first visit for mechanical LBP to a primary care clinic of the Group Health in the Seattle area (USA) who were followed up at 4 months. In this cohort, 65% of patients had LBP for less than 4 weeks, while the remaining 35% had a longer, variable duration of LBP. Mlekusch et al[31] recruited 113 patients with chronic LBP without radicular pain, from a University Pain Clinic in Bern (Switzerland) who were followed up at 12–15 months. The authors reported that some patients received predominantly interventional treatments (eg, steroid injections, neural therapy, radiofrequency, surgery, acupuncture, and electrothermal therapy) between baseline assessment and follow-up. Nordeman et al[30] investigated 113 females with chronic LBP with or without leg pain identified through a search of medical records of eight primary health care clinics in Sweden, and were followed up for 2 years after baseline assessment.

Risk of bias assessment

Regarding the risk of bias evaluation (Table 2), three domains with high risk of bias were identified across the three included studies, which potentially compromise the validity of these results. These domains were as follows: the representativeness of samples, the reporting of QST assessment, and the adequacy of the outcome measure. However, all three studies satisfactorily described their samples, had low attrition bias (follow-up rates more than 90%), and reported statistical adjustment for relevant demographic or clinical/psychological factors.

Association of QST findings with clinical outcomes

All three studies investigated the association of pressure pain responses with LBP outcomes in univariate and multivariate analyses. LeResche et al[29] found a significant association between pressure pain threshold (PPT) at the back and at the thenar eminence of the hand, with clinically significant

Table 1 Characteristics of samples in the included studies

Characteristics	LeResche et al[29]	Mlekusch et al[31]	Nordeman et al[30]
Geographical area	USA (Seattle)	Switzerland	Sweden
Setting	Primary care	Tertiary care	Primary care
Population under study	Acute LBP	Chronic LBP	Chronic LBP
Exclusion criteria for LBP	LBP due to neoplastic, infectious or inflammatory cause, pregnancy or major trauma	LBP with radicular pain confirmed by MRI finding of nerve compression together with symptoms or signs of nerve dysfunction	LBP due to pregnancy, known spinal disorders, or other severe disorders
Female, n (%)	157[a] (61.8)	113 (57)	130 (100)
Mean age (SD), years	47.4 (12.4)	50.8 (15.4)	45 (10)
Mean pain duration (SD), years	LBP ≤30 days (in 65% of sample)	6.1 (6.4)	9.6 (8.8)
Follow-up duration	4 months	12 to 15 months	2 years
Loss to follow-up (%)	6	0	5
Events, n (%)[b]	44 (30)	N/A	27 (22)

Notes: [a]The cohort was 571, but only 157 participated in the QST; [b]for LeResche et al,[29] this is the number of people who had clinically significant pain at 4 months; for Nordeman et al,[30] this is the number of people who were in the "no work ability" category at 2 years.
Abbreviations: LBP, low back pain; SD, standard deviation; N/A, not applicable; MRI, magnetic resonance imaging; QST, quantitative sensory testing.

Table 2 Risk of bias assessment using the adapted version of the QUIPS tool

Reference	Sampling		Study attrition	Prognostic factors measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
	Sample defined	Sample representative					
LeResche et al[29]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes
Mlekusch et al[31]	Yes	No	Yes	Yes	Yes	Yes	Yes
Nordeman et al[30]	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes

Abbreviation: QUIPS, Quality in Prognostic Studies.

pain intensity at 4 months (odds ratio [OR]: 0.66 [95% CI 0.44–0.96] and 0.62 [95% CI 0.40–0.92], respectively). However, this association was not significant when adjusted for age and sex in the multivariate model. In a study by Nordeman et al,[30] results from the univariate analysis revealed that people with chronic LBP with higher PPT – measured at eight tender points – were significantly more likely to be able to work at 2 years (OR: 1.4 [95% CI 1.1–1.9]). In the multivariate analysis, when age; functional status; psychological, environmental, and health-related factors; activity; and participation limitations were entered into the model as independent variables, PPT was no longer a significant independent predictor of work status at 2 years. However, reduced walking speed (measured by the 6-minute walk test), higher depression (measured by the Hospital Anxiety and Depression Scale-depression subscale), and previous inability to work remained in the final model, explaining 51% of the variance in the outcome at 2 years. Mlekusch et al[31] found no association of pressure pain tolerance threshold measured at the toe with change in pain intensity at 12–15 months in people with chronic LBP, when controlling for baseline pain intensity (r=0.03 [95% CI –0.21–0.28). When adjusted for demographics and psychological and clinical variables, the association remained nonsignificant (r=–0.01 [95% CI –0.28–0.27]).

The prognostic value of cold pressor testing was reported in two studies. In LeResche et al,[29] cold pain sensitivity was assessed as the average pain intensity at 10, 20, and 30 seconds after immersion of the hand in cold water at 4°C– 5°C. In both the univariate and adjusted analyses, there was no significant association of cold pressor pain rating with clinically significant pain at 4 months (OR: 1.04 [95% CI 0.72–1.51] and 0.91 [95% CI 0.61–1.36], respectively). In Mlekusch et al,[31] cold pain tolerance was measured as the time participants could tolerate immersion of their hand in cold water at 0°C (up to a maximum of 2 minutes). The association of cold pain tolerance with change in pain intensity at 12–15 months was near null in both the univariate (r=−0.02 [95% CI –0.23–0.28]) and adjusted analyses (r=−0.00 [95% CI –0.26–0.25]).

CPM was assessed in two studies,[29,31] with noxious cold water as the conditioning stimulus in both studies. In LeResche et al,[29] heat pain was used as the test stimulus, measured before and again during immersion of the hand in cold water. In Mlekusch et al,[31] pressure pain tolerance was used as the test stimulus measured before and again after removal of the hand from the cold water. The CPM response was measured as the difference between heat pain rating and pain threshold, before and after the conditioning stimulus. Both studies reported no association of the CPM response with outcomes in the acute (OR: 1.11 [95% CI 0.77–1.62]) and chronic (r=−0.40 [95% CI –0.80–0.00]) LBP samples studied.

Finally, one study[29] assessed mechanical temporal summation using repeated application of a von Frey filament at the forearm. No significant association was observed between temporal summation and clinically significant pain at 4 months, in both the univariate (OR: 0.92 [95% CI 0.63–1.31]) and adjusted (OR: 0.88 [95% CI 0.58–1.27]) analyses. A summary of these results is presented in Table 3.

Discussion

This systematic review has revealed a surprising finding that there are very few studies which investigated the prognostic value of QST responses in people with LBP. In the three studies that were included in this review, none reported any significant association between the QST responses tested and LBP outcomes measured between 4 months and 2 years in both acute and chronic LBP.

Other studies have reported negative findings between QST responses and LBP outcomes. For example, in a systematic review of cross-sectional analyses, no correlation was found between QST responses and spinal pain and disability, regardless of the QST modality used, the site of assessment, or pain duration.[32] The authors of the review noted this observed finding may be because pain thresholds (eg, pressure pain detection threshold) were predominantly assessed in the included studies, rather than suprathreshold or dynamic QST tests. In another example, O'Neill et al[33] investigated risk factors for LBP in the general population, and found that people with lower PPT (below the 10th percentile of PPT distribution) were not at higher risk of developing future LBP. Whether or not this result would have been different if suprathreshold measures of pain sensitivity were used is unknown. However, if indeed dynamic QST tests are more clinically relevant measures of pain sensitivity, then we would have expected an association in the studies reporting these measures in the current review. One explanation could be the low prevalence of pain hypersensitivity in the cohorts investigated. Indeed, one of the three studies[31] in this review did report that only a small proportion of people (approximately 25%) with severe long-lasting LBP had QST responses below the 10th percentile of normative data distribution, indicative of widespread pain hypersensitivity. It remains unknown whether this may have been a factor in the other two studies as prevalence data regarding pain hypersensitivity were not available.

When prospective studies investigating other pain conditions were examined, there are examples where QST

Table 3 Summary of the main findings

Reference	Stimulus	Pain measure	Site	Other variables	Outcome measure	Statistical analysis	Results (univariate analyses)	Conclusions
LeResche et al[29]	Pressure	Pain threshold	Back and hand	Age Sex	Clinical significant pain measured by the Graded Chronic Pain Scale: "no" defined as grade 0 or I; "yes" defined as grade II, III, IV	Univariate and multivariable logistic regression	Only PPT at the back and PPT at the thenar eminence were significantly associated with clinically significant pain at 4 months (P<0.5)	None of the QST measures were significant predictors of clinical significant pain at 4 months after controlling for patient age and sex
	Cold	Pain magnitude rating	Hand					
	Mechanical	Temporal summation	Forearm					
	CPM	Cold bath (CS) and heat pain (TS)	Hand (CS) and forearm (TS)					
Mlekusch et al[31]	Pressure	Pain tolerance	Toe	Pain severity and duration, age, sex, catastrophizing, depression, intake of opioids	Change score in average pain intensity over the last 24 hours measured by numeric rating scale (NRS11)	Univariate and multivariable linear regression	None of the QST variables showed an association with change score in pain severity at 1 year	None of the QST measures were significantly associated with change score in pain severity at 1 year in both the unadjusted and adjusted analyses
	Cold	Pain tolerance (time to withdrawal)	Hand					
	CPM	Cold bath (CS) and PPtol (TS)	Hand (CS) and toe (TS)					
Nordeman et al[30]	Pressure	Pain threshold	Trapezius, supraspinatus, gluteal, and knee bilaterally	Age, baseline work ability, wa king test, hand grip strength, number of pain localizations, widespread pain, pain severity, fatigue, activity limitation, social support, risk of long-term disability, stress, anxiety, depression, general health status	Work ability: "no" defined as full-time sick leave or full-time disability pension; "yes" defined as work or study, applying for work, parental leave, or part-time disability pension	Univariate and forward stepwise logistic regression	PPT was significantly associated with work ability at 2 years (P=0.018)	Wa king ability together with depression score and baseline work ability were significant predictors accounting for 51% of the variance in work ability at 2 years

Abbreviations: PPT, pressure pain threshold; CPM, conditioned pain modulation; PPtol, pressure pain tolerance; CS, conditioning stimulus; TS, test stimulus; QST, quantitative sensory testing.

responses do predict outcomes. For example, cold pain hypersensitivity and PPTs have been found to be of prognostic value in both whiplash-associated disorders[11–13] and lateral epicondylalgia.[14] Further, a recent systematic review showed that responses to psychophysical tests (ie, lower thermal, mechanical, and electrical pain tolerances or thresholds) explained up to 54% of the variance in postoperative pain following gynecological, orthopedic, and thoracotomy surgical procedures.[34] For example, cold pain tolerance measured preoperatively was identified as an independent risk factor for early postoperative pain in cholecystectomy.[35] While these studies in musculoskeletal and perioperative pain have shown an association of QST findings with outcome, the overall number of prospective studies examining the predictive capacity of QST to identify those at greatest risk of persistent pain and poor functional outcomes remains small; therefore, further research is needed to confirm these results.

In the studies included in the present review, a number of methodological limitations that need to be taken into consideration when interpreting these findings were identified. The first concern was the "representativeness of the samples". It is well established that the most useful prognostic studies are those which assemble an inception cohort,[26,27] yet only survivor cohorts were recruited in the studies in this review.

For example, in two studies[30,31] the participants had chronic LBP with a mean pain duration of 9.6 (standard deviation [SD] 8.8) years and 6.1 (SD 6.4) years. One study[29] attempted to assemble a LBP cohort of less than 30 days duration. However, 35% of the participants had duration longer than 30 days, and the pain duration details were not provided for this sample. Further, in Mlekusch et al,[31] only patients seeking care to a pain clinic were included, which further limited the generalizability of these results.[26] The second methodological issue pertains to the "measurement of prognostic factors". It was mostly unclear whether QST measures were performed in the same manner for all participants since information about the test protocol (eg, patient positioning, order of the tests, description of assessor training, number of assessors, and use of standardized instructions) as well as blinding of QST assessors were not reported. Standardized testing procedures ensure adequate reliability of QST measures.[36,37] Poor reliability of QST measures can dilute or mask prognostic information.[38] The last methodological issue is the "adequacy of the outcome measures". In Nordeman et al,[30] the validity of the applied work status categories is unclear (eg, part-time disability pension was classified as "able to work"). Moreover, the responsiveness of the work outcome used in this survivor cohort of chronic LBP was low, as illustrated by the low change (1%) in people's ability to work from baseline to 2 years.

Strengths and limitations

The strengths of this systematic review were that the research question was well defined with respect to the study design, population of interest, prognostic variables, and outcomes, and a thorough search strategy was used to identify all possible studies including unpublished data. The main limitations were that only a small number of studies met the inclusion criteria and they were heterogeneous with regard to LBP duration, clinical outcomes, follow-up duration, and statistical methods, which precluded quantitative analysis. In addition, the studies only assessed a limited range of QST measures, namely, mechanical and cold pain threshold and tolerance, temporal summation, and CPM. Therefore, it is not known whether other test modalities alone or in combination may have prognostic value in LBP. Additionally, the risk of bias issues discussed earlier further limit the generalizability of the findings.

Future perspectives

Future studies that aim to investigate the prognostic value of QST measures should focus on an inception cohort design, employ multiple QST modalities that are comprehensively described, and use standardized protocols, blinded assessors, and validated and appropriate outcome measures. Additionally, it would be valuable to concurrently assess known clinical and psychosocial predictors to account for the complexity and heterogeneity of LBP.

Conclusion

Due to the paucity of prospective cohort studies and the methodological shortcomings of available studies, it remains unknown whether QST measures are predictive of outcome in LBP. Given the developing body of literature suggesting QST as prognostic value for pain and function in various pain conditions, future prospective prognostic outcome studies of QST in LBP would be worthwhile.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Ovid Medline search

1. exp cohort studies/	39. hyp?esthesia.ti,ab.
2. incidence/	40. peripheral sensit*.ti,ab.
3. follow up stud*.mp.	41. central sensit*.ti,ab.
4. prognos*.mp.	42. spinal sensit*.ti,ab.
5. predict*.mp.	43. central pain.ti,ab.
6. course.mp.	44. (quantitative sensory test* or QST).mp.
7. inception.mp.	45. experim* pain.mp.
8. exp survival analysis/	46. ((pain adj test*) or (pain adj measure*)).mp.
9. exp risk/	47. bedside exam*.mp.
10. observational study/	48. psychophysic*.mp.
11. longitudinal studies/	49. Electrophysiologic*.mp.
12. or/1-11	50. (temporal summation or windup or wind up).mp.
13. back pain/	51. (second* adj pain).ti,ab.
14. low back pain/	52. (two-point discrimination or TPD).mp.
15. back disorder*.mp.	53. tactile acuity.ti,ab.
16. (lumbar adj pain).ti,ab.	54. (cold pressor test or CPT).mp.
17. sciatica/	55. (diffuse noxious inh bitory control or DNIC).mp.
18. sciatic neuropathy/	56. (pain modul* or descending modul*).mp.
19. Intervertebral Disc Degeneration/	57. (conditioned pain modulation or CPM).mp.
20. (dis* adj1 prolapse*).ti,ab.	58. offset analgesia.mp.
21. (dis* adj1 herniat*).ti,ab.	59. neural inh bition/
22. (facet adj joint*).ti,ab.	60. (nociceptive withdrawal reflex or NWR or nociceptive flexion reflex or NFR).mp.
23. backache.ti,ab.	
24. dorsalgia.mp.	61. (reflex receptive field or RRF).mp.
25. or/13-24	62. (spinal reflex* or (RIII adj reflex)).mp.
26. exp Pain Perception/	63. pain threshold/
27. pain, referred/	64. Nociceptors/
28. allodynia.ti,ab.	65. ((pressure or thermal or cold or heat or eletrical or mechanical) adj pain).ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
29. neuralgia/	
30. hypersensit*.mp.	
31. hyperpathia.ti,ab.	
32. exp somatosensory disorders/	
33. sensory profile*.mp.	66. ((cold or warm) adj detection).ti,ab.
34. hyp?algesia.ti,ab.	67. ((pain adj2 tolerance) or (pain adj2 processing) or detection threshold).ti,ab.
35. hyperalg?esia.ti,ab.	
36. paresth?esia.ti,ab.	68. or/26-67
37. hyperesth?esia.ti,ab.	69. 12 and 25 and 68
38. dysesth?esia.ti,ab.	70. 69 not randomized controlled trial/

Chapter 6

The long-term reliability of Quantitative Sensory Testing in healthy individuals

6.1 Preface

The interpretation of QST findings in research and clinical settings is based on the assumption that the measures are stable and reproducible. In Chapter 6, the long-term reliability of QST using static and dynamic tests was evaluated in healthy individuals at three time points over a 4-month period.

This chapter is presented as the manuscript accepted for publication in *Pain*:

Marcuzzi A., Wrigley P.J., Dean C.M., Adams R., Hush J.M. (2017) "The long-term reliability of static and dynamic Quantitative Sensory Testing in healthy individuals" *Pain* (accepted for publication March 2017).

6.2 Co-authors' statement

As co-authors of the paper, "The long-term reliability of static and dynamic Quantitative Sensory Testing in healthy individuals", we confirm that Anna Marcuzzi has made the following contributions to this study:

- Conception and design of the research
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript
- Critical appraisal of the content

Associate Professor Julia Hush _____ Date 5 Dec 2016

Dr Paul Wrigley_____ Date 5 Dec 2016

Professor Catherine Dean _____ Date 5 Dec 2016

Dr Roger Adams _____ Date 5 Dec 2016

6.3 The long-term reliability of static and dynamic Quantitative Sensory Testing in healthy individuals

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Keywords

Quantitative sensory testing; reliability; sensory testing; conditioned pain modulation; pain threshold

Disclosure

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We confirm that the manuscript has not been published elsewhere and is not under consideration by another journal.

The authors have no conflicts of interest to declare.

6.3.1 Abstract

Quantitative sensory tests (QST) have been increasingly used to investigate alterations in somatosensory function in a wide range of painful conditions. The interpretation of these findings is based on the assumption that the measures are stable and reproducible. To date, reliability of QST has been investigated for short test-retest intervals. The aim of this study was to investigate the long-term reliability of a multimodal QST assessment in healthy people, with testing conducted on three occasions over 4-months. Forty-two healthy people were enrolled in the study. Static and dynamic tests were performed, including cold and heat pain threshold (CPT, HPT), mechanical wind up (WUR), pressure pain threshold (PPT), two-point discrimination (TPD) and conditioned pain modulation (CPM). Systematic bias, relative reliability and agreement were analysed using repeated measure ANOVA, intraclass correlation coefficients ($ICCs_{3,1}$) and standard error of the measurement (SEM), respectively. Static QST (CPT, HPT, PPT and TPD) showed good to excellent reliability (ICCs: 0.68 to 0.90). Dynamic QST (WUR and CPM) showed poor to good reliability (ICCs: 0.35 to 0.61). A significant linear decrease over time was observed for mechanical QST at the back (PPT and TPD) and for CPM ($p<0.01$). Static QST were stable over a period of 4 months; however, a small systematic decrease over time was observed for mechanical QST. Dynamic QST showed considerable variability over time; in particular, CPM using PPT as the test stimulus did not show adequate reliability, suggesting that this test paradigm may be less useful for monitoring individuals over time.

6.3.2 Introduction

Quantitative sensory tests (QST) are commonly used to investigate changes in somatosensory system function in a wide range of painful conditions, including musculoskeletal disorders (Pavlaković and Petzke 2010). Static QST involving threshold determination are commonly used to provide insight into the basal state of the nociceptive system (Arendt-Nielsen and Yarnitsky 2009). More recently, dynamic QST procedures, including temporal summation and conditioned pain modulation, have been introduced to assess mechanisms of pain processing (Arendt-Nielsen and Yarnitsky 2009). All QST responses rely on the participant's perception, therefore a number of factors such as attention, cooperation, motivation and anxiety are known to influence results (Backonja, Walk et al. 2009). While these factors are difficult to control, standardised protocols have been developed to minimize sources of variability from methodological and environmental influences (Rolke, Baron et al. 2006).

The interpretation of QST findings from the research or clinical setting is based on the assumption that the measurements are stable and reproducible. Research into the reliability of QST measures has to date been conducted with short test-retest intervals ranging from hours to weeks, and the results have demonstrated acceptable reliability in healthy individuals (Chong and Cros 2004), in particular for static QST (Backonja, Attal et al. 2013). However, the stability of QST over a longer period of time is largely unknown. Establishing adequate reliability of QST over the longer-term is important for monitoring sensory dysfunction over time as well as for using QST to evaluate responses to interventions.

The aim of this study was to investigate the long-term reliability of a multimodal QST assessment that included four static and two dynamic measures, with testing conducted on three occasions over a 4-month period.

6.3.3 Methods

Study design

Data were collected as part of a longitudinal prospective study assessing QST responses in a clinical cohort of both acute low back pain and healthy individuals, with the assessor blinded to the participant's condition. Participants were tested at 2 months and 4 months after the baseline assessment. The study protocol was approved by the Human

Research Ethics Committee at Macquarie University (Approval Reference No. 5201400840) and all participants gave written informed consent.

Participants and baseline characteristics

Participants were recruited from the local community in the Sydney metropolitan area between February 2015 and April 2016. Exclusion criteria were: 1) any pain at time of testing; 2) previous back surgery; 3) pregnancy; 4) any pain condition that had lasted for longer than one month over the last year affecting daily function and work ability; 5) any condition that can affect sensory function (e.g. diabetes mellitus, neurological disease, severe cognitive impairment); 6) any pain syndrome (e.g. fibromyalgia, osteoarthritis, irritable bowel syndrome); 7) substance abuse problem in the past 24 months or long term use of medications that may impact on cognitive or sensory function; or 8) being unable to read, write and understand English.

At baseline, demographic data (gender, age, height, weight, and race), pain catastrophising (Pain Catastrophising Scale, PCS) (Sullivan, Bishop et al. 1995) and psychological distress (Depression Anxiety and Stress Subscales Questionnaire, DASS-21) (Lovibond and Lovibond 1995), were collected.

Quantitative sensory testing (QST) procedure

All testing was conducted at the Physiotherapy Research Lab at Macquarie University, Australia. Prior to data collection, the QST protocol was trialled on 12 people not included in the analysis, to ensure consistency of the testing procedure across participants during the study period.

Participants were asked to limit their intake of caffeinated drinks and alcohol beverages as well as to refrain from taking sleeping medications 24 hours before testing. Tests were conducted in the same manner for all participants, in a quiet room maintained at constant temperature (23 ±1°C). Standardised instructions were read aloud to participants on each session. The following order of testing was used: cold and heat pain thresholds (CPT, HPT), mechanical wind up ratio (WUR), pressure pain threshold (PPT), two-point discrimination (TPD) and conditioned pain modulation (CPM). All participants underwent a training session to become familiar with the testing procedure before data were collected. CPT, HPT, WUR, PPT were performed according to the QST protocol of the German Research Network on Neuropathic Pain (DFNS) (Rolke, Magerl et al. 2006) at 3 body sites: at the hand, and bilaterally at the back. The testing

site on the spine was a random level chosen from T12 to S1. This was required to maintain the investigator blinded to the participant's condition (see below). Previous investigations have shown no significant differences in QST responses at different levels of the trunk in healthy subjects (Pfau, Krumova et al. 2014).

All tests were performed by a DFNS-trained researcher (AM) who had 5 years of clinical experience as a physiotherapist and 30 hours of training in QST testing. The investigator (AM) was blinded to participant condition (i.e. healthy control or low back pain). However, blinding was not possible for 10 people due to scheduling issues. QST protocols are described in detail below and reported in Table 1.

Thermal pain thresholds

Cold and heat pain thresholds (CPT, HPT) were measured using a 30x30mm ATS thermode (PATHWAY, MEDOC, Ramat Yishai, Israel). The temperature was decreased or increased at a ramp rate of 1°C/s starting at a baseline temperature of 32°C until participants pressed a button. The final threshold was calculated as the mean value of 3 consecutive measurements.

Wind up ratio

Wind up ratio (WUR) was measured comparing the perceived magnitude of pain from a single pinprick stimulus (256 mN, MRC System GmbH, Heidelberg, Germany) with that of a series of 10 pinprick stimuli of the same force delivered at 1/s rate within an area of 1 cm^2. The subject was instructed to give a pain rating both for the single stimulus and at the end of the 10 stimulus series using a 101-point Numeric Rating Scale (NRS101). This procedure was repeated 5 times at different skin sites within the testing area. If a pain rating of 0/100 was reported in more than 3 single stimulus assessments the WUR could not be calculated, therefore the intensity of the pinprick was increased to 512 mN and the procedure repeated. If the same outcome occurred for the 512 mN pinprick, WUR was designated as a missing value. The final WUR was calculated as the mean pain rating of 5 series of repeated pinprick stimuli divided by the mean pain rating of 5 single stimuli.

Pressure pain threshold

Pressure pain threshold (PPT) was measured using a pressure algometer (FDK40, Wagner Instrument, Greenwich, CT, USA) with a probe area of 1 cm^2. The pressure was gradually increased at a ramp rate of 50 kPa/s and participants were instructed to

verbally stop the test when the sensation of pressure alone changed to one of pressure and pain. The final threshold was calculated as the mean value of 3 consecutive measurements.

Two-point discrimination

The two-point discrimination threshold (TPD) was measured using a stainless steel digital calliper (150 mm Vernier calliper, Kincrome). The calliper was applied at L3 level for all participants, perpendicular to the back, until the first blanching of the skin. Ascending test series were performed by starting from 0 mm distance between the two tips and increasing the distance by 2 mm steps until the participant was able to perceive two points instead of one. Similarly, the descending series were applied where the distance was decreased by 2 mm starting from 100 mm until one point instead of two was felt. The participants were asked to say they felt one if they were unsure. A conservative approach was used whereby the TPD value of each run (ascending or descending) was recorded only when a consistent response was obtained for three consecutive stimuli. For example, if in the ascending series two points were first felt at 40 mm, then the distance was increased by 2 mm up to 44 mm and the threshold recorded as 40 mm only if successive trials were confirmed as two points. Otherwise, the stimulus was repeated starting from 40 mm until consistency was obtained. The final threshold was calculated as the mean value of two ascending and two descending runs.

Conditioned pain modulation

Conditioned pain modulation (CPM) was performed using two test stimuli: one thermal and one mechanical. The thermal test stimulus involved 30-seconds of heat (ATS thermode 30x30 mm PATHWAY, MEDOC, Israel) delivered to the volar aspect of the non-dominant forearm. The intensity of the heat stimulus was determined individually, based on the temperature that induced a pain score of 60 (*pain60*) on a 0-100 numeric rating scale (NRS101). The identification of *pain60* was determined from a series of increasing or decreasing 30 second heat stimuli starting at a temperature of 45°C with an inter-stimulus interval of 30 seconds. When *pain60* could not be identified, a pain rating ranging between 50 and 65 was accepted. The thermode was moved slightly between subsequent stimuli to avoid sensitisation of the skin. The mechanical test stimulus used was the pressure pain threshold (PPT) measured at the upper trapezius muscle. Measurement was made one third proximally between the spinal process of C7

and the acromion using a pressure algometer (FDK40, Wagner Instrument, Greenwich, CT, USA) with a probe area of 1 cm^2 and application rate of 50 kPa/s. The participant was instructed to verbally stop the test when the sensation of pressure alone changed to one of pressure and pain. The mean value of three consecutive measurements was used as final PPT threshold.

The conditioning stimulus (CS) was immersion of the contralateral foot in a cold water bath maintained at 10.5±1°C for 2 minutes. The bath consisted of a container divided into two by a perforated perspex sheet. One chamber was filled with ice and water that was stirred to maintain the other chamber at a constant temperature and continuously monitored by a thermometer with a digital display. Participants were instructed to immerse their foot in the water up to the ankle without touching the sides or bottom of the bath. They could withdraw the foot from the cold bath if the pain became intolerable. The time the foot was kept in the water was recorded.

Participants were asked to rate pain intensity of the foot while in the cold bath at 30, 60 and 90 seconds on the NRS101 scale. A second assessment of the heat stimulus was performed during the last 30 seconds of CS, and finally the three PPT measurements were performed immediately after CS. The final CPM scores were the difference in *pain60* (NRS101) or in PPT test stimuli before and after the CS with a negative value indicating an inhibitory response and a positive value indicating a facilitatory response.

Table 1 QST testing protocol details

Test	Testing sites	Equipment	Duration
Cold pain threshold (CPT)	Dorsum of the left hand (C7 dermatome) Lower back bilaterally (2 cm lateral to the spinous process)	30x30mm ATS thermode (PATHWAY, MEDOC, Ramat Yishai, Israel)	Up to 2 minutes (each site)
Heat pain threshold (HPT)	Dorsum of the left hand (C7 dermatome) Lower back bilaterally (2 cm lateral to the spinous process)	30x30mm ATS thermode (PATHWAY, MEDOC, Ramat Yishai, Israel)	Up to 2 minutes (each site)
Wind up ratio (WUR)	Dorsum of the left hand (C7 dermatome) Lower back bilaterally (within 3 cm lateral to the spinous process)	256 mN pinprick (MRC System GmbH, Heidelberg, Germany)	~2 minutes (each site)
Pressure pain threshold (PPT)	Thenar eminence of the left hand Lower back bilaterally (2 cm lateral to the spinous process)	Algometer (FDK40, Wagner Instrument, Greenwich, CT, USA)	~2 minutes (each site)
Two-point discrimination (TPD)	Lower back bilaterally at L3 level	Digital calliper ruler (150 mm Vernier calliper, Kincrome)	Up to 6 minutes (each side)
Conditioned pain modulation (CPM)	*Test stimuli* Heat pain: proximal volar aspect of forearm (dominant side) PPT: one third proximally between the spinal process of C7 and the acromion (dominant side) *Conditioning stimulus* Cold bath: foot contralateral side	Heat pain: 30x30mm ATS thermode (PATHWAY, MEDOC, Ramat Yishai, Israel) PPT: Algometer (FDK40, Wagner Instrument, Greenwich, CT, USA) Cold bath: container divided into two by a perforated perspex sheet	~15 to 20 minutes

Statistical analysis

Data were analysed using SPSS, version 22 (SPSS Inc., Chicago, Illinois). Three time points were assessed: baseline, 2 months and 4 months. Side to side differences of QST at the back (i.e. CPT, HPT, WUR, PPT, TPD) across the three time points were explored using repeated measures analysis of variance (RM-ANOVA) with within-group factors of Time (3 levels: Baseline, 2 months and 4 months) and Side (2 levels: left side and right side). No significant interaction between Time and Side and no significant effect for Side (all $p > 0.05$) were observed for any of the variables tested at the back, therefore the QST responses of the left and right back sides were averaged and the following statistical analyses were performed using the single mean value for the back. Listwise deletion was used to handle missing data which were limited to one case for WUR and two cases for CPM.

Mean values and SDs of QST variables at three time points were reported. Residuals vs fitted values plots of QST variables across the three time points were explored to investigate heteroscedasticity (where the amount of error changes with the magnitude of the QST variable values) and logarithmic transformation was carried out if unequal error variance was detected (Brehm, Scholtes et al. 2012). To facilitate the interpretation of log-transformed values, anti-log transformation was carried out in order to provide measures of absolute reliability (i.e. SEM and MDD, see below) in the original units. To investigate systematic bias of QST variables across the three sessions, RM-ANOVA with polynomial contrasts was carried out with Time as the within-group factor. Orthogonal polynomial contrasts were used to investigate significant trends of the data across the 3 sessions. Intraclass correlation coefficients (ICCs) were obtained using a single measure, consistency, two-way mixed effect model ($ICC_{3,1}$), as a measure of relative reliability of QST variables across the three time points. ICC values were interpreted as: >0.75 excellent reliability, 0.60-0.75 good reliability, 0.40-0.59 fair reliability, and <0.40 poor reliability (Shrout and Fleiss 1979). The standard error of the measurement (SEM) was calculated for each QST variable as a measure of absolute reliability. SEM quantifies the precision of individual responses across the three time points and has the advantage of being in the original units as the measurement of interest (Weir 2005). SEMs were calculated as the square root of the mean square error term from the repeated measures ANOVA (Weir 2005). The SEM index was then used to calculate the minimum detectable difference (MDD) using the formula SEM x 1.96 x $2^{1/2}$, which is the smallest change that can be considered a real change beyond the measurement error (Weir 2005).

6.3.4 Results

Forty-eight participants were enrolled in the study. Six participants did not attend all three sessions (4 withdrew after the first session, 1 after the second session and 1 missed the second session). These six people with incomplete datasets were therefore excluded. A total of 42 participants (21 (50%) females, mean age (SD): 30.2 (10) years) were included in the final analysis. Demographic and psychological variables are reported in Table 2.

Table 2 Demographic and psychological variables

Characteristics	
Female, n (%)	21 (50%)
Age, years (range)	30.2 (10) (18 to 58)
Height, cm	169.5 (10.5)
Weight, Kg	65.1 (12.8)
BMI, Kg/m^2	22.4 (2.6)
Race, n (%)	
White/Caucasian	25 (59%)
Asian	12 (29%)
Other	5 (12%)
Pain catastrophising, PCS (0-52)	7.1 (6.0)
Stress, DASS 21 (0-42)	6.0 (5.6)
Anxiety, DASS 21 (0-42)	2.7 (3.7)
Depression, DASS 21 (0-42)	2.5 (3.3)

Data are presented in Mean (SD) unless otherwise specified. BMI: body mass index; PCS: Pain Catastrophising Scale; DASS-21: Depression, Anxiety and Stress Scale.

Psychological profiles were in the normal range. On average, the time that elapsed from baseline to the 2 month sessions was 58.6 (SD 8.8) days, and 116 (SD 11.8) days to the 4 month sessions. Means, SDs and ranges for all QST variables are reported in Table 3.

Table 3 Mean (SD) and range of QST variables at the three time points

	Baseline	**2 Months**	**4 Months**
CPT hand, °C	10.3 (9.1) (0.0 to 28.2)	11.0 (8.0) (0.0 to 27.1)	10.8 (8.2) (0.0 to 27.3)
CPT back, °C	10.4 (10.2) (0.0 to 27.1)	10.9 (10.8) (0.0 to 28.4)	11.0 (10.7) (0.0 to 27.0)
HPT hand, °C	43.5 (3.8) (34.4 to 49.5)	43.2 (3.3) (36.7 to 49.7)	43.7 (3.1) (36.8 to 49.0)
HPT back, °C	43.1 (3.0) (36.7 to 49.3)	42.6 (3.1) (35.1 to 47.3)	43.0 (2.9) (37.0 to 48.4)
WUR hand, ratio	1.7 (1.0) (1.0 to 7.4)	2.0 (1.3) (1.0 to 7.6)	1.9 (0.8) (1.0 to 4.4)
WUR back, ratio	2.1 (1.2) (1.1 to 7.3)	2.4 (2.1) (1.1 to 14.4)	2.2 (1.2) (1.1 to 7.0)
PPT hand, kPa	414 (160) (173 to 1017)	386 (143) (180 to 847)	388 (126) (210 to 803)
PPT back, kPa	525 (180) (163 to 1092)	472 (160) (163 to 965)	476 (160) (195 to 1138)
TPD back, mm	60.5 (13.3) (35.5 to 89.2)	59.0 (11.9) (34.7 to 84.5)	57.6 (11.5) (32.7 to 84.0)
CPM heat, °C	-19.6 (15.6) (-50.0 to 10.0)	-16.2 (14.7) (-45.0 to 10.0)	-14.0 (14.6) (-50.0 to 20.0)
CPM PPT, kPa	-77 (77) (-270 to 30)	-60 (74) (-217 to 77)	-45 (65) (-200 to 77)

Data are presented in Mean (SD) (range). CPT: cold pain threshold; HPT: heat pain threshold; WUR: wind up ratio; PPT: pressure pain threshold; TPD: two-point discrimination; CPM: conditioned pain modulation.

Reliability of QST variables

The results of reliability analyses are summarized in Table 4 and presented below.

Thermal pain thresholds

No significant trend component of change over time, either linear or quadratic, was observed for CPT or HPT (all $p>0.05$) (Table 4). CPT and HPT at the hand and at the

back demonstrated good to excellent reliability, with $ICC_{3,1}$ values ranging from 0.68 to 0.79. For the CPT, the SEM value was lower at the hand compared to the back, indicating that CPT, over the 4 month period, is a more precise measure at the hand. For the HPT, the SEM value was lower at the back compared to the hand indicating that HPT, over the 4 month period, is a more precise measure when conducted at the back.

Wind up ratio

A systematic increase in WUR measured at the hand was observed in the linear trend ($p=0.03$), but this was not evident when measured at the back ($p=0.94$). WUR demonstrated fair to good reliability with $ICC_{3,1}$ values ranging from 0.51 to 0.61. SEM values were lower at the hand indicating that WUR, over the 4 month period, is more precise when measured at the hand than at the back.

Pressure pain threshold

A significant linear decrease over time in PPT measured at the back was observed (mean PPT difference baseline to 4 months: 49.3 kPa, $p=0.02$), but no significant trend component of change over time was evident at the hand ($p=0.12$). $ICC_{3,1}$ values showed excellent reliability of PPT measures (0.74 and 0.77 for the hand and the back, respectively). The SEM values were lower at the hand compared to the back indicating that PPT, over the 4 month period, is a more precise measure at the hand.

Two-point discrimination threshold

A significant linear decrease over time in TPD threshold was observed (mean TPD difference baseline to 4 months: 2.9 mm, $p<0.01$). TPD demonstrated excellent reliability with an $ICC_{3,1}$ value of 0.90.

Conditioned pain modulation

Mean (SD) and reliability estimates for the conditioning stimulus, the heat pain and PPT test stimuli are reported in Appendix 1. A significant linear decrease over time in CPM using both heat and PPT test stimuli was observed (mean CPM difference baseline to 4 months: 5.6/100 NRS (heat) and 31.5 kPa (PPT), $p<0.05$). CPM demonstrated poor to fair reliability with $ICC_{3,1}$ values of 0.35 and 0.50 with the PPT and heat as test stimuli, respectively.

Table 4 Measure of reliability of QST tests over the 4 month period: systematic bias (RM-ANOVA), relative reliability ($ICC_{3,1}$), absolute reliability (SEM) and minimum detectable difference (MDD)

	RM-ANOVA p value		**$ICC_{3,1}$** (95% CI)	**SEM**	**MDD**
	Linear	**Quadratic**			
CPT hand, °C	0.571	0.534	0.77 (0.66-0.86)	4.02	11.1
CPT back, °C	0.607	0.833	0.79 (0.68-0.87)	4.83	13.4
HPT hand, °C	0.706	0.123	0.68 (0.53-0.80)	1.93	5.3
HPT back, °C	0.851	0.106	0.76 (0.63-0.85)	1.49	4.1
WUR $hand_{log}$ ratio	0.031*	0.362	0.51 (0.32-0.68)	0.118 (1.31#)	0.327 (2.12#)
WUR $back_{log}$ ratio	0.936	0.581	0.61 (0.44-0.75)	0.122 (1.32#)	0.339 (2.18#)
PPT hand, kPa	0.120	0.256	0.76 (0.64-0.85)	73.0	202.2
PPT back, kPa	0.009‡	0.063	0.76 (0.64-0.86)	80.6	223.2
TPD back, mm	0.006‡	0.875	0.90 (0.83-0.94)	3.94	10.9
CPM heat, NRS101	0.032*	0.762	0.50 (0.31-0.67)	10.60	29.3
CPM PPT, kPa	0.023*	0.991	0.35 (0.16-0.54)	58.16	161.1

RM-ANOVA: Repeated Measure Analysis of Variance; CPT: cold pain threshold; HPT: heat pain threshold; WUR: wind up ratio; PPT: pressure pain threshold; TPD: two-point discrimination; CPM: conditioned pain modulation; ICC: intraclass correlation coefficient; SEM: standard error of the measurement; MDD: minimal detectable difference. #Anti-log transformed values. *$p<0.05$; ‡$p<0.01$

6.3.5 Discussion

This is the first study to investigate the long-term reliability of a range of static and dynamic QST measures, assessed on three occasions and at different body sites, in a cohort of healthy people. The main results are: (1) there was good to excellent reliability of the static QST measures assessed (i.e. CPT, HPT, PPT and TPD), while the reliability of dynamic QST tests (i.e. WUR and CPM) was lower; (2) there was a significant systematic decrease during the 4 month period for the static mechanical tests at the back (i.e. PPT and TPD), while no systematic change was observed for the static thermal tests at any sites; (3) the dynamic QST measures (i.e. CPM and WUR), significantly and systematically changed during the 4 month period; and (4) less variability was observed for measures at the hand compared with the back (with the exception for HPT) for QST tests measured at two body sites.

The high reliability of the static QST, as indicated by the ICC estimates above 0.70, indicates that these tests have a good ability to discriminate between individuals (de Vet, Terwee et al. 2006), even when testing is performed over long time periods. In other words, individuals preserve their ranking relative to the others over time. In contrast, the reliability of the dynamic QST measures was found to be lower. One explanation for this might be the differences in responses involved. Static tests that

determine a threshold provide a measure of the basal state of the nervous system, and are considered to involve a stable and reproducible endpoint that identifies one point on a scale of sensation (Arendt-Nielsen and Yarnitsky 2009). In contrast, dynamic tests such as CPM and temporal summation involve the assessment of more complex mechanisms of nociceptive modulation (Arendt-Nielsen and Yarnitsky 2009), including multiple and integrated central processing. It is perhaps not surprising that the dynamic and more complex nature of these responses results in higher variability. On the other hand, it should be noted that ICC estimates are also influenced by the range of measurement values (i.e. inter-individual variability) relative to the intra-individual variability between sessions (Portney and Watkins 2000). In this respect, CPM and WUR are calculated as a difference and ratio between scores, restricting the inter-individual range of values. Therefore, the lower ICC estimates observed for these dynamic tests should be expected and need to be interpreted in light of this caveat.

Short test-retest intervals (of the order of days and weeks) are commonly chosen in reliability studies with the assumption that the construct to be measured is stable over a short time frame, thereby minimizing possible sources of variability beyond the measurement error. When such investigations have been conducted previously in QST studies of healthy individuals, acceptable short-term reliability has been reported for thermal and mechanical tests, which is supported by our findings over longer intervals, particularly for static QST measures (Chong and Cros 2004, Backonja, Walk et al. 2009). However, regarding CPM testing, inconsistent results have been previously reported in healthy individuals. Intrasession reliability has been found to be good to excellent (ICC values ranging from 0.57 to 0.85) in two studies and intersession reliability (test-retest intervals from 1 day to 28 days) has been found to be poor to excellent (ICC values from 0.09 to 0.82) in four studies (Kennedy, Kemp et al. 2016). Taken together, these findings suggest that physiological variability of pain modulation over time is an important factor that can affect CPM reliability. Nonetheless, it is likely that methodological differences in CPM paradigms can account for such variability. Indeed, the lack of an accepted protocol for CPM testing has been a recent topic of discussion in the field (Yarnitsky, Bouhassira et al. 2015). Specifically, several factors related to CPM testing parameters, such as the timing, stimulus modality, duration, intensity and location, are recognised to impact on CPM responses (Treister, Eisenberg et al. 2010, Yarnitsky 2015). Such methodological influences might also explain

differences in reliability estimates between the two CPM paradigms tested in the current study, using heat pain and PPT test stimuli (ICC 0.50 and 0.35, respectively). In addition to the difference in stimulus modality, the paradigms used differed with respect to timing of test stimulus presentation (i.e. parallel vs sequential) and stimulation type (i.e. suprathreshold vs threshold).

Of interest was the finding that the static mechanical test responses at the back (i.e. PPT and TPD) showed a small, but significant systematic decrease over time, which was not observed for the thermal tests (CPT and HPT). This has been reported previously for PPT, with reduction between repeated testing sessions in shorter retest intervals (Jones, Kilgour et al. 2007, Yarnitsky 2015). Jones et al (Jones, Kilgour et al. 2007) suggested that a learned behavioural response or anticipatory cue might contribute to participants responding sooner to the pressure test in subsequent testing sessions. While this is an appealing explanation, it is not clear why this would occur only for mechanical tests and not for thermal tests. One factor might be that mechanical tests involve a greater extent of interaction between the examiner and the subject compared to thermal tests. However, future research is needed to corroborate these findings.

Systematic bias was also noted with the dynamic QST measures, whereby the CPM effect decreased and the WUR at the hand increased over time. It is possible that a different type of learning effect could explain the systematic decrease in CPM effect, whereby familiarity with the noxious conditioning stimulus (cold water bath at 10.5°C for 2 minutes) from a previous session could result in a reduced threat value for this stimulus, thus reducing the extent of descending inhibitory response. This is supported by evidence that the affective-motivational and cognitive-evaluative determinants of pain are involved in threat perception, in contrast to the sensory-discriminative pathways that are responsible for perception of stimulus intensity (Watson 2010). To our knowledge, this effect of a systematic reduction in CPM effect over time has not been reported in a previous reliability study. Regarding the systematic increase in WUR at the hand, the magnitude of this statistically significant increase from baseline to 4 months (0.2) was too small to be of clinical relevance.

Clinical implications and future research

The high reliability of static QST tests shown here indicates that these measures are suitable for monitoring individuals over time, even with retest intervals of many

months, which might be a useful attribute when monitoring the effects of an intervention for chronic pain. Particular caution should be taken when interpreting changes in mechanical tests such as PPT, where a small systematic decrease over time has been observed, mostly between the first and second measurement session. The low reliability for CPM testing, in particular using PPT as the test stimulus, suggests that this testing paradigm may be less useful for longitudinal studies. This finding supports a previous suggestion by Pud et al (Pud, Granovsky et al. 2009) regarding the questionable use of test-pain thresholds in CPM due to their high variability. It will be valuable in future research to further explore the reliability of CPM protocols, to specifically estimate which combination of test and conditioning stimuli have the highest reliability in healthy individuals.

Relative reliability estimates such as the ICCs reported here provide a measure of the extent to which a measurement can distinguish between individuals over and above the measurement error. In contrast, the SEM is an absolute reliability index, which reflects the agreement between repeated measures (i.e. how close repeated scores are) within each individual, providing information about the precision of the measurement. Therefore the MDD values derived from the SEM data reported in this study will be useful for determining sample sizes for future clinical studies and for clinicians and researchers looking to identify clinically meaningful changes in somatosensory function over longer periods of time.

Strengths and limitations

The first strength of this study is the wide range of QST measures evaluated, including static and dynamic tests. Secondly, this study provides reliability estimates in a cohort of healthy individuals screened for conditions that might affect somatosensory function. Establishing adequate reliability of QST measures in the absence of pathology is important when QST results are used as outcome measures in clinical populations. Thirdly, since this analysis was part of a larger study assessing QST responses in an acute low back pain cohort and in healthy individuals, the assessor was blinded to participants' conditions, a feature which reduces test application bias.

The following limitations need to be acknowledged. Firstly, it is unknown whether the order of testing influenced reliability estimates, as a counterbalanced design was not possible due to the number of variables assessed. Secondly, while efforts were made to

test participants at the same time of day for each session, this was not always possible. The stability of QST measures with the circadian cycle has been demonstrated (Geber, Klein et al. 2011), but is unknown for CPM. Lastly, for the CPM testing, PPT was applied after the heat pain test stimulus has ended, therefore it cannot be excluded that the latter could have impacted on the higher variability of the CPM effect using PPT. However, we have also assessed test-retest reliability for the two test paradigms separately in a cohort of 33 healthy males, and confirmed superior reliability of CPM using heat pain as a test stimulus compared with PPT (unpublished data).

6.3.6 Conclusions

Static mechanical and thermal QST of threshold determination investigated in this study were stable over a period of 4 months; however, the reproducibility of mechanical tests was affected by a small, but significant systematic decrease over time, therefore particular caution should be taken when interpreting changes associated with these measures. Dynamic QST showed considerable variability over time, possibly owing to the more complex nature of these responses as well as methodological factors. Assessment of CPM using PPT as the test stimulus did not show adequate reliability, suggesting that this test paradigm may be less useful for monitoring individuals over time.

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Appendix 1 Mean (SD) and reliability estimates of CPM assessment variables

	Baseline	2 Months	4 Months	RM-ANOVA p value		$ICC_{(3,1)}$ (95% CI)
				Linear	Quadratic	
Withdrawal from CS, n (%)	1 (2.5)	2 (5)	2 (5)	---	---	---
CS tolerance (sec)	118.0 (12.6)	116.1 (17.3)	116.4 (16.1)	---	---	---
CS (NRS101)						
30 sec	47.4 (24.4)	49.1 (21.9)	46.5 (23.9)	0.866	0.419	0.70 (0.56-0.81)
60 sec	58.9 (24.9)	60.6 (23.6)	60.1 (24.3)	0.573	0.564	0.78 (0.68-0.87)
90 sec	64.1 (23.6)	66.5 (22.7)	65.6 (23.7)	0.423	0.419	0.78 (0.67-0.87)
TS heat temperature (°C)	46.5 (1.3)	46.5 (1.3)	46.4 (1.2)	0.480	0.557	0.69 (0.55-0.81)
TS heat pre CS (NRS101)	55.1 (9.6)	56.3 (8.3)	54.6 (9.2)	0.575	0.463	0.38 (0.19-0.57)
TS heat post CS (NRS101)	35.6 (16.2)	40.1 (18.2)	40.8 (17.1)	0.072	0.283	0.56 (0.39-0.71)
TS PPT pre CS (kPa)	385.8 (134.0)	338.0 (114.0)	337.5 (105.1)	0.003‡	0.113	0.63 (0.46-0.76)
TS PPT post CS (kPa)	462.6 (179.1)	398.1 (135.9)	382.6 (123.0)	0.001‡	0.188	0.59 (0.41-0.73)

Data are presented in Mean (SD) unless otherwise specified. CS: conditioning stimulus; TS: test stimulus; NRS: numeric rating scale; PPT: pressure pain threshold; ICC: Intraclass correlation coefficient. ‡$p<0.01$

Chapter 7

The temporal development of somatosensory changes in acute low back pain

7.1 Preface

In Chapter 2 it was recognised that there is currently a lack of longitudinal data investigating somatosensory changes in low back pain. In Chapter 7, this is addressed with the report of a longitudinal study designed to explore the temporal development of somatosensory changes from soon after onset of low back pain to 4 months.

A paper based on this Chapter has been submitted for consideration for publication to *Pain Practice* and it is currently under review:

Marcuzzi A., Wrigley P.J., Dean C.M., Graham P.L., Hush J.M. (2016) (under review) "From acute to persistent low back pain: a longitudinal investigation of somatosensory changes using quantitative sensory testing" *Pain Practice* (submitted December 2016).

7.2 Co-authors' statement

As co-authors of the paper, "From acute to persistent low back pain: a longitudinal investigations of somatosensory changes using quantitative sensory testing", we confirm that Anna Marcuzzi has made the following contributions to this study:

- Conception and design of the research
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the manuscript
- Critical appraisal of the content

Associate Professor Julia Hush _____ Date 5 Dec 2016

Dr Paul Wrigley_____ Date 5 Dec 2016

Professor Catherine Dean _____ Date 5 Dec 2016

Dr Petra Graham _____ Date 5 Dec 2016

7.3 From acute to persistent low back pain: a longitudinal investigation of somatosensory changes using quantitative sensory testing

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Keywords

Somatosensory function, low back pain, acute pain, quantitative sensory testing, persistent back pain

Disclosure

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7.3.1 Abstract

Generalised pain hypersensitivity is commonly associated with chronic LBP. However, there are currently no longitudinal data regarding the temporal development of such sensory disturbances from the acute stage of LBP. Twenty-five people with acute LBP (< 3 weeks duration) and forty-eight pain-free controls were prospectively assessed at baseline using quantitative sensory testing (QST) with the assessor blinded to group allocation, and again at 2 and 4 months. Psychological variables were concurrently assessed. People with acute LBP were classified based on their average pain severity over the prior week at 4 months as recovered (≤1/10 NRS) or persistent (≥2/10 NRS) LBP. In the persistent LBP group, (1) there was a significant decrease in pressure pain threshold (PPT) between 2 and 4 months ($p<0.013$), and at 4 months PPT was significantly different from the recovered LBP group ($p<0.001$); (2) a trend towards increased temporal summation was found at 2 months and 4 months, at which point it exceeded 2 SDs beyond the pain-free control reference value. A gain in cold pain sensation was observed in the recovered LBP group from baseline to 2 months ($p<0.001$). Pain related psychological variables were significantly higher in those with persistent LBP compared to the recovered LBP group at all time points ($P<0.05$). Changes in mechanical pain tests occurring in the subacute stage warrant further longitudinal evaluation to better understand the role of somatosensory changes in the development of persistent LBP. Even mild pain self-efficacy impairments noted at baseline may be worthwhile in acute LBP.

7.3.2 Introduction

Low back pain (LBP) remains a clinical challenge and has the highest disability burden worldwide (Vos, Flaxman et al. 2013, Manchikanti, Singh et al. 2014). After an episode of LBP, up to two thirds of people still experience variable levels of pain after one year (Henschke, Maher et al. 2008, Vasseljen, Woodhouse et al. 2013) and a percentage of people (around 10%) will be significantly disabled as a result of LBP (Carey, Garrett et al. 2000). The reasons underlying failure to recover from an acute episode of LBP are not yet understood. Furthermore, consensus has not been achieved about which factors are most highly associated with poor outcome in LBP (Hayden, Chou et al. 2009). While psychosocial and pain-related factors such as poor coping strategies, job dissatisfaction, leg pain and higher pain intensity at LBP presentation have been shown to be significantly associated with delayed recovery, they explain only a limited proportion (ranging from 29% to 46%) of the variance in LBP outcomes (Kent and Keating 2008).

During the last few decades, research has demonstrated that several musculoskeletal chronic pain conditions, including LBP, are associated with generalised pain hypersensitivity, (Roussel, Nijs et al. 2013) most likely reflecting increased excitability and/or changes in pain modulation within the central nervous system (Curatolo, Arendt-Nielsen et al. 2006). It is suggested that such somatosensory alterations are important determinants for the transition to persistent pain from an acute episode of LBP (Handwerker 2012). Previous prospective studies in acute whiplash injury have shown a differential development of pain hypersensitivity to cold and mechanical stimuli as well as spinal cord hyperexcitability, in people reporting persistent pain and disability at 6 months compared to those who recover (Sterling, Jull et al. 2003, Sterling 2010). In LBP, while research investigating somatosensory function in the acute stage is developing (Marcuzzi, Dean et al. 2015), to our knowledge, no longitudinal studies designed to evaluate temporal changes have been published. Therefore, the time course of sensory disturbances from early after onset of LBP to later stages when chronic pain develops remains unknown.

The aim of this exploratory study was to investigate and compare the temporal development of somatosensory changes in people with acute LBP from as early as 3 weeks from onset up to 4 months, with pain-free controls. This knowledge will assist in

understanding mechanisms involved in the development of chronic LBP and factors associated with poor outcomes.

7.3.3 Methods

Study design

An inception cohort study was employed to explore quantitative sensory testing (QST) responses in people with acute LBP followed up until 4 months. Three assessments were performed: at < 3 weeks from LBP onset (baseline), then 2 months and 4 months after pain onset. Pain-free controls were assessed at the same three time points: at baseline, and 2 and 4 months later.

Participants

Twenty-five people with acute LBP and 48 pain-free controls were enrolled in the study. People with LBP were recruited from primary care practices (medical, physiotherapy, chiropractic clinics) and from the local community via advertisements, in the Sydney metropolitan area from February 2015 to April 2016. Participants were enrolled consecutively if they: (1) were adults (≥ 18 years old); (2) had LBP for less than 3 weeks; (3) had an average pain intensity during the last week of at least 3 on an 11-point numeric rating scale (NRS11, where 0 indicated no pain and 10 the worst pain imaginable). Acute LBP was defined as pain and discomfort localised below the costal margin and above the inferior gluteal folds with or without leg pain (Van Tulder, Becker et al. 2006) lasting more than 24 hours but less than 3 weeks preceded by a pain-free period of at least 1 month (de Vet, Heymans et al. 2002). Subjects were excluded if they had possible serious spinal pathology (i.e. spinal fracture or malignancy) based on the presence of red flags (Downie, Williams et al. 2013), previous back surgery, pregnancy, any pain condition that has lasted for longer than one month over the last year affecting daily function and work ability, diabetes mellitus, diagnosed co-morbid pain syndrome (e.g. fibromyalgia, osteoarthritis, irritable bowel syndrome), diagnosed neurological disease, unstable psychiatric disorder or psychosis, severe cognitive impairment (arising from head injury or other comorbidities), substance abuse problem in the past 24 months, long term use of medications that may impact on cognitive or sensory function (e.g. opiates intake greater than daily morphine equivalent 40mg), unable to read, write and understand English. Participants were allowed to continue their usual care for LBP and medications and/or treatments received were recorded. All

participants were provided with a copy of The Back Book (a resource recommended for use in primary care) (Royal College of General Practitioners 2002). Pain-free controls were recruited from the local community via advertisements. The exclusion criteria for the control group were the same as the LBP group plus any pain at time of testing. The study protocol was approved by the Human Research Ethics Committee at Macquarie University (Approval Reference No. 5201400840). All participants gave written informed consent.

Demographic, clinical and psychological variables

Demographic information collected included gender, age, body mass index (BMI), race and work status. People with LBP provided the following clinical information: LBP duration, pain intensity at time of testing, average pain intensity and worst level of pain over the last week scored from 0 (no pain) to 10 (the worst possible pain) on an 11 point numeric rating scale (NRS11), level of function measured by the Functional Rating Index (FRI) scored from 0 (high functional level) to 40 (low functional level) (Feise and Menke 2001), and disability level measured by the Roland Morris Disability Questionnaire (RMDQ) scored from 0 (no disability) to 24 (high disability) (Roland and Morris 1983).

All participants completed the following questionnaires: Depression, Anxiety and Stress Scale (DASS-21) scored from 0 (not at all) to 42 (extremely) (Lovibond and Lovibond 1995), and Pain Catastrophizing Scale (PCS) scored from 0 (not at all) to 52 (all the time) (Sullivan, Bishop et al. 1995). Participants with LBP also completed the Pain Self-Efficacy Questionnaire (PSEQ) scored from 0 (not at all confident) to 60 (completely confident) (Nicholas 2007), the Short-form McGill Pain questionnaire (SF-MPQ) to measure the sensory and emotional/affective dimensions of pain (Melzack 1987) and the PainDETECT questionnaire to screen for neuropathic features of LBP (Freynhagen, Baron et al. 2006). All questionnaires and clinical information (i.e. pain intensity and functional/disability levels) were collected at all three assessments.

Quantitative sensory testing (QST) protocol

A rigorous protocol was followed for all QST testing. Participants were asked to limit the intake of caffeinated drinks and alcohol beverages as well as refrain from taking sleeping medications 24 hours before testing. Tests were conducted in a quiet room maintained at a constant temperature, in the following order: cold and heat pain

thresholds (CPT, HPT), mechanical wind up ratio (WUR), pressure pain threshold (PPT), two-point discrimination (TPD) and conditioned pain modulation (CPM). All participants underwent a training session first to familiarise with the testing procedure. CPT, HPT, WUR, PPT were performed according to the QST protocol of the German Research Network on Neuropathic Pain (DFNS) (Rolke, Magerl et al. 2006). Measurements were taken at 3 body sites: bilaterally at the back and at the dorsum of the left hand (except for PPT, which was tested at the thenar eminence). For people with LBP, the testing site at the back was in the area of maximal pain, nominated by participants and the level confirmed through palpation by an experienced physiotherapist. A random level at the back (from T12 to S1) was chosen for pain-free controls. Previous investigations have shown no significant differences in QST responses at different levels of the spine in healthy controls subjects (Pfau, Krumova et al. 2014). A DFNS-certified researcher (AM) performed all tests blinded to participants' LBP or pain-free control status, and standardised instructions were used for all tests.

Thermal pain thresholds

Cold and heat pain thresholds (CPT, HPT) were measured using a 30x30mm ATS thermode (PATHWAY, MEDOC, Ramat Yishai, Israel). The temperature was decreased or increased at a ramp rate of 1°C/s starting at a baseline temperature of 32°C until participants pressed a button. Three consecutive measurements were performed and used in the analysis.

Wind up ratio

Wind up ratio (WUR) was measured comparing the perceived magnitude of pain of a single pinprick stimulus (256 mN, MRC System GmbH, Heidelberg, Germany) with that of a series of 10 pinprick stimuli of the same force delivered at 1/s rate within an area of 1 cm^2. The subject was instructed to give a pain rating for the single stimulus and after a 10 second wait, at the end of the 10 stimulus series. The pain score was reported using a 101 point numeric rating scale (NRS101). This procedure was repeated 5 times at different skin sites within the testing area. If a pain rating of 0/100 was reported following 3 single stimulus attempts with the 256 mN probe the ratio score could not be calculated. In these situations the force of the pinprick was increased to 512 mN and the procedure repeated again. If the same outcome occurred for the 512 mN pinprick, WUR was handled as a missing value. The final WUR was calculated as

the mean pain rating from the 5 series of repeated pinprick stimuli, divided by the mean pain rating from the 5 single stimuli.

Pressure pain threshold

Pressure pain threshold (PPT) was measured using a pressure algometer (FDK40, Wagner Instrument, Greenwich, CT, USA) with a probe area of 1 cm^2. The pressure was gradually increased at a ramp rate of 50 kPa/s and the participants were instructed to verbally stop the test when the sensation of pressure alone changed to one of pressure and pain. Three consecutive measurements were performed and used in the analysis.

Two-point discrimination

The two-point discrimination threshold (TPD), a measure of tactile acuity, was measured according to established protocol (Moberg 1990) using a stainless steel calliper ruler (150 mm Vernier calliper, Kincrome). The calliper was applied at the L3 level bilaterally (for all participants), perpendicular to the back until the first blanching of the skin. An ascending series was performed starting from 0 mm distance between the two tips and increasing the distance by 2 mm until the participant was able to perceive two points instead of one. Similarly, a descending series was applied where the distance was decreased by 2 mm until one point instead of two was perceived. The participants were asked to state that they felt one point if they were unsure. The TPD value was recorded only when a consistent response was reported for three consecutive measurements. For example, if in the ascending series two points were first felt at 40 mm the threshold was recorded as 40 mm only if two successive trials were also reported as two points (i.e. measurements at 42 and 44 mm were also perceived as two points). Otherwise the stimulus was repeated from 40 mm until a consistent response was obtained. Two ascending and two descending measurements were performed and used in the analysis.

Conditioned pain modulation

<u>Heat pain - test stimulus</u>

The test stimulus was a 30-second thermal heat contact (ATS thermode 30x30 mm PATHWAY, MEDOC, Israel) delivered to the volar aspect of the non-dominant forearm. The intensity of the heat stimulus was determined individually based on the temperature that induced a pain score of 60 (*pain60*) on a 0-100 numeric rating scale (NRS101). The identification of *pain60* was determined from a series of increasing or

decreasing 30 second heat stimuli starting at a temperature of 45°C with an inter-stimulus interval of 30 seconds. When *pain60* could not be identified, a pain rating ranging between 50 and 65 was accepted. The thermode was slightly moved around in between subsequent stimuli to reduce sensitisation of the skin.

Cold pressor test – conditioning stimulus

The conditioning stimulus (CS) was immersion of the contralateral foot in a cold water bath maintained at 10.5±1°C for 2 minutes. The bath consisted of a container divided into two by a perforated perspex sheet. One chamber was filled with ice and water that was stirred to maintain the other chamber at a constant temperature and continuously monitored by a thermometer with a digital display. Participants were instructed to immerse their foot in the water up to the ankle without touching the sides or bottom of the bath. They could withdraw the foot from the cold bath if the pain became intolerable. The time the foot was kept in the water was recorded.

CPM procedure

Participants were asked to rate pain intensity of the foot while in the cold bath at 30, 60 and 90 seconds on an NRS101 scale. A second assessment of the heat stimulus was performed during the last 30 seconds of CS. The final CPM scores were the difference in test stimulus pain rating before and after the CS with a negative value considered an inhibitory response and a positive value considered a facilitatory response.

Statistical analysis

There is no standardised approach for measuring recovery from LBP (Kamper, Stanton et al. 2011). In this exploratory study, people with LBP were classified into two groups based on their average pain intensity score over the previous week (NRS11) at 4 months: people reporting a NRS≤1 were classified as recovered LBP and those reporting NRS≥2 as persistent LBP, as reported previously (McGuirk, King et al. 2001, Hancock, Maher et al. 2007). Group differences in continuous variables (demographic and clinical) at baseline between recovered and persistent LBP and pain-free controls were compared using nonparametric one-way ANOVA Kruskall-Wallis tests. Categorical variables were compared using chi-squared tests of association. For the QST variables tested at the back, it was decided *a priori* that only the values of the affected side of people reporting unilateral LBP would be used in the analysis while for people with bilateral (or central) LBP, and for pain-free controls, the values of the left

and right sides would be averaged. Two QST variables (WUR and PPT) were highly skewed so a log transformation was used to avoid potential issues with modelling assumptions.

Linear mixed effects models were used to model the change over time in QST variables and clinical and psychological variables (RMDQ, FRI, PSEQ, PCS, DASS-21) between groups, with a random intercept used to control for the repeated measures for each individual within a time point and over time. Use of a random slope to control for an individual's change over time was also explored but did not improve the model fit and was not retained. Time was treated as categorical in order to model possible non-linear changes and because it produced the best model fit compared to continuous time. The initial model looked for the presence of a significant interaction between time and groups. Because multiple testing was performed on related outcome variables, a Bonferroni type correction was used to adjust the significance level for the 11 QST outcome measures and the 5 clinical and psychological variables, and was set at α=0.003 (0.05/16). If the interaction was significant, the groups were compared at specific time points using Tukey pairwise multiple comparisons (corrected α=0.05). If there was no significant interaction then the interaction term was removed and the main effects model was retained to determine if there was a significant change over time after adjusting for groups, or a significant difference between groups after adjusting for time. All available data were used in the analysis with the linear mixed-effects model providing unbiased mean effect estimates under the assumption that any missing values were missing at random (Ibrahim and Molenberghs 2009).

In order to further illustrate sensory profiles of the LBP groups across the three time points, QST data were z-transformed using pain-free controls values as reference data using the following expression, z-scores: $(\text{mean}_{\text{single individual}} - \text{mean}_{\text{controls}})/\text{SD}_{\text{controls}}$ (Rolke, Magerl et al. 2006). For clarity of data presentation, the algebraic sign of z-scores for each QST variables was adjusted so that z-values above 0 indicated a gain of function (i.e. higher sensitivity compared to controls) and z-values below 0 indicated a loss of function (i.e. reduced sensitivity compared to controls). These z-plots were presented for QST variables from the DFNS protocol.

All the analyses were performed using R statistical software.

7.3.4 Results

Study participation

Figure 1 shows the flow chart of recruitment and screening of participants. A total of 246 individuals were screened for the study. Of 98 potentially eligible participants, 73 (25 people with LBP and 48 controls) provided consent to participate and were enrolled in the study. Two people with LBP and 4 pain-free controls withdrew after the baseline assessment; 1 control did not attend the first follow up, and 1 person with LBP and 1 control did not attend the second follow up session.

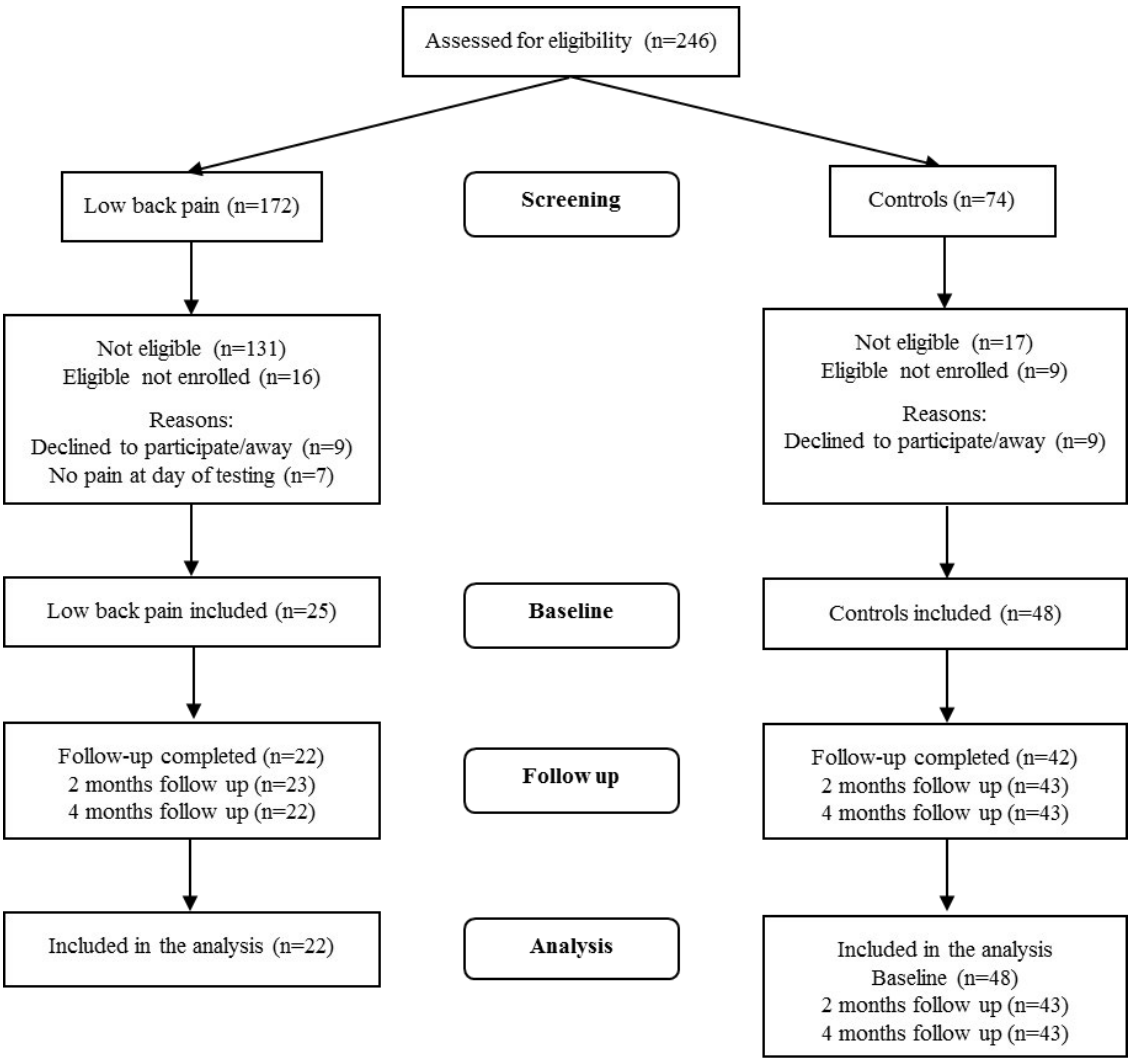

Figure 1 Screening and study participation flow diagram adapted from Consort Transparent Reporting of Trials

Participants

Twenty-two people with LBP completed the study and were therefore included in the analysis. Fifteen people were classified as recovered LBP (NRS≤1 at 4 months) and 7 people were classified as persistent LBP (NRS≥2 at 4 months). This classification was consistent with a significantly higher level of functional pain interference (assessed with the FRI) reported in the persistent LBP group compared to the recovered LBP group at 4 months (p=0.003) (Table 3). Although recruitment targeted both primary care clinics and the community, the majority of LBP participants (88%) who were enrolled in the study were from the community and not actively seeking health care.

Demographic and clinical features at baseline are reported in Table 1. The recovered and the persistent LBP were assessed, on average, as early as 10 and 13 days from onset of LBP, respectively. There were no statistically significant differences between the LBP groups and the pain-free controls in demographic variables with the exception of BMI, which was higher in the LBP groups (p=0.04). Among the LBP groups, those with persistent LBP had significantly higher pain intensity (NRS11) compared to the recovered LBP group, at baseline (p=0.03) and at 2 months (p=0.002). Medication intake and treatments received during the 4 month period in both LBP groups are reported in Table 2.

Table 1 Demographic and clinical characteristics of recovered and persistent low back pain groups and pain-free controls at baseline

	Recovered LBP N=15	**Persistent LBP** N=7	**Pain free controls** N=48
Female, n (%)	8 (53.3)	3 (42.9)	25 (52.1)
Age, years	32.5 (13.2)	30.6 (11.9)	30.0 (9.8)
BMI, Kg/m^2	24.8 (3.2)*	24.3 (2.7)*	23.2 (5.9)
Race, n (%)			
White/Caucasian	9 (60.0)	4 (57.1)	28 (58.3)
Asian	4 (26.7)	1 (14.3)	15 (31.3)
Other	2 (13.3)	2 (28.6)	5 (10.4)
Current work status, n (%)			
Student	9 (60.0)	3 (42.9)	29 (60.4)
Employed	6 (40.0)	3 (42.9)	17 (35.4)
Unemployed/retired	0 (0.0)	1 (14.3)	2 (4.2)
Pain duration, days	9.9 (6.4)	13.1 (3.2)	NA
Average pain intensity, NRS11	3.8 (1.4)*	5.4 (1.5)*	NA
Neuropathic screening, PainDETECT, n (%)			
Nociceptive (0-12 score)	15 (100)	5 (71.4)	NA
Unclear (13-18 score)	0 (0.0)	2 (28.6)	NA
Neuropathic (19-38 score)	0 (0.0)	0 (0.0)	NA
Pain descriptors, SF-MPQ			
Sensory (0-33)	7.7 (4.2)	10.9 (5.7)	NA
Affective/emotional (0-12)	1.0 (1.0)	2.7 (2.6)	NA

Data are presented as Mean (SD) unless otherwise specified. LBP: Low back pain; BMI: body mass index; NRS11: Numeric Rating Scale (0-10). *p<0.05

Table 2 Use of medications and treatment in the 24 hours before assessment in people with low back pain, at three time points

	Recovered LBP N=15			**Persistent LBP** N=7		
	Baseline	2 months	4 months	Baseline	2 months	4 months
Participant taking medications, n (%)	4 (26.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)
Medication type	Simple analgesic (acetaminophen, NSAIDs)	NA	NA	NA	Simple analgesic (NSAIDs)	NA
Participant receiving treatment, n (%)	5 (33.3)	4 (26.7)	2 (13.3)	3 (43.0)	2 (28.6)	0 (0.0)
Treatment type	Physiotherapy Chiropractic Massage	Physiotherapy Chiropractic Massage	Physiotherapy Chiropractic	Physiotherapy	Physiotherapy	NA

LBP: Low back pain; NSAIDs: nonsteroidal anti-inflammatory drug; NA: not applicable.

Clinical and psychological variables

Longitudinal data for clinical and psychological variables are reported in Table 3. For disability levels measured by the RMDQ, no significant interaction between time and group was found. After adjusting for groups, the RMDQ scores significantly decreased over time ($p<0.001$). For the level of functional pain interference measured by the FRI, a significant interaction between time and group was observed ($p<0.001$). Post-hoc tests showed that in both LBP groups the level of functional pain interference significantly decreased from baseline to 2 months ($p<0.004$) and in the recovered LBP group, further decreased from 2 to 4 months ($p=0.008$). No differences in FRI scores were found at baseline between LBP groups ($p=0.509$), however the persistent LBP group had significantly higher levels of functional pain-interference at 2 and 4 months compared with the recovered LBP ($p<0.001$).

A significant interaction between time and group was observed for all three psychological variables assessed ($p<0.001$). Post-hoc tests showed that pain-self efficacy and pain catastrophising significantly improved (i.e. PSEQ increased and PCS decreased) in both LBP groups from baseline to 2 months ($p<0.001$) and in the persistent LBP group, further improvement was shown from 2 to 4 months ($p<0.043$). However, the persistent LBP group had significantly lower levels of pain self-efficacy and higher levels of pain catastrophising compared to the recovered LBP at all time points ($p<0.047$) (Figure 2). Depression, anxiety and stress (DASS-21) scores were low and in the normal range in all three groups. Post-hoc tests showed that DASS-21 scores significantly decreased in recovered LBP from baseline to 2 and 4 months ($p<0.004$), and in persistent from baseline to 2 months ($p=0.011$). A significant difference was observed between the LBP groups and the pain-free controls at baseline ($p<0.044$), but no significant differences were observed between groups at 2 and 4 months.

Table 3 Clinical and psychological variables in people with low back pain at three time points

	Recovered LBP N=15			Persistent LBP N=7		
	Baseline	2 months	4 months	Baseline	2 months	4 months
Clinical variables						
Pain intensity (average prior week), NRS11	3.8 (1.4)	1.3 (1.3)	0.3 (0.6)	5.4 (1.5)	3.3 (0.8)	3.3 (1.4)
Disability, RMDQ (0-24)	4.9 (1.1)	2.2 (0.8)	1.1 (0.3)	6.7 (2.0)	3.1 (1.0)	2.4 (1.0)
Function, FRI (0-40)‡	13.3 (1.7)	6.0 (1.7)	2.9 (0.8)	14.7 (2.2)	11.4 (2.0)	10.9 (1.4)
Psychological variables						
Pain self-efficacy, PSEQ (0-60)‡	52.3 (3.0)	58.1 (1.1)	59.1 (0.4)	32.2 (5.8)	45.0 (6.8)	48.7 (2.4)
Pain catastrophizing, PCS (0-52)‡	7.0 (2.0)	3.7 (0.7)	2.5 (0.8)	17.0 (2.8)	11.9 (3.1)	6.9 (1.8)
DASS-21 total score (0-126)‡	19.3 (3.7)	13.5 (3.5)	9.8 (2.5)	23.1 (7.6)	18.3 (7.7)	19.7 (8.9)
Depression (0-42)	5.3 (1.8)	3.2 (1.1)	2.9 (1.2)	5.7 (2.3)	4.3 (2.4)	7.1 (4.0)
Anxiety (0-42)	3.9 (0.9)	3.2 (1.0)	1.7 (0.5)	7.7 (2.8)	6.6 (2.5)	4.6 (1.9)
Stress (0-42)	10.1 (1.9)	7.1 (1.8)	4.3 (1.5)	9.7 (3.1)	7.4 (3.1)	8.0 (3.1)

Values are reported as Mean (SE). LBP: Low back pain; NRS: Numeric Rating Scale; RMDQ: Roland-Morris Disability Questionnaire; FRI: Functional Rating Index; PSEQ: Pain Self Efficacy Questionnaire; PCS: Pain Catastrophizing Scale; DASS-21: Depression, Anxiety and Stress Scale. ‡ Significant interaction time*group: $p<0.001$

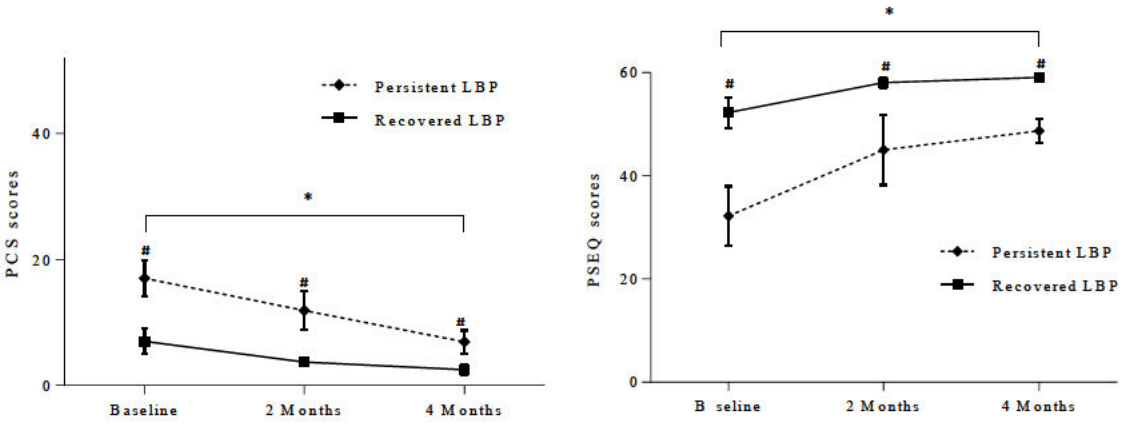

Figure 2 Mean (SE) pain-self efficacy (PSEQ) and pain catastrophizing (PCS) scores in persistent and recovered LBP groups at three time points. # Significant difference between groups $p<0.05$; * Significant change over time $p<0.001$

Quantitative sensory testing

Longitudinal data for QST variables at three time points and linear mixed effect model analyses are reported in Table 4.

Thermal pain threshold

There was a significant interaction between time and group for CPT at the hand ($p<0.001$) (Table 3). Post-hoc tests showed that in the recovered LBP group, CPT at the hand significantly increased from baseline to 2 months ($p<0.001$) and normalised by 4 months, as also illustrated in the z-score plot (Figure 3A), while in the persistent LBP group and in the pain-free controls, CPT at the hand remained unchanged over the 4 months. For CPT at the back and HPT at both sites, no significant interactions between time and group were observed, and no significant main effects for time and for group were observed after removing the interaction term.

Wind up ratio

No significant interaction between time and group was found for WUR at both sites ($p>0.05$). No significant main effects for time and for group were observed ($p>0.05$) after removing the interaction term. The z-score plots (Figure 3B) illustrate that compared with the recovered LBP group, the persistent LBP group shows a trend towards an increase in WUR at the hand between baseline and 2 months, with a further increase at 4 months, then reaching a difference of 2 SDs from controls.

Pressure pain threshold

There was a significant interaction between time and group for PPT at the hand ($p=0.003$) and at the back ($p<0.001$). Post-hoc tests showed a significant decrease in PPT at both sites in pain-free controls from baseline to 2 months ($p<0.014$) and in the persistent LBP group from 2 to 4 months ($p<0.013$), while in the recovered LBP group PPT remained unchanged ($p>0.05$). No significant differences were observed between groups at any time points for PPT at the hand ($p>0.05$). For PPT at the back, the persistent LBP group had significantly lower PPT compared to the recovered LBP group at 4 months ($p<0.001$) as illustrated in the z-score plots (Figure 3B).

Table 4 Descriptive statistics of QST variables at three time points and linear mixed effect model analyses

	Recovered LBP			**Persistent LBP**			**Pain-free controls**			**Interaction Time*Group**	**Main effect^** P value	
	Baseline	2 months	4 months	Baseline	2 months	4 months	Baseline	2 months	4 months	P value	Time	Group
CPT, °C												
Hand	8.1 (2.0)	13.5 (2.0)	11.6 (2.0)	12.5 (3.0)	13.1 (3.0)	14.7 (3.0)	10.9 (1.2)	11.3 (1.2)	11.2 (1.2)	<0.001*		
Back	15.7 (2.6)	13.6 (2.6)	13.3 (2.6)	15.8 (3.8)	17.2 (3.8)	16.8 (3.8)	11.4 (1.6)	11.6 (1.6)	11.7 (1.6)	0.060	0.964	0.332
HPT, °C												
Hand	43.6 (0.8)	42.1 (0.8)	43.6 (0.8)	42.0 (1.1)	42.6 (1.1)	42.4 (1.1)	43.3 (0.4)	43.1 (0.4)	43.6 (0.4)	0.732	0.219	0.654
Back	42.4 (0.8)	42.5 (0.8)	43.1 (0.8)	42.0 (1.1)	42.0 (1.1)	41.6 (1.1)	42.7 (0.5)	42.3 (0.5)	42.7 (0.5)	0.216	0.039	0.814
WUR‡, ratio												
Hand	2.1 (0.4)	2.0 (0.4)	2.3 (0.6)	2.1 (0.6)	3.6 (1.3)	4.2 (1.6)	1.7 (0.1)	1.9 (0.2)	1.9 (0.1)	0.155	0.023	0.072
Back	2.6 (0.4)	2.4 (0.4)	2.3 (0.4)	2.7 (0.7)	2.4 (0.7)	3.9 (0.7)	2.2 (0.3)	2.3 (0.3)	2.1 (0.3)	0.371	0.956	0.672
PPT‡, kPa												
Hand	451 (39)	464 (39)	485 (39)	373 (57)	399 (57)	345 (57)	409 (22)	383 (22)	384 (22)	0.003*		
Back	604 (46)	624 (46)	645 (46)	441 (66)	436 (66)	374 (66)	505 (26)	452 (26)	457 (26)	<0.001*		
TPD back, mm	62.3 (3.0)	60.8 (3.0)	59.1 (3.0)	66.0 (4.3)	59.7 (4.3)	59.0 (4.3)	61.5 (1.7)	60.1 (1.7)	58.8 (1.7)	0.087	<0.001*	0.941
Cold pressor test, NRS101	54.9(6.0)	53.8 (6.0)	49.3 (6.0)	71.2 (8.7)	63.3 (8.7)	63.8 (8.8)	55.7 (3.4)	57.9 (3.4)	56.7 (3.4)	0.017	0.280	0.423
CPM heat, NRS101	-16.3 (3.7)	-16.0 (3.7)	-17.5 (3.7)	-21.8 (5.5)	-26.4 (5.5)	-14.2 (5.8)	-20.0 (2.1)	-15.8 (2.2)	-13.4 (2.3)	0.243	0.174	0.687

Values are reported as Mean (SE) unless otherwise specified. LBP: Low back pain; NRS: Numeric Rating Scale; CPT: cold pain threshold; HPT: heat pain threshold; WUR: wind up ratio; PPT: pressure pain threshold; TPD: two-point discrimination; CPM: conditioned pain modulation. ‡Analysis performed on log-transformed variables; ^P values of main effects after removing the interaction term *Bonferroni corrected significance level: $\alpha<0.003$

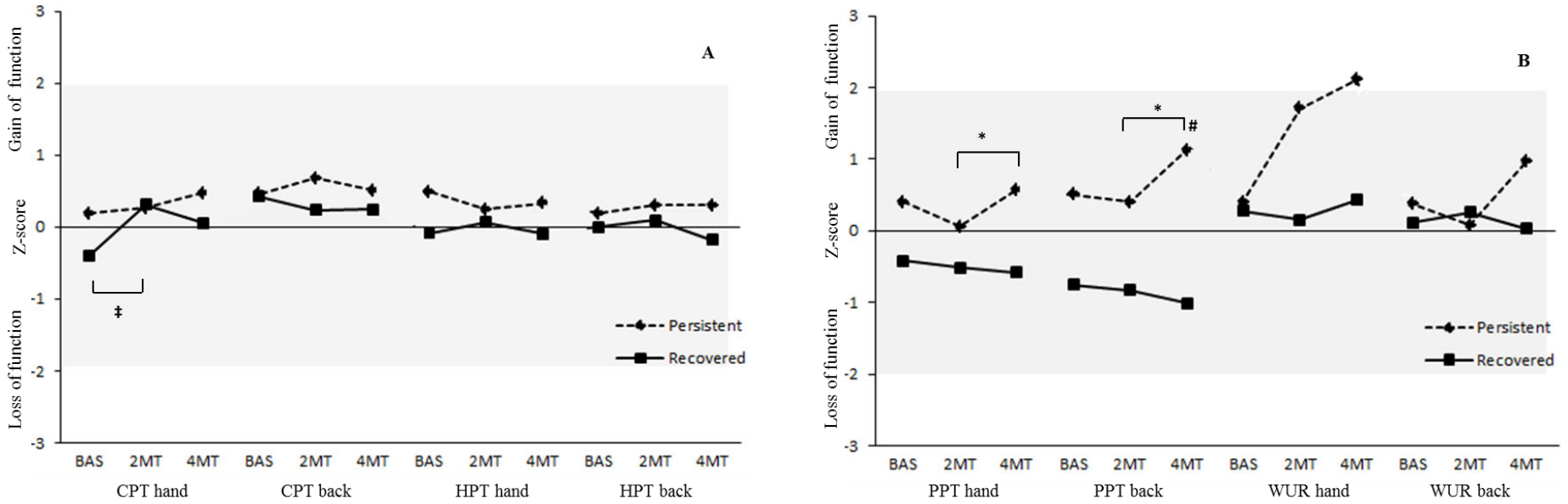

Figure 3 Sensory profiles of LBP groups for QST variables of the DFNS protocol at three time points. **A**: Thermal QST variables; **B**: Mechanical QST variables. Shaded area represents 95% confidence interval of reference values from controls. BAS: baseline; 2MT: 2 months; 4MT: 4 months. CPT: Cold pain threshold; HPT: heat pain threshold; PPT: Pressure pain threshold; WUR: wind up ratio. ‡Significant change over time in recovered LBP, $p<0.001$; *Significant change over time in persistent LBP, $p<0.001$; #Significant difference between LBP groups, $p<0.001$

Two-point discrimination threshold

There was no significant interaction between time and group for TPD (p=0.08). A significant main effect for time was observed after removing the interaction term. After adjusting for groups, TPD showed a significant decrease from baseline to 4 months (p<0.001).

Cold pressor test

There was no significant interaction between time and group for the cold pressor test (p=0.017). No significant main effects for time and for group were observed (p>0.05) after removing the interaction term.

Conditioned pain modulation

There was no significant interaction between time and group for the CPM response (p=0.243). No significant main effects for time and for group were observed (p>0.05) after removing the interaction term (Figure 4).

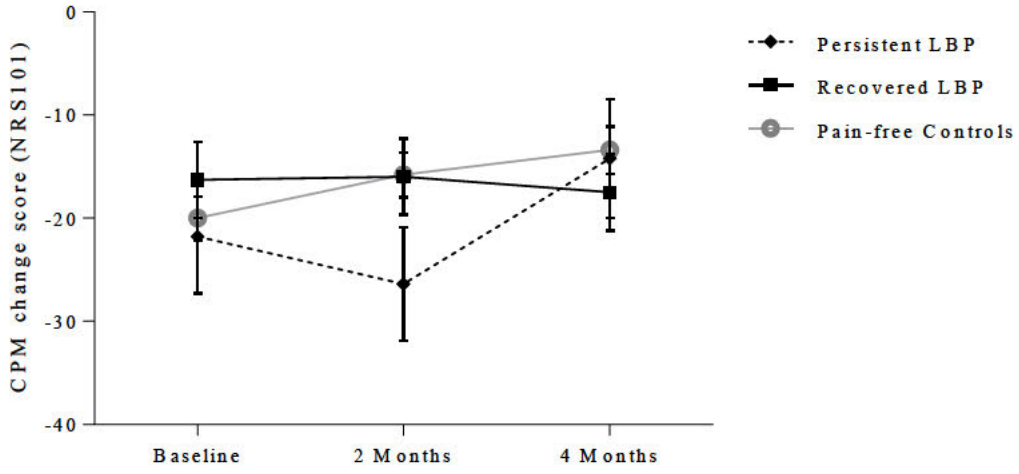

Figure 4 Mean (SE) CPM scores in persistent, recovered LBP groups and pain-free controls at three time points. NRS: Numeric Rating Scale

7.3.5 Discussion

This is the first longitudinal study to report the time course of somatosensory function in an inception cohort of acute LBP followed up until 4 months. A comprehensive QST protocol encompassing static and dynamic tests was used, and longitudinal changes in pain-related psychological factors were concurrently evaluated.

The main finding of this study was that an increase in mechanical pain sensitivity was observed in the persistent LBP group, suggesting potential underlying changes in the nervous system sensitivity occurring in the subacute stage. Specifically, an increase in pressure pain sensitivity was seen between 2 to 4 months; and an earlier trend towards increased temporal summation was identified between baseline and 2 months, and 2 to 4 months, at which point it exceeded 2 SDs beyond the pain-free control reference value (though not reaching statistical significance). In addition to the temporal changes in mechanical sensitivity in the persistent LBP group, a gain in cold pain sensation was observed in the recovered LBP group from baseline to 2 months, which normalised from hypoesthetic to the pain-free values by 2 months.

Pressure pain testing

When the z-score plots (Figure 3B) for pressure pain testing are examined, the two LBP groups diverge with sensitivity in the persistent LBP significantly increasing over time (particularly at the back), and significant differences from the recovered LBP at 4 months. Enhanced responses to pressure pain testing may reflect underlying sensitisation mechanisms such as the recruitment of silent nociceptors following persisting stimulation (Treede, Rolke et al. 2002). A similar increase in pressure pain sensitivity at the back has been reported in other sectional studies in subacute LBP (Farasyn and Meeusen 2005, Farasyn and Meeusen 2007). However, it is important to note the tendency for PPT to significantly decrease over time (i.e. control values reduce from baseline to 2 months, $p<0.02$). This phenomenon of a systematic decrease in PPT in pain-free controls has previously been reported, particularly between the first and the second measurements (Jones, Kilgour et al. 2007). This emphasises the importance of longitudinal comparative analyses with pain-free controls to identify potential clinically meaningful differences.

Temporal summation

The increase in temporal summation (WUR) at the hand in the persistent LBP group during the 4 month period is noteworthy, given that it was 2SD higher than the mean control value. The failure to reach statistical significance may be due to the relatively large variance, particularly in the persistent LBP group.

To the best of our knowledge only one published study has reported on a range of QST variables in acute LBP ($\leq$ 4 weeks from onset) using a prospective study design

(Starkweather, Lyon et al. 2016) with QST performed at baseline. These authors reported that generalised hyposensitivity to thermal (non-noxious) stimuli, as well as enhanced temporal summation at the hand (but not at the back) measured in acute LBP, differentiated people who had not recovered at 6 months from those who had. Unlike in the Starkweather study (Starkweather, Lyon et al. 2016), we did not find any differences in temporal summation (WUR) between the LBP groups at baseline; however, we identified a trend towards an increase in WUR amplitude in the persistent LBP group at the subacute stage. Two other cross-sectional studies have shown early enhancement of temporal summation in people with acute LBP (< 4 weeks duration), compared with healthy controls (Manresa, Neziri et al. 2013, Starkweather, Ramesh et al. 2016), demonstrating that, in some subgroups of people with LBP, central hyperexcitability may be dectected in the very early stages of LBP.

Thermal pain testing

Among the thermal pain tests (cold and heat) including the cold pressor test, only the CPT showed a differential change over time (Figure 3A) with CPT at the hand significantly increasing (return to normal) in the recovered LBP group from baseline to 2 months. However, while this change was statistically significant, the magnitude of CPT change (within 1 SD of pain-free controls) is unlikely to be clinically meaningful.

Tactile acuity

This study provides the first data on tactile acuity in acute LBP as well as serial measures over time, until the onset of chronic LBP. The results showed no differences in TPD threshold between the two LBP groups and the controls, suggesting that tactile acuity is not impaired in acute, subacute or early chronic LBP in the cohort studied. However, there was a small, but significant decrease in TPD threshold over time, indicating an improvement in tactile acuity, although these changes were within the measurement error range (Catley, Tabor et al. 2013). A previous systematic review has demonstrated a relatively consistent presence of altered tactile acuity in chronic LBP, particularly when measured at the area of greatest pain (Catley, O'Connell et al. 2014). Studies included in the review investigated people with longstanding chronic LBP (e.g. from 30 to 108 months) and may reflect functional changes that develop over longer periods of time, compared with the maximum 4 month duration of LBP in our study. The lack of changes in tactile acuity in our study may also be due to the fact the

measurement was performed at a standardised site at the back (L3), rather than the most painful site, due to the need to maintain blinding of assessor.

Conditioned pain modulation

Our result that those with acute LBP had a significant CPM effect that did not differ from pain-free controls, adds to the limited literature on this topic. One previous report of CPM in acute LBP (< 4 weeks duration) also found no significant differences in CPM effect from controls (Mlekusch, Neziri et al. 2016). It has been suggested that ongoing persistent pain may impair the balance in descending spinal cord modulation reducing CPM inhibition and/or increasing facilitation (Pud, Granovsky et al. 2009). However, the literature reporting changes in CPM in chronic LBP is sparse and somewhat conflicting with some studies reporting altered pain inhibition (Correa, Costa et al. 2015, Rabey, Poon et al. 2015) and others showing no difference in CPM effect (Julien, Goffaux et al. 2005, Vlckova, Srotova et al. 2014, Mlekusch, Neziri et al. 2016) compared to controls. In other chronic pain conditions such a fibromyalgia or headache, CPM dysfunction has been more consistently documented (Lewis, Rice et al. 2012). The current longitudinal analysis did not find changes in descending pain inhibition with LBP persistence, at least in the early months in this study sample. However, in light of the methodological variability of CPM testing (Pud, Granovsky et al. 2009), it is also not possible to exclude that the test was unable to detect changes if they did exist.

Psychological factors

Of interest was that the only measures that differentiated the persistent from recovered LBP groups at baseline were psychological measures of self-efficacy (PSEQ) and pain catastrophising (PCS). Clinically significant lower self-efficacy scores were noted at baseline for the persistent LBP compared to the recovered LBP group (baseline PSEQ (SD) = 32.2 (5.8) mild impairment and 52.3 (3.0) minimal impairment, respectively (Electronic Persistent Pain Outcomes Collaboration)). This would suggest that even mild PSEQ impairment may be noteworthy at baseline in acute LBP.

Psychological distress and pain-related cognitions both reduced over time in both LBP groups, although significant differences between the two groups were maintained at all time points. The improvements in pain-related psychological variables, particularly in the persistent LBP group align with the concurrent reduction of pain severity and disability levels (measured by RMDQ) observed at all three time points assessed (Table

3). This may reflect the fact that our sample was primarily community-based with relatively low initial levels of psychological distress and inherently greater capacity to cope with, and adapt to, pain over time.

Strengths and limitations

The strengths of this study are that established protocols were used for multimodal QST testing by a single DFNS-trained assessor; that we were able to assemble and follow up an inception cohort of people at as early as 3 weeks from onset of LBP; and that we reduced bias by blinding the investigator to participants' condition.

The following limitations of the study are acknowledged: first, the sample size was relatively small, so we may have been underpowered to detect statistically significant differences between groups at different time points, particularly for some QST measures. Nonetheless, the results from this novel time series provide insights into longitudinal changes which will be valuable for the design and conduct of future research. Second, while the recruitment strategy aimed to target both primary care clinics and the community, the majority of people were recruited from the community. Therefore, these results are most relevant to people not seeking care for LBP.

7.3.6 Conclusions

The results of this exploratory study suggest that to understand the role of somatosensory changes in the development of acute to persistent LBP, mechanical pain tests (i.e. PPT and temporal summation) are variables of potential significance to further investigate. The fact that higher levels of pain-related cognitions at baseline distinguish persistent LBP from the recovered LBP groups emphasizes the importance of concurrent evaluation of psychological contributors, in particular confidence to manage pain (self-efficacy) and pain related worries (catastrophizing). In future studies of samples seeking care for LBP, psychological factors such as depression and anxiety (which were not observed at clinical levels in this community sample) would also be important to assess. While changes in endogenous pain modulation continue to be of great interest, efforts need to first focus on the standardisation of a CPM protocol to improve the reliability and interpretability of the test.

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Chapter 8

Discussion

8.1 Preface

The aims of this thesis were to investigate changes in somatosensory function from the acute stage of low back pain using QST, to explore the prognostic utility of this information, and establish the long-term reliability of QST responses in pain-free individuals. In this chapter the main findings of this thesis are summarised, followed by a critical discussion of the findings and their implications. Limitations of this work are acknowledged and suggestions for future research are presented. Final remarks are provided to conclude the thesis.

8.2 Summary of main findings

8.2.1 Are changes in somatosensory function a feature of acute and subacute low back pain?

A systematic review was undertaken to investigate whether and what types of somatosensory changes are features of acute and subacute spinal pain, as reported in Chapter 2. Meta-analyses were performed where possible to quantify the extent of such changes at the site of spinal pain, and in areas unrelated to the site of pain, in patients compared to controls.

Fifteen studies met the eligibility criteria for inclusion in this review, of which only four assessed low back pain (Farasyn and Meeusen 2005, Farasyn and Meeusen 2007, Biurrun Manresa, Neziri et al. 2013, Mlekusch, Neziri et al. 2016) reporting on results from 7 different sensory tests. Although the evidence was sparse, the results of these studies did suggest early changes in central pain processing could be detected in *acute* low back pain. Evidence included widespread mechanical hypersensitivity using suprathreshold stimuli (pain tolerance threshold) and spinal cord hyperexcitability, measured with electrophysiological tests (i.e. nociceptive withdrawal reflex (NWR) threshold, reflex receptive field (RRF) area, and electrical temporal summation) (Biurrun Manresa, Neziri et al. 2013, Mlekusch, Neziri et al. 2016). Only one study investigated CPM (Mlekusch, Neziri et al. 2016) and no differences were found in the CPM effect between acute low back pain and controls. For pressure pain sensitivity, pooled data showed a large effect estimate at the back (-1.7 (95%CI -2.05 to -1.49)) indicating significantly lower PPT in *subacute* low back pain compared to healthy controls, however no widespread effect for PPT was demonstrated in these two studies (-0.18 (95%CI, -0.42 to 0.06)) (Farasyn and Meeusen 2005, Farasyn and Meeusen 2007).

In contrast to the small number of studies on low back pain, a much larger number of studies reported on acute whiplash injury, of which two thirds provided longitudinal data. Meta-analyses revealed consistent evidence for thermal and widespread mechanical pain hypersensitivity in *acute* whiplash injury; however, the widespread effects were not demonstrated in the *subacute* stage of whiplash. Interestingly, the available longitudinal data suggested that prominent central nervous system sensitivity (e.g. widespread effects and spinal cord hyperexcitability) apparent early after onset of

whiplash injury persisted only in people who did not recover (Sterling, Jull et al. 2003, Kasch, Qerama et al. 2005, Sterling 2010). These findings suggest the involvement of central sensitisation in the development of chronic pain after whiplash injury, although they do not prove a causal relationship. Similar to low back pain, CPM was found unaltered in acute whiplash injury (Kasch, Qerama et al. 2005).

It is noteworthy that several risk of bias issues were identified in the studies included in the systematic review. These may have resulted in an overestimate of effect sizes regarding differences in pain sensitivity between patients and controls, particularly for whiplash injury. These included the lack of blinding of assessors in the majority of studies, which can increase reporting and outcome bias; lack of clarity regarding sampling methods, which can contribute to selection bias; and the lack of control for confounders of QST results. The last two were more commonly encountered in whiplash injury studies.

Overall, this systematic review highlighted that there is very little knowledge regarding the assessment of somatosensory function in acute low back pain. Limited sensory modalities have been assessed and only cross-sectional information is available. The evidence regarding early changes is conflicting. In order to address this gap in knowledge and to overcome some of the methodological limitations identified in previous studies, a prospective longitudinal study was designed using an inception cohort of acute low back pain (< 3 weeks from onset) to compare somatosensory function with a pain-free control group. A comprehensive QST protocol was used encompassing four mechanical and thermal static and two dynamic measures tested at different body areas. One assessor performed all the tests and was blinded to participants' conditions. These findings are reported below.

8.2.2 Can somatosensory changes be detected soon after the onset of low back pain using a comprehensive QST protocol?

A cross-sectional analysis of the baseline data from the longitudinal study was conducted to investigate whether changes in somatosensory function could be identified in people as early as 3 weeks from onset of low back pain compared to pain-free individuals (Chapter 3). A secondary analysis was performed to explore whether QST responses could distinguish between people with acute low back pain when stratified by levels of pain severity.

At a group level, the results showed that there were no significant differences in any of the QST variables assessed between people with and without acute low back pain. When those with low back pain were stratified based on their pain severity, those with moderate/severe low back pain (pain intensity ≥ 5/10 NRS11) had significantly higher cold pain sensitivity (measured by cold pain threshold at the hand and cold pressor test at the foot) compared with those with mild low back pain.

8.2.3 Is CPM impaired in acute low back pain compared to pain-free controls and does the test stimulus used matter?

A separate analysis of the cross-sectional baseline data was conducted to investigate whether changes in the CPM effect could be detected in acute low back pain, compared with pain-free controls (Chapter 4). An additional aim was to investigate the relationship between CPM responses using two different test stimuli.

It was found that an overall inhibitory CPM effect was preserved in acute low back pain using both heat pain and PPT as test stimuli (i.e. decrease in heat pain rating and increase in PPT after the conditioning stimulus). This CPM effect did not differ from pain-free controls, suggesting that endogenous pain inhibition was normally functioning at early stages (< 3 weeks from onset) of low back pain. When the relationship *between* CPM responses using the heat pain and PPT test stimuli was examined, no correlation was found in people with low back pain or pain-free controls (r=-0.02, p=0.94, and r=0.11, p=0.52, respectively). Furthermore, the percentage agreement in the individual CPM responses was low, when comparing the thermal and mechanical stimuli (i.e. inhibitory, facilitatory CPM or non-respondent) in both low back pain (52%) and pain-free controls (68%).

8.2.4 Can QST responses predict outcomes in low back pain?

A systematic review was conducted to summarise the available literature investigating the prognostic ability of QST responses in low back pain (Chapter 5). Prospective longitudinal studies reporting on the association between QST responses and low back pain outcomes at follow-up were included.

Despite an extensive search strategy that retrieved more than 6000 articles, only three prospective prognostic studies assessing QST met the inclusion criteria to address the research question. The results showed that none of the QST variables assessed, including pressure and cold pain testing, dynamic tests of temporal summation and

CPM, were significantly associated with low back pain status at follow up in acute or chronic low back pain cohorts.

Prognostic studies in low back pain are challenging to perform and numerous methodological issues have been described (Pincus, Burton et al. 2002, Kent and Keating 2008). Likewise, the studies included in this review had a high risk of bias relating to the representativeness of the samples, the measurement of QST variables and the adequacy of the outcome measures. These methodological issues impacted on the validity of the results and limited conclusions that could be drawn from the review.

8.2.5 Is QST reliable for monitoring individuals over time?

A novel study investigating the long-term reliability of QST testing in pain-free individuals was conducted (Chapter 6). Four static and two dynamic QST measures were assessed on three occasions, over a 4-month period.

It was found that static thermal and mechanical tests of threshold determination had good to excellent reliability with intraclass correlation coefficients (ICCs) >0.70, while lower reliability was observed for dynamic tests. In particular, CPM using PPT as the test stimulus did not show adequate reliability over time (ICC=0.35) to support its ongoing use in longitudinal research or clinical applications. An unexpected finding was that static mechanical test responses (at the back), and the CPM effect, were found to systematically decrease over the 4-month period, which may result from a learning effect for these measures.

8.2.6 What is the time course of somatosensory changes from acute to persistent low back pain?

To conclude this thesis an exploratory longitudinal analysis investigating the time course of somatosensory changes in people with acute low back pain, stratified by their clinical status at 4 months, was reported (Chapter 7). Longitudinal changes in pain-related psychological factors were concurrently evaluated.

Twenty-two people with acute low back pain completed the study, of which fifteen were classified as recovered (pain intensity at 4 months ≤1/10 NRS11) and seven as persistent pain (pain intensity at 4 months ≥2/10 NRS11). Prospective reference data were also collected from forty-eight pain-free individuals at the same time points. It was found that the time course of somatosensory function differed between the recovered

and the persistent low back pain groups. Specifically, in the persistent low back pain group, an increase in pressure pain sensitivity was seen between 2 and 4 months ($p<0.013$), and at 4 months it was significantly different from the recovered low back pain group ($P<0.001$). An earlier non-significant trend towards increased temporal summation was found in the persistent low back pain group by 2 months through to 4 months, at which point it exceeded 2 SDs beyond the pain-free control reference value. In addition to temporal changes in the persistent low back pain group, a gain in cold pain sensation was observed in the recovered low back pain group from baseline to 2 months ($P<0.001$), which normalised from hypoesthetic to the pain-free values by 2 months. Due to the small magnitude of change in cold pain sensitivity, it is unclear whether this finding is of clinical value.

Overall, these findings suggest that somatosensory changes, particularly for mechanical pain sensitivity, can be detected at the subacute/early chronic stage of low back pain. Interestingly, the only measures that differentiated the two low back pain groups at baseline were the psychological measures of self-efficacy (PSEQ) and pain catastrophising (PCS). In particular, clinically significant lower self-efficacy scores were noted at baseline for the persistent compared to the recovered low back pain group, suggesting that even mild impairment in PSEQ may be noteworthy in the acute stage of low back pain.

8.3 Critical discussion and implications of the findings

The work presented in this thesis contributes to the body of evidence regarding changes in somatosensory function occurring in acute low back pain. In particular, novel longitudinal data tracking somatosensory changes from the acute to early chronic stage of back pain were obtained. The concurrent assessment of pain-free individuals provided useful methodological insights into QST testing.

While the first systematic review (Chapter 2) found some evidence for widespread sensory changes in acute low back pain in specific sensory modalities (Biurrun Manresa, Neziri et al. 2013, Mlekusch, Neziri et al. 2016), differences in sensory function at baseline were not found in the clinical study presented in this thesis (Chapter 3). However, this is consistent with more recently published research in acute low back pain, in which unaltered mechanical (O'Neill, Kjær et al. 2011, O'Neill, Manniche et al. 2014) and thermal (Hübscher, Moloney et al. 2014) pain sensitivity was reported,

compared to healthy controls. It would be expected that some degree of pain sensitisation would occur soon after the onset of low back pain as a result of the inflammatory response to tissue damage, although the exact source of nociception is not readily identified in most low back pain cases (Deyo 2002). Perhaps the inconsistent findings described above reflect the heterogeneity of those classified with non-specific low back pain (Artus, van der Windt et al. 2010), whereby changes in somatosensory function in subgroups or particular individuals might exist, but are difficult to identify at a group level. Such heterogeneity may be even more evident in the acute stage, when the majority of clinical changes occur (Downie, Hancock et al. 2016).

It is therefore possible that somatosensory changes detectable by QST depend to some extent on symptom severity in acute low back pain. Indeed, the subgroup analysis of the baseline acute low back pain data reported in Chapter 3 showed a significant difference in cold pain sensitivity between people with higher, compared with lower, pain severity. This has been reported in whiplash injury (Sterling, Jull et al. 2004). The mechanisms underlying cold pain sensitivity appear to be complex and can include psychological distress (Wallin, Liedberg et al. 2012), altered sympathetic nervous system function (Zhao, Chen et al. 2007), and genetic factors (Nielsen, Stubhaug et al. 2008). Nonetheless, it is of interest that cold pain sensitivity, measured by the cold pain threshold, is emerging as a useful prognostic factor in other musculoskeletal conditions such as whiplash injury and epicondylalgia (Sterling, Jull et al. 2005, Coombes, Bisset et al. 2015). It should be noted that information about the prognostic value of sensory tests in low back pain, including cold pain thresholds, is very limited, as identified in the systematic review presented in Chapter 5. The data are also somewhat conflicting: one study has shown that cold pressor test responses in acute low back pain were *not* predictive of low back pain outcomes at 4 months (LeResche, Turner et al. 2013). Taken together, this indicates that future prospective, high quality studies are needed to provide more definitive conclusions about the prognostic value of cold pain sensitivity in acute back pain.

In this thesis, descending modulation of pain was also evaluated in low back pain, using CPM testing; topical methodological issues related to CPM assessment were also investigated (Chapter 4). Consistent with existing literature reviewed in Chapter 2, it was found that the efficiency of endogenous pain inhibition was preserved, at least in this sample, in the early stage of low back pain. When two different modes of test

stimuli for testing CPM (heat and pressure) were compared, the CPM responses at the group level were found to have no correlation. Further, a low agreement between individual CPM responses using the two test stimuli was found in both low back pain and pain-free controls. This lack of correlation and poor agreement between differing test stimuli in CPM is supported by two previous studies (Nahman-Averbuch, Yarnitsky et al. 2013, Schliessbach, Siegenthaler et al. 2014). These data will be valuable in the future development of standardised CPM protocols. Although differences in CPM were not detected at the group level in the cohort examined for this thesis, there is preliminary evidence from other studies for the clinical utility of individual CPM responses (Yarnitsky, Crispel et al. 2008, Wilder-Smith, Schreyer et al. 2010). Whether this may be the case in low back pain it will require further investigation (LeResche, Turner et al. 2013, Mlekusch, Schliessbach et al. 2013, Dubois, Cantin et al. 2016). Given the current interest in clinical applications of CPM testing, the results reported in Chapter 4 are particularly important. They highlight the fact that the choice of CPM protocol is critical, in particular when used to guide clinical reasoning, for example for estimating prognosis, or monitoring response to treatment in patients.

Following on from the methodological considerations above, an important contribution of the data presented in this thesis is new information about the long-term reliability of QST responses. Previous literature on test-retest reliability over a short period of time (i.e. hours, days or a few weeks) has confirmed that QST measures have adequate reliability, particularly for static tests (Chong and Cros 2004, Backonja, Attal et al. 2013). However, if researchers and clinicians aim to use QST to monitor somatosensory dysfunction, or evaluate responses to interventions in their patients, they need to ensure that the measure is stable and reproducible over longer periods of time. This issue of the long-term reliability of QST measures was addressed in Chapter 6 and the results have some important implications. It was confirmed that static tests maintain high reliability (over the 4 month period), and so are suitable for monitoring individuals over this longer time-frame. However, a caveat to this is that longitudinal data from mechanical tests (e.g. the commonly used PPT test) can systematically decrease over time, even in people without pain. Interestingly, the reliability of dynamic tests was considerably lower, possibly due to the more complex nature of these responses. Another clinically relevant finding was that CPM testing using suprathreshold heat pain test stimulus was

more stable than PPT; indeed, the latter was the least reliable, and therefore may be less suitable for longitudinal monitoring.

It was discussed above that somatosensory changes measured by QST do not seem to be a consistent feature of acute non-specific low back pain, at least at the group level. In contrast, there is a large body of evidence showing that chronic low back pain is characterised by widespread sensory hypersensitivity (Roussel, Nijs et al. 2013) suggesting that multiple central nervous system changes have occurred once the condition has become chronic. Indeed, pressure pain testing at the back has been identified as the most discriminative QST measure to distinguish between people with chronic low back pain from healthy controls (Neziri, Curatolo et al. 2012). Results from this thesis (Chapter 2) add to this picture, with evidence of local deep tissue pain hypersensitivity occurring in the *subacute* stage of low back pain compared with healthy controls. The findings of the longitudinal analysis (Chapter 7) further suggest that changes in local pressure pain sensitivity might not be apparent until the late subacute/early chronic stage (i.e. > 2 months) of low back pain. At 4 months, pressure pain testing could distinguish between persistent and recovered low back pain groups (Chapter 7). As with changes in PPT, a meaningful increase in temporal summation, compared with our control sample, was identified in people with persistent pain in the subacute stage, although it did not reach statistical significance. This may reflect potential underlying changes in the nervous system sensitivity over time in those with persistent pain. However, since this study was exploratory and with consideration of the reliability data reported in Chapter 6, caution is needed when interpreting these results. Of note, the psychological variables of pain self-efficacy and pain catastrophising were the most discriminative to distinguish between persistent and recovered low back pain at baseline. Interestingly, the differences in cold pain sensitivity between subgroups of people with low back pain identified at baseline in Chapter 3 could not be confirmed in the longitudinal analysis. This may result from the different analysis performed, and loss of participants (n=3) with acute low back pain after the baseline assessment, with subsequent reduction in statistical power to detect differences between groups.

8.4 Limitations

The first limitation of the thesis to acknowledge is that the sample size of acute low back pain participants was relatively small. Extensive recruitment strategies were used

and 250 people were screened for the study, however only 25 people with acute low back pain were eligible for inclusion. The main reasons for exclusion were the duration of pain exceeding 3 weeks, and the severity of pain being lower than our established criteria for pain intensity ≥ 3/10 (NRS11). In contrast, a larger number of pain-free controls were available, which provided useful reference data. As a result, it is possible that the study was underpowered to detect statistically significant differences between the low back pain and the pain-free controls groups. However, at the time when CPM data were analysed, existing literature supported the use of a sample size of 25 to detect significant differences between low back pain and the pain-free controls (Correa, Costa et al. 2015, Mlekusch, Neziri et al. 2016).

Another factor to consider is that, despite recruitment efforts targeting both the community and primary care, participants who took part in this research were predominantly from the community (88%). While pain severity at baseline (4.4/10 NRS11) in this low back pain sample was comparable to the others using cohorts seeking care (Campbell, Foster et al. 2013), the level of psychological distress and disability were lower, reflecting a high functioning group. Therefore, the findings of this thesis may be most relevant to people not seeking care for low back pain. This population has been shown to comprise more than half (56%) of people following an acute episode of low back pain, based on an Australian population-based study (Walker, Muller et al. 2004). Nonetheless, further investigations of clinical cohorts will be also valuable.

A final potential limitation relates to the CPM testing, which was performed using two test stimuli (heat pain and PPT), as per current consensus recommendations (Yarnitsky, Bouhassira et al. 2015). In order to limit the burden on participants, the two test stimuli were applied consecutively within the same testing session, as advised by one of the authors of the consensus paper (*pers. comm*.). However, because the PPT was applied after the heat pain test stimulus, it cannot be excluded that the latter might have impacted on the variability of CPM responses using PPT. To investigate this further, a CPM test-retest reliability study was performed during a one-week period, in which the two test stimuli were applied separately (data not reported in this thesis), and the results confirmed superior reliability for the heat pain test. This suggests that the use of two test stimuli within the same testing session is acceptable, although this needs to be confirmed.

8.5 Suggestions for future research

The body of research investigating somatosensory function in low back pain is fast growing. Nonetheless, the results of this thesis highlight the need for future longitudinal studies to better understand the temporal development of somatosensory changes between onset and when low back pain becomes chronic. The exploratory longitudinal study reported in this thesis has helped to identify particular sensory variables that may be valuable to focus on in future studies in low back pain, using larger samples. These include pressure pain sensitivity, wind up ratio and cold pain sensitivity. The possibility of temporal changes in the CPM effect will also be of interest to evaluate further. However, the results of this thesis showed that CPM testing using PPT as test stimulus has poor reliability, therefore this paradigm may need to be reconsidered for future longitudinal investigations.

The association of psychological variables, such as depression, anxiety, pain catastrophising, and fear avoidance with pain intensity and disability in low back pain has been demonstrated (Henschke, Maher et al. 2008, Mok and Lee 2008). The findings reported in Chapter 3 showed that more intense low back pain was associated with cold pain sensitivity (reduced cold pain threshold) and greater pain-related distress (i.e. higher pain catastrophizing and lower pain self-efficacy scores) compared to those with mild symptoms. While it was beyond the scope of this thesis to investigate such relationships, a number of previous investigations in whiplash injury suggest an association exists between psychological variables and pain sensitivity, including pain catastrophising and cold pain sensitivity (Sterling, Hodkinson et al. 2008, Rivest, Côté et al. 2010, Wallin, Liedberg et al. 2012). This would be valuable to explore in low back pain, particularly to elucidate the relationship between psychological variables and QST measures for pain sensitivity, especially in clinical (treatment seeking) samples.

The work presented in this thesis also highlights the need for high quality prospective studies to investigate whether QST responses are useful prognostic factors in low back pain. In light of the discussion above, cold pain sensitivity may be a relevant variable to investigate. To account for the heterogeneity of low back pain, future prospective studies should adopt a multivariable approach that includes known predictors (e.g. psychosocial and pain-related factors) in order to establish whether QST testing adds prognostic value in predicting outcomes in low back pain (Moons, Royston et al. 2009).

8.6 Conclusion

The work presented in this thesis has contributed to the body of evidence regarding somatosensory function from the early stages of low back pain, as well as providing novel methodological insights into QST testing. Conclusions from this thesis are: (1) widespread sensory changes to specific modalities can be detected in acute low back pain, although the evidence is somewhat limited; (2) in the cohort of acute low back pain studied, cold pain sensitivity was associated with higher symptom severity; (3) endogenous pain inhibition appeared to be preserved in this cohort of acute low back pain; (4) CPM responses using thermal and mechanical test stimuli were not correlated; (5) the prognostic value of QST measures in low back pain remains unclear, due to the limited number and high risk of bias of available studies; (6) static QST of threshold determination was stable over a 4-month period, while dynamic tests, in particular CPM, displayed considerable variability; (7) people with persistent low back pain displayed an increase in mechanical pain sensitivity in the subacute stage; and (8) in the acute stage, higher levels of pain-related cognitions distinguished those with persistent low back pain from those who recovered, emphasizing the importance of concurrent evaluation of psychological features in future longitudinal studies.

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Appendix 1 (pages 167-169) of this thesis have been removed as thev mav contain sensitive/confidential