Trait Characteristics of Centrally Sensitised People with Non-specific Chronic Low Back Pain: Relationships between Sensory Profiles, Trait Anxiety-related Personality Types, the Extent of Central Sensitisation Symptoms and Pre-morbid Lived Experiences**.**

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Joint-PhD

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Declarations

There are no conflicts of interest to be declared. This was a self-commissioned and self-funded PhD thesis.

Abstract

Central sensitisation (CS) is a pain mechanism common to many chronic musculoskeletal pain conditions, the aetiology of which remains unclear. There is a paucity of evidence observing trait characteristics of sensory sensitivity, trait anxiety and personality types in people with non-specific chronic low back pain (NSCLBP). The aim of this thesis was to identify pre-morbid trait characteristics in people with NSCLBP and CS and to explore their possible role in the development of CS pain. The objectives were to 1) observe the range of CS symptom scores using the Central Sensitisation Inventory (CSI), 2) identify four trait sensory profiles (Sensory Sensitive, Sensation Avoiding, Low Registration and Sensation Seeking), trait anxiety and four personality types (defensive high anxious, high anxious, repressor and low anxious), 3) investigate the relationships between these trait characteristics and the extent of CS symptoms; and 4) explore the context of pre-morbid lived experiences in which CS pain developed in light of individual trait characteristics. An international cross-sectional observational study using a mixed methods design was carried out, with a core quantitative study using questionnaires and a concurrent nested qualitative study using semi-structured interviews.

Results showed that in a NSCLBP population with CS predominant pain 1) there were positive correlations between the Sensory Sensitive, Sensation Avoiding and Low Registration sensory profiles and a) the extent of CS symptoms and b) high trait anxiety; 2) the extent of CS symptoms could be predicted by trait anxiety, extreme defensive high anxious personality type and the two sensory profiles with a passive adaptive response (Sensory Sensitive and Low Registration); 3) there was a significantly high prevalence of high

extreme, a) Sensory Sensitive, Sensation Avoiding, Low Registration scores and the defensive high anxious personality type in the high CSI sub-group (CSI ≥ 40); and b) Low Registration scores and repressors in the low CSI sub-group (CSI < 40). The themes from the qualitative study exploring the pre-morbid lived experiences of people with NSCLBP and CS were: sensitivity, developmental learning differences, trauma and personal characteristics of low confidence and control, which highlighted the context in which CS pain developed.

The results of this thesis lead to a proposal that pre-morbid contexts and characteristics of trait anxiety and sensory processing may lead to heightened sensitivity and physiological arousal to stressors, and a personality type-dependent response. A response of attention towards, and interpretation for, threat-related stimuli may lead to CS symptoms in people with NSCLBP and CS. A longitudinal study from a premorbid baseline is recommended to confirm the predictive role of these trait characteristics in the development of CS pain.

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How might trait sensory processing characteristics, trait anxiety and personality types contribute to the development of   central sensitisation pain?

1.1 Introduction

Almost one in five Europeans suffer moderate to severe chronic pain which seriously affects their social and work lives; nearly half of whom report inadequate pain management (Breivik et al., 2006). The mechanisms behind different chronic pain presentations depend on the various patho-anatomical and patho-physiological contributions (Nijs et al., 2010).

The term chronic pain lacks specificity in terms of the predominant pain mechanism responsible for the extended pain timeframe. Chronic pain may be the manifestation of a single pain mechanism or of a mixed presentation depending on the extent to which peripheral- (PNS) and central nervous system (CNS) factors contribute (Nijs et al., 2014; Phillips & Clauw, 2011). The existing theoretical framework in pain neuroscience identifies three broad sub-classifications of pain mechanisms of which central sensitisation is one. The other two pain mechanisms are sub-classified as nociceptive and neuropathic. Nociceptive pain is pain caused by activation of high threshold nociceptors (Aδ and C fibres) by intense tissue-damaging (potential or actual) noxious mechanical, chemical (inflammatory) or thermal stimuli (Costigan et al., 2009; Smart et al., 2012). Neuropathic pain is pain arising

from a primary lesion or dysfunction in the nervous system itself, in peripheral or central neurons (Moseley & Butler, 2015; Smart et al., 2012). Both these definitions define pain related to a clear tissue or neural pathology. However, chronic pain without a clear patho-anatomical cause is a phenomenon involving alterations in central pain processing (Cauda et al., 2014; Moseley & Butler, 2015; Nijs et al., 2014; Nijs et al., 2010; Smart et al., 2012) manifesting as central sensitisation pain. Central sensitisation pain is defined as a dysregulation of the central nervous system causing neuronal hyper-excitability, characterized by generalized hypersensitivity of the somatosensory system to both noxious and non-noxious stimuli (Mayer et al., 2012; Neblett et al., 2013; Nijs et al., 2010). Central sensitisation will be described in more detail in the following narrative review.

This thesis focusses specifically on the central sensitisation pain mechanism, a chronic pain mechanism common to many musculoskeletal pain conditions (Arendt-Nielsen et al., 2018). The direction of enquiry in this thesis arose from clinical observations, which may be familiar to many physiotherapists, that some people develop chronic central sensitisation (CS) pain after a musculoskeletal injury, whereas other people make a full recovery.

This thesis presents a group of studies written up for publication (articles 1 to 6) using mixed methods and represents the process by which the over-arching thesis objective (Tashakkori & Creswell, 2007) was investigated. The over-arching thesis objective was:

To investigate sensitivity-related trait characteristics of centrally sensitised people from a non-specific chronic low back pain population and to explore how these characteristics might be related to CS pain.

The current chapter will present an introduction to the key concepts of trait anxiety, personality types and sensory processing, followed by a narrative review (article 1) which will explore the plausibility of the hypothesis that trait characteristics of sensory processing, trait anxiety and personality types may contribute to the development of CS pain. Chapter 2 will present a systematic literature review (article 2) in which the existing knowledge surrounding the predictive factors in CS pain in musculoskeletal pain populations will be investigated, following which the research questions underlying the current thesis will be put forward. Chapter 3 will present an overview of the mixed method study design chosen to answer the over-arching objective for the current thesis, followed by the pilot study article (article 3) which tested the quantitative study methods and concept plausibility. Chapter 4 will present the two quantitative studies (articles 4 and 5) which form the core component of the mixed methods study and use quantitative methods to investigate the trait characteristics of a group of people with NSCLBP and CS. Chapter 5 will present the supplementary qualitative study (article 6) implemented to explore pre-morbid experiences in a sub-group of the participants. Chapter 6 will discuss the integrated results and findings from the studies in articles 4, 5 and 6, including strengths and limitations. Finally, chapter 7 will conclude the thesis and provide recommendations for clinical application. Further research suggestions will also be summarised. A 'road map' is presented at the introduction of each chapter to assist the reader in orientation through the thesis, beginning with the introduction and narrative review (figure 1).

Core Component

3 Methodology Pilot Study (Article 3)

4 Core Quantitative Studies (Articles 4 & 5)

1 Introduction Narrative review (Article 1)

2 Systematic Review (Article 2) Research Questions

5 Concurrent Nested Qualitative Study (Article 6)

Supplementary Component

6 Discussion of integrated findings

7 Conclusions & Recommendations
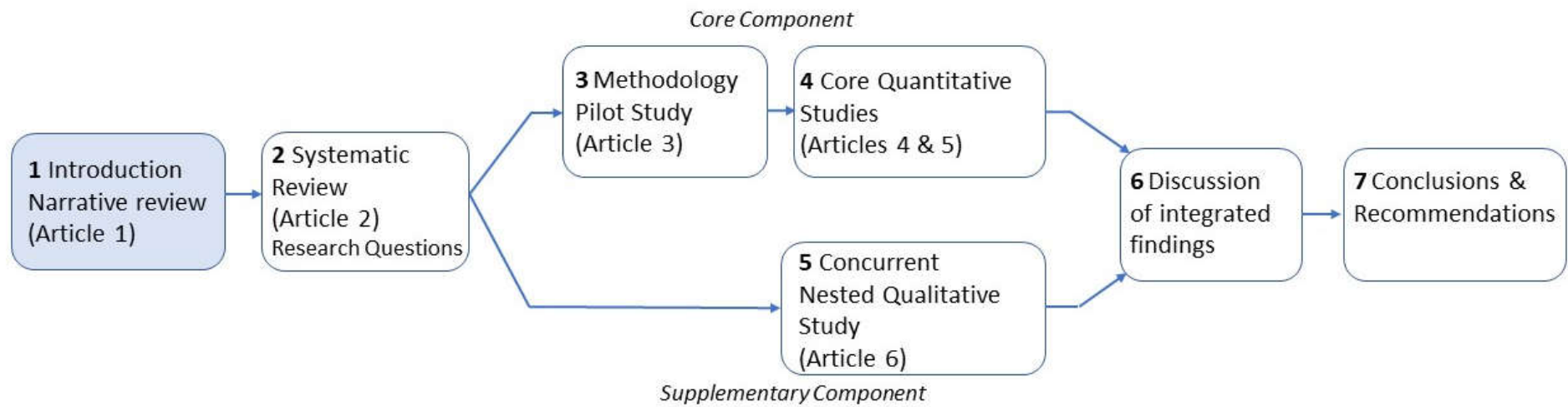
Figure 1: Roadmap through the thesis: introduction and narrative review.

The reader may also find it helpful to refer to the following table which shows the articles by number and chapter reference, their titles and journals to which each have been submitted. (Table 1).

Table 1: The list of articles written for publication in the thesis, the article number, the chapter in which it is presented, the title and the journal to which it is submitted and / or published.

Article number	Thesis chapter	Title	Journal submitted to / published
1	1	How might trait sensory processing characteristics, trait anxiety and personality types contribute to the development of central sensitisation? A narrative Review	Clinical Journal of Pain (Submitted; see appendix 1)
2	2	What are the predictors for altered central pain modulation in chronic musculoskeletal pain populations? A systematic review	Pain Physician. (Published; see reference list)
3	3	Trait anxiety and sensory processing profile characteristics in patients with non-specific chronic low back pain and central sensitisation - A pilot observational study	Journal of Bodywork and Movement Therapies. (In press; see reference list)
4	4	The extent of central sensitisation symptoms can be predicted by trait sensory profiles, trait anxiety and extreme personality type in people with non-specific chronic low back Pain.	The European Journal of Pain (Submitted; see appendix 4)
5	4	Prevalence of extreme trait sensory profiles and personality types in non-specific chronic low back pain with predominant central sensitisation: Secondary analysis of an international observational study.	Clinical Journal of Pain (Submitted; see appendix 4)
6	5	Exploring pre-morbid experiences and personal characteristics of a group of centrally sensitised people with non-specific chronic low back pain. A qualitative study.	The Brazilian Journal of Physical Therapy. (Submitted; see appendix 5f)

1.2 Key concepts

Three key concepts in the current thesis which will be studied in relation to CS are: trait anxiety, the nature of trait-anxiety related personality types and aspects of sensory processing. These concepts will be introduced and discussed in the next section.

1.2.1 Trait Anxiety

A salient function of anxiety is to assist in the detection of impending danger to the individual in potentially threatening environments, a function requiring the attentional system in threat detection (Eysenck, 1997). Trait anxiety is an enduring and stable characteristic indicative of the proneness of an individual to respond to psychological threats with physiological arousal (Eysenck, 1997; Eysenck & Derakshan, 2011; Spielberger, 1983; Spielberger, et al., 1970). Physiological arousal is a somatic manifestation of state anxiety (Rosa Esteve & Camacho, 2008), which is a transient emotional experience in response to a concurrent psychological threat, as opposed to the long term, stable nature of trait anxiety (Spielberger, 1983).

It is hypothesised in the current thesis that individuals with high trait anxiety may be more prone to respond to stressors with physiological arousal, which in turn may lead to an increased sensitivity to sensory stimuli when these are interpreted as threatening. This may in turn lead to increased sensitisation towards sensory stimuli through hypervigilance, a characteristic of pain related fear and anxiety (Peters et al., 2002). Increased sensitisation may lead to increased CS symptoms.

Trait anxiety can be measured using the State-Trait Anxiety Inventory (STAI) (Spielberger, 1983), the psychometric properties of which will be outlined in articles 4 and 5. Normative data for the STAI was calculated based on working adults (n = 1,838) , high-school students (n = 424), college students (n = 855) and military recruits (n = 1,964) in 1970 (Spielberger, 1983). More recent work by Kendall et al, (2000) found similar normative data which supports Spielberger's original findings. The validation process for the STAI included 600 participants from neuropsychiatric and medical surgery populations, which may overlap in terms of health differences with people with NSCLBP and CS.

The decision to use the STAI in the current thesis was affirmed on the basis that many subsequent authors have used the tool to measure trait anxiety in other related populations. For example, those with somatic sensitivity (Rosa Esteve & Camacho, 2008; Smári, et al., 2003), chronic musculoskeletal pain (McCracken et al.,1996; Franklin et al., 2016; Franklin et al., 2014; Vlaeyen et al., 1995) and cancer pain (Poleshuck et al., 2006). The use of the STAI by Franklin and colleagues (Franklin et al., 2016; Franklin et al., 2014) was not to identify trait anxiety alone, but to use the measure as part of the identification of four personality types, by combining the STAI scores with measures of defensiveness. It is hypothesised in the current thesis that the tendency to interpret stimuli for threat may vary depending on the nature of individual personality types, where those with high trait anxiety-related personality types may be more likely to interpret for threat (Eysenck, 1997).

1.2.2 Personality types

The four personality types to be investigated in this thesis, among individuals with non-specific chronic low back pain and central sensitisation, are based on those described by

Weinberger and colleagues (Weinberger et al., 1979). Weinberger et al (1979) recognised the difficulties encountered in research when using self-report measures to identify and differentiate individuals with high and low trait anxiety. These difficulties appeared to be based on individual defensiveness levels among research participants. Previous authors had proposed various personality types which Weinberger et al., (1979) had considered conceptually self-contradictory and therefore, in order to maximised clarity, they proposed four personality types as follows:

Repressor: low trait anxiety, high defensiveness;

High Anxious: High trait anxiety, low defensiveness.

Defensive High Anxious: high trait anxiety, high defensiveness.

Low Anxious: low trait anxiety, low defensiveness.

Weinberger et al., (1979) used the State-Trait Anxiety Inventory (Spielberger, 1983) to measure trait anxiety and defensiveness was measured using the Marlowe Crowne Social Desirability Scale (Crowne & Marlowe, 1960). It was hypothesised that, compared with low anxious individuals, individuals with a repressor personality type (repressors) self-report their levels of experienced anxiety as being lower, despite showing concurrent high measures of physiological arousal (Weinberger et al., 1979). Conversely, high anxious individuals would self-report moderate anxiety which would be congruent to the physiological arousal recorded concurrently. Weinberger et al. (1979) postulated that to experimentally establish discrepancies between self-report anxiety and physiological responses to threatening information would confirm that repressors behave differently than low anxious and high anxious individuals. Moreover, they postulated that this should be

taken into consideration in research which involves the measuring of anxiety and self-report measures.

The study by Weinberger et al., (1979) was the first to demonstrate significant differences in the way low anxious, high anxious and repressor individuals respond to psychological stressors (phrases of neutral, sexual or aggressive content), verbally and physiologically, using a phrase association task intervention in healthy, young (age 15 to 23) students. All the participants had similar baseline physiological measures. Following a phrase association task their somatic cognitive and anxiety levels were recorded, followed by their own perception of their proneness to anxiety (trait anxiety).

The study provided construct validity for differentiation between low anxious, high anxious and repressor personality types. They concluded that repressors tend to under-report their cognitive anxiety, that their somatic anxiety is higher than their reported cognitive anxiety and that the experimental procedure served to further diminish their self-perception of trait anxiety. Conversely, their high anxious and low anxious counterparts showed congruence between somatic and cognitive anxiety measures. Furthermore, contrary to repressors, the high anxious individuals displayed increased self-perception of anxiety proneness following the procedure.

The article by Weinberger et al., (1979) does not discuss the limitations of their research, which may be due to the era in which it was written. Methodological limitations include the sample size calculation not being described, nor information about refusals to participate nor any drop-outs. The study did not divide the group with high trait anxiety scores (above

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the median score for normative studies) into high and low defensiveness, despite having defined defensive high anxious as the fourth personality type at the start of the article. This may have been due to their observations that defensive high anxious individuals were uncommon in healthy populations. Lastly, the delivery of the threatening information was by verbal means. No visual information was provided to know whether repressors respond to visual threats in a similar way.

Despite these limitations, subsequent authors have confirmed the findings of Weinberger and colleagues (1979) in terms of the differences in self-report tendencies among repressors compared with the other three personality types (Nazanin Derakshan & Eysenck, 2005; Derakshan et al., 2007; Franklin et al., 2015; Franklin et al., 2014; Furnham & Traynar, 1999; Myers, 2000, 2010).

In addition to anxiety-specific literature, Weinberger's four personality types (Weinberger et al., 1979) have been applied to populations with cancer pain (Phipps & Steele, 2002; Prasertsri, et al., 2011; Zachariae et al., 2004), chronic pain (Burns, 2000a, 2000b; Vendemia, 1999) and, more specifically, chronic low back pain (Franklin et al., 2016; Franklin et al., 2014; Lewis et al.,2012).

Two key studies used in the current thesis are those by Franklin and colleagues (Franklin et al., 2016; Franklin et al., 2014). The objectives of the investigations by Franklin and colleagues were to identify differences in 1) the way the four personality types experience and respond to chronic low back pain (Franklin et al., 2014) and 2) attentional biases between the four personality types in individuals with chronic low back pain (Franklin et al.,

2016). The first study (Franklin et al., 2014) recruited individuals from target shooting and hockey sports populations, all of whom had reported low back pain within the previous 6 months. Their personality types were measured using the same outcome measures used in the current thesis for defensiveness and trait anxiety. Pain intensity, treatment history, depression, disability levels and satisfaction with treatment were also measured. Pain intensity was measured using the numeric rating scale, but measures of central sensitisation were not specified.

Franklin et al., (2014) found that all four personality types reported similar levels of pain, however it was the defensive high anxious individuals who reported greater levels of disability and depression. This may have some implication if defensive high anxious individuals were to have their levels of CS symptoms measured, because CS symptoms are also associated with disability and depression (Carroll, 2011; Clauw, 2015; Smart et al., 2012). Of the four personality types, it was found that the defensive high anxious individuals (92%) sought more than one treatment intervention the most, and repressors predominantly self-managed their pain and sought one or more treatment interventions the least (10%), (Franklin et al., 2014). The implications of these findings for this study is that in a group of individuals with NSCLBP and CS, recruited from outpatient treatment provider clinics, the majority of them may be more likely to be defensive high anxious individuals.

In the second study by Franklin and colleagues (2016), the attentional biases of individuals with chronic low back pain were identified. This was the first study to test Eysenck's 'four factor theory' of cognitive biases in individuals with chronic low back pain. Eysenck's four factor theory will be described in more detail below. A dot probe paradigm intervention was

used in a chronic low back pain population from a hospital pain rehabilitation centre in which participants were shown threat-related to back pain-, positive- and neutral images. The personality types were identified using extreme anxiety and defensiveness scores in order to ensure sufficient heterogeneity between the four personality groups. Among the results it was found that individuals with a defensive high anxious personality type showed attentional bias towards threat-related visual stimuli more so than high-anxious individuals who demonstrated no bias. Conversely, repressors showed an avoidant bias to the threatening images.

Although a predominant CS pain presentation was not tested for in the latter study (Franklin et al., 2016), the results suggest that individuals with chronic low back pain and an extreme defensive high anxious personality type may be more likely to attend to stimuli which they may interpret as back-pain related and threatening. Only visual stimuli were tested and whether or not defensive high anxious individuals may interpret other bodily sensations as threatening as well remains unknown. The study did, however, partly confirm Eysenck's four factor theory with regard to individuals with chronic low back pain.

Eysenck's Four factor theory of trait anxiety

Eysenck's four factor theory (Eysenck, 1997) underpins some of the interpretation framework included within this thesis and was designed to be applied to Weinberger's four personality types. Eysenck's four factor theory is based on the assumption that there are consistent cognitive biases which operate via four different factors within the emotional system. These cognitive biases are the attentional and interpretational biases and they differ between each of the four personality types (Eysenck, 1997). The four factors of the

emotional system which influence the individual's experience of anxiety, in response to psychological threats, are:

 (i) the cognitive appraisal of the 'stressful' situation;

(ii) the individual's attention to and interpretation of the concurrent physiological arousal;

(iii) the individual's action tendencies;

(iv) the negative thoughts and emotions in relation to the uncertainty of the outcome (e.g. worries).

The theory suggests that negative experiences contained in the long-term memory may influence the four factors outlined above, which in turn determine the emotional experience of anxiety. Furthermore, the cognitive biases are assumed to be affected by the prevailing level of state anxiety.

Eysenck (1997) stated that defensive high anxious and high anxious individuals would show attentional bias towards sensory stimuli and interpretational bias for threat. Conversely the theory states that repressors are more likely to interpret against threat and show avoidant bias towards sensory stimuli.

Implications

The implications of Eysenck's four factor theory for this thesis are firstly that the processing of threat-related stimuli may be magnified or minimised depending on the levels of trait anxiety and defensiveness of the individual and that this concept may play a role in the development of CS. Individuals with cognitive biases for threat, and attentional biases

towards threat-related stimuli may be the individuals more prone to sensitisation towards sensory stimuli. This may have implications for identifying those at risk of developing CS pain. Secondly, if the cognitive biases are affected by the prevailing state anxiety, stressors may automatically increase physiological arousal associated with state anxiety even before the anxiety is perceived as an emotional experience by the individual, and this may further influence the cognitive biases. It is proposed in this thesis that individuals with a low threshold for sensory stimulation - high trait sensory sensitivity, may be more prone to physiological arousal from 'over-stimulation' than those with high neurological thresholds for sensory stimulation (low trait sensory sensitivity). Trait sensory sensitivity is a component of trait sensory processing.

1.2.3 Trait Sensory Processing and Sensory Profiles

A measure of trait sensory processing is a measure of the way in which an individual generally responds to sensations, indicative of stable and enduring sensory processing preferences (Brown & Dunn, 2002). Individuals may show patterns of sensory processing which show a tendency towards trait sensory hyper-sensitivity (low neurological threshold to sensory stimuli) and/or trait sensory hypo-sensitivity (high neurological threshold to sensory stimuli), (Brown et al., 2001). Levels of trait sensory sensitivity form a further important component of the current thesis. It is hypothesised in the current thesis that individuals with high trait sensory sensitivity may be prone to physiological arousal from sensory 'over stimulation' or from sensory stimulation perceived as threatening, and that there may a high prevalence of individuals with high trait sensory sensitivity in a population of individuals with a predominant CS pain presentation.

Sensory sensitivity can be measured using the Adolescent / Adult Sensory Profile (AASP), (Brown & Dunn, 2002; Brown et al., 2001), the psychometric properties of which will be described in articles 4 and 5. The AASP is said to 1) capture important and relevant information about an individual's trait sensory processing tendencies, 2) clearly link sensory processing with daily experiences and activities and 3) be applicable to adults with or without illnesses or disabilities (Brown & Dunn, 2002). The AASP identifies four trait sensory profiles by combining neurological thresholds to sensory stimuli with a behavioural response to discomfort experienced from sensory over- or under-stimulation (Brown & Dunn, 2002; Brown et al., 2001). The four trait sensory profiles are:

Sensory Sensitive: Low neurological threshold, passive behavioural response;

Sensation Avoiding: Low neurological threshold, active behavioural response;

Low Registration: High neurological threshold, passive behavioural response;

Sensation Seeking: High neurological threshold, active behavioural response.

To date the AASP has been used to investigate trait sensory profiles in healthy adult populations (Engel-Yeger, 2012; Engel-Yeger & Dunn, 2011a, 2011b, 2011c) as well as populations with sensory processing differences: children with developmental learning difficulties (Engel-Yeger net al., 2011a), Asperger syndrome (Dunn et al., 2002), autism (Pfeiffer et al., 2005) and attention deficit hyperactivity disorder (ADHD) (Dunn & Bennett, 2002), adults with sensitive skin disorders (Engel-Yeger et al, 2011b) and adults with schizophrenia (Brown et al., 2002). Furthermore, the AASP has been used to find associations between anxiety and pain catastrophising in adults (Engel-Yeger & Dunn, 2011b, 2011c).

To date there is no published data for use of the AASP in chronic musculoskeletal pain populations. However, a recent study has validated the use of the Dutch version of the AASP in a NSCLBP population with CS symptoms (Graper et al., *unpublished*). The results of this study are detailed in article 4. A concurrent study is currently being undertaken to validate the use of the English version of the AASP in individuals with NSCLBP or fibromyalgia, and CS symptoms (Clark et al., *at data collection stage*).

Implications

The implications for the use of the AASP in this thesis is that CS is characterised by somato-sensory hyper-sensitivity (Nijs et al., 2010, 2014) and therefore if individuals already have 'natural' trait sensory sensitivity, they may be more prone to sensory 'over-stimulation' or sensory 'overwhelm' in the face of new, unexpected or excessive sensory stimulation, including nociceptive stimulation. This may be further compounded if individuals tend to have a passive adaptive response to sensory over stimulation.

The narrative review is now presented which investigates the hypothesis that trait characteristics of sensory processing, trait anxiety and personality types may play a role in the development of central sensitisation pain. A review based on the following presentation has been submitted to the Clinical Journal of Pain (Appendix 1).

1.2 Article 1: How might trait sensory processing characteristics, trait anxiety and personality types contribute to the development of central sensitisation pain?

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Abstract

Background: Central sensitisation (CS) has been receiving much attention over recent years and this may be because of the impact CS has on western society and its associations with poor outcomes. There is still limited understanding surrounding the development of CS. CS manifests as somatosensory hyper-sensitivity to sensory stimuli due to altered central pain modulation in the central nervous system. Other factors which contribute to sensory sensitivity include sensory processing functions, anxiety and the nature of personality types and these may play a combined role in the development of CS.

Objective: The objective of this narrative review was to explore overlapping physiological and behavioural aspects of CS, sensory processing and anxiety, and to propose a model which discusses why trait anxiety, personality types and sensory profiles may be factors in the development of CS.

Method: Four electronic data bases were searched from their inception for articles in five subject areas: sensory processing, anxiety, trait-anxiety related personality types, stress responses and CS. Information was synthesized qualitatively.

Findings: Trait sensory processing differences of sensory hyper- and hypo-sensitivity are associated with anxiety and stress responses. Physiological and behavioural responses to stressors may vary between individual trait-anxiety related personality types. Sensory hyper-sensitivity, anxiety and chronic stress responses are linked to CS.

Conclusion: The review provides level IV evidence as to why the physiological and behavioural mechanisms of CS may involve trait sensory processing differences, trait anxiety and related personality types. A model is presented describing a proposed pathway to CS. Clinically, early identification of individuals at risk of CS might inform appropriate management to enable more favourable outcomes. Further research to investigate aspects of trait sensory processing and trait anxiety characteristics in people with CS, as possible contributory factors in the development of CS, is warranted.

Introduction

Central sensitisation (CS) as a predominant pain mechanism may contribute towards persistent pain and disability in many chronic musculoskeletal pain populations, such as non-specific chronic low back pain (Nijs et al., 2015), osteoarthritis of the knee (Girbes, Nijs, Torres-Cueco, & Cubas, 2013), neck pain associated with whiplash (Coppieters et al., 2015), shoulder pain (Sanchis et al., 2015) and fibromyalgia (Meeus & Nijs, 2007). CS is defined as a dysregulation of the central nervous system causing neuronal hyper-excitability, characterized by generalized hypersensitivity of the somatosensory system to both noxious and non-noxious stimuli (Mayer et al., 2012; Nijs et al., 2010). The International Association for the Study of Pain labels patients having CS as a predominant pain mechanism as having 'nociplastic pain' (http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Nociplasticpain). Individuals with CS experience higher levels of pain disproportional to the extent of tissue pathology, pain that is not distributed in the plausible dermatomal distribution and which has no clear pattern of provocation and easement (Nijs et al., 2014; Nijs et al., 2010; Smart et al., 2012). This review focusses on chronic CS and its links to trait sensory sensitivity and anxiety characteristics.

It is currently unclear why some individuals develop CS following a musculoskeletal pain onset while others make a full recovery. Pre-morbid characteristics, measured prior to the onset of chronic CS, may be important factors in the identification of "at risk" patients. To date, according to the authors' knowledge, there has only been one systematic review published in which pre-morbid predictors were investigated longitudinally in the development of chronic CS, in musculoskeletal pain populations (Clark et al., 2017). The systematic review found moderate evidence for increased risk of a transition from acute

musculoskeletal pain to chronic CS when there had been baseline (pre-morbid or acute stage) sensory sensitivity, evidence of somatization (physical symptoms representing psychological distress) and a negative self-expectation of recovery (Clark et al., 2017). Individual characteristics of sensitivity may play a role in the development of CS, particularly trait characteristics involving sensory sensitivity and related mechanisms.

"Trait" is indicative of a patient's own characteristics and there is growing speculation that CS may be more likely to develop in individuals who may be prone to sensitisation through character traits. CS syndromes have been shown to be familial and coexist with somatoform disorders such as fatigue, sleep disturbance and memory difficulties (Diatchenko et al., 2013; Phillips & Clauw, 2011). Furthermore, individuals have different "volume control" settings on their pain and sensory processing and many are prone to "sensory amplification" (Phillips & Clauw, 2011); (p.144). Only the naturally hypersensitive may exhibit hyperalgaesia, or sensory hypersensitivity, eluding to trait sensitivity characteristics (Ablin & Clauw, 2009).

However, up to now the interplay between trait sensory profiles, trait anxiety and (the development of) CS has not been studied or discussed in detail. Therefore, these compelling yet largely unexplored interactions will be explored here. This review examines various physiological and behavioural aspects of sensory sensitivity which are found in trait sensory profiles, trait anxiety and the nature of personality types, and discusses how these might be linked to the development of CS.

Method

Articles were sourced from four electronic databases (Science Direct; Embase, CINAHL, PubMed) which were searched from their inception to November 2017. Articles were included if they were 1) published in English, 2) were on the topic of the physiological mechanisms of CS, sensory processing, trait anxiety and stress responses and 3) included randomized controlled trials, observational studies, case control studies and reviews. Articles were excluded if they were 1) about CS in non-musculoskeletal pain populations, 2) about sensory processing disorders in schizophrenia populations, 3) not published in English. Information was sought for the purpose of answering the following specific research question: "How might trait characteristics of sensory sensitivity and trait anxiety contribute towards the development of CS?" Information was synthesized qualitatively and a proposed model for the development of CS based on the contributions of trait characteristics was developed.

The findings are discussed under the following headings – Central Sensitisation, Sensory Processing, Sensory Stimulation and Pain, Anxiety, Anxiety and Pain, Personality Types. Clinical implications are presented following the presentation of the proposed model of the "pathway to CS".

Central sensitisation (CS) may be linked to stress responses

Some authors propose that CS is a disease of the brain rather than specific body areas (Phillips & Clauw, 2011). Others suggest that chronic pain depends on personal processes and meanings because threat perception is important in chronic pain conditions (Sullivan et al., 2013). It is likely that both views hold some truth because physiological changes, including those associated with autonomic arousal, occur in the central nervous system (CNS) in response to stressors. Physical and emotional stressors may be perceived or may be unconscious and may threaten the homeostatic and/or emotional wellbeing of the individual (Schouten et al., 2013; Woda et al., 2016). Trait sensory sensitivity and trait anxiety are related to a proneness to physiological arousal to stressors (Acevedo et al., 2018; Eysenck, 1997; Eysenck et al., 2007; Lionetti et al., 2018; Walsh et al., 2015). Stress responses involve the autonomic nervous system and responses by the hypothalamic-pituitary-adrenal (HPA) axis in which cortisol is released as part of the anti-inflammatory response, (Hannibal & Bishop, 2014; Koolhaas et al., 2011; Woda et al., 2016). Chronic reactivation of the stress response and repeated releases of cortisol may result in cortisol dysfunction (Hannibal & Bishop, 2014). Cortisol dysfunction and a dysfunctional HPA axis have been found in conditions linked to CS such as fibromyalgia and chronic low back pain (Griep et al., 1998; Tak & Rosmalen, 2010).

The psychological response to perceived physiological arousal to stressors may vary depending on trait-anxiety related personality types. High trait anxiety personality types are prone to attend to somatic symptoms and interpret them as threatening (Eysenck, 1997;

Franklin et al., 2016; Franklin et al., 2014; Walsh et al., 2015). These cognitive biases may lead to heightened sensitivity to sensory stimuli and pain in some people.

The sensory processing functions of sensory sensitivity and multisensory integration are modulated by anxiety whereby, the greater the levels of anxiety, the greater the sensory hypersensitivity in high trait anxious individuals in experimentally induced environments (Viaud-Delmon et al., 2011). Forebrain functions such as emotion, stress, cognitions, attention and motivation may influence the pain experience (Zusman, 2002). This facilitatory influence has been referred to as cognitive-emotional sensitisation (Brosschot, 2002).

CS may therefore be closely linked to individual sensory processing functions (trait sensory hyper-sensitivity) and trait anxiety.

Sensory Processing

Sensory processing is defined as the act of registering, modulating and organising of sensory information from the environment (Engel-Yeger & Dunn, 2011a) and of creating an appropriate response output (Davies et al., 2009). Sensory input may be received from peripheral sensors (Davies et al., 2009) and may also include central input from cerebral efferent connections including connections from emotional and psychological networks (Aron et al., 2012). Key components of sensory processing which may be relevant to the development of CS are 1) neural thresholds for sensory reception (sensory sensitivity) and 2) sensory gating.

Neural thresholds for sensory reception

The range of neural thresholds for receiving sensory information sits on a normally distributed continuum from high threshold (hypo-sensitive) to low threshold (hyper-sensitive, according to findings from cross sectional studies of healthy (non-pain) populations (Brown et al., 2001; Dunn & Brown, 1997).

Whether or not an individual will experience discomfort (or even pain) from sensory over-stimulation, or under-stimulation depends partly on their ability to respond adaptively (Dunn, 1997). Brown et al., (2001) describe the adaptive behavioural response to received sensory stimuli, as being on a continuum between passive and active (Brown et al., 2001). For healthy function, there must be adequate sensory stimulation and that under- or over-stimulation leads to discomfort, which in turn should lead to an adaptive response. Some individuals respond actively, whereas others are passive and do not respond adaptively, to various extents (Brown & Dunn, 2002; Brown et al., 2001). Individuals with a low neural threshold for sensory stimulation, and passive responders to sensory over-stimulation, may become 'overwhelmed' by excessive sensory stimuli and this may be a factor in the development of CS. Excessive sensory stimuli may exceed the homeostatic capacity of the individual such that the stimuli become stressors (Schouten et al., 2013). The perception of, and behavioural response to, sensory stimuli depends partly on the sensory gating function of the central nervous system (CNS).

Sensory gating

Sensory gating is the function of the CNS that serves to filter or attenuate irrelevant sensory stimuli so that the individual can attend to priority information with minimal distraction (Davies et al., 2009; Legrain et al., 2011). Sensory gating is a physiological function considered to be executed in the prefrontal and hippocampal networks (Grunwald et al., 2003). An individual's ability to attend to a task or to particular sensory stimuli depends on their ability to gate, or filter out, unnecessary or irrelevant stimuli (Ansari & Derakshan, 2011; Berggren & Derakshan, 2013; Berggren et al., 2013). The act of holding attention is a behavioural response to stimulation (and motivation) in a sensory environment and is dependent on efficient sensory processing function i.e. neural thresholds, sensory gating, meaningful interpretation and behavioural output (Viaud-Delmon et al., 2011). Furthermore, the ability to control attention on a task without distraction is significantly diminished in those with high trait anxiety (Ansari & Derakshan, 2011; Berggren & Derakshan, 2013). Trait anxiety is an enduring (i.e. relatively stable) personality trait, indicative of differences in an individual's proneness to reactions of state anxiety when faced with a perceived psychological threat or stressful situation (Spielberger, 1983).

The phenomena of sensory processing and anxiety may be linked by the positive correlations found between trait sensory hypersensitivity profiles and trait anxiety (Engel-Yeger & Dunn, 2011a, 2011b). For the reasons outlined above it is plausible that sensory processing functions, particularly high sensory sensitivity (low neural thresholds and diminished sensory gating), share interrelating mechanisms with anxiety. Reduced sensory gating may be a physiological factor in the development of CS based on the resulting

sensory hyper-sensitivity. Increased sensory sensitivity is apparent in people with high trait anxiety through reduced inhibitory control of distracting sensory stimuli, in experimental circumstances (Berggren & Derakshan, 2013; Eysenck et al., 2007).

Sensory stimulation and pain

The question must be asked as to when a sensory stimulus becomes a painful stimulus. An example of a 'normal' sensory stimulus becoming a painful one is in the condition of hyper-acusis, in which normal sound volume is registered by the sufferer as painful in the ears (Baguley, 2003). This may be similar in concept to that of allodynia, insomuch as a normally innocuous stimulus, such as light touch, may be registered as painful by the individual (Latremoliere & Woolf, 2009; Woolf, 2011). In theory, if an individual is sensitive to sensory stimuli because of a low neurological threshold or hypervigilance towards threatening stimuli, they may become sensitized towards them to the point where the stimuli may become painful. At this point the stimuli may have exceeded the homeostatic capacity of the individual and become stressors, creating a stress response (Schouten et al., 2013). Stress is associated with poor sleep and chronic stress and sleep deprivation have been observed to result in a number of physiological changes involving increased glial activation and low grade neuroinflammation, leading to heightened pain sensitivity (Nijs et al., 2017).

Figure 2 illustrates a proposed pathway to CS from trait sensory sensitivity (and a passive adaptive response to over-stimulation) and trait anxiety, in which an individual is more prone to autonomic physiological arousal in the presence of stressors (Eysenck, 1997).
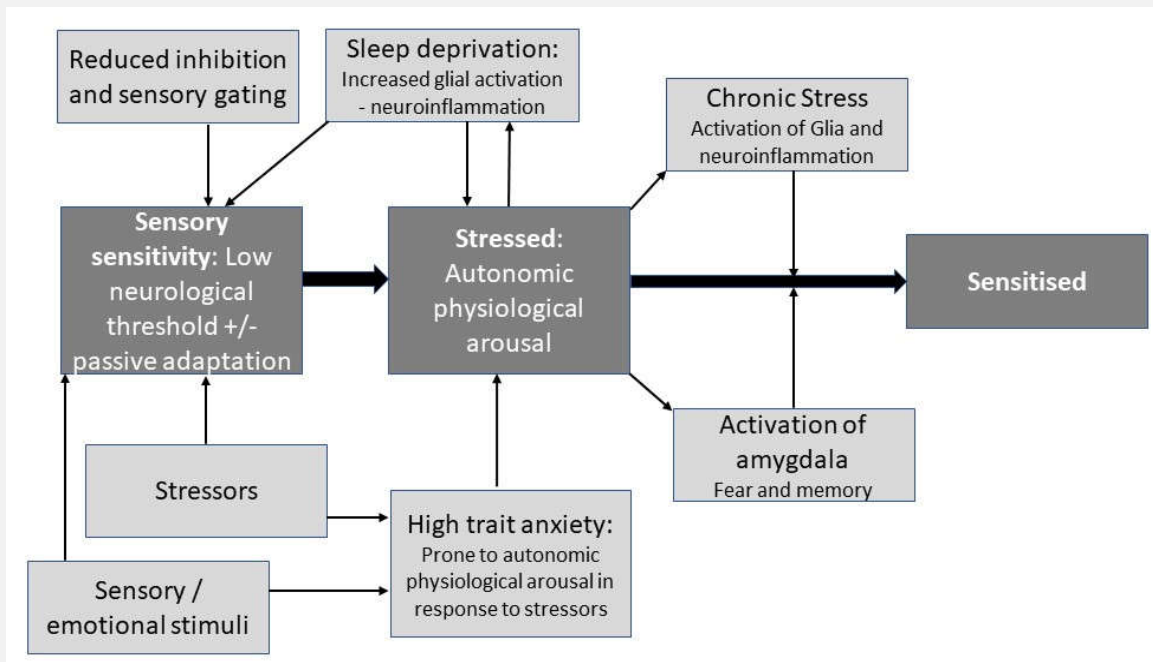
Figure 2: Schematic presentation of the proposed mechanism of CSwhich might begin with trait characteristics of sensory sensitivity to stressors (sensory profiles and trait anxiety) resulting in autonomic physiological arousal, activation of the amygdala and, when chronic, activation of glia and neuroinflammation.

Anxiety

Anxiety is known to be linked to chronic pain (Baliki et al., 2008; Borsook et al., 2007; Carleton et al., 2009; Dickens et al., 2002; Esteves et al., 2013; Feuerstein et al., 1985; Franklin et al., 2014; Kinnealey & Fuiek, 1999; Mundal et al., 2014; Nordstoga et al., 2017; Rosa Esteve & Camacho, 2008). High trait anxiety indicates a proneness to respond to stressors with physiological arousal (Eysenck, 1997). Chronic pain patients have been found to have increased levels of activity in the anterior cingulate cortex associated with autonomic responses (Farmer et al., 2012). Another key brain area involved in both anxiety and CS is the amygdala, often referred to as the fear-memory centre of the brain. The amygdala has a key role in negative emotions and pain-related memories (Li et al., 2013). In addition to the amygdala, the anterior cingulate cortex takes part of the central fear network in the brain (Kattoor et al., 2013). Recent research supports the cardinal role of the

amygdala as a facilitator of chronic pain development, including sensitisation of CNS pain pathways (Hadjikhani et al., 2013; Kattoor et al., 2013; Kim et al., 2013; Li et al., 2013; Schwedt et al., 2013; Simons et al., 2012). These findings suggest possible neurophysiological overlaps between anxiety and CS, involving a low neural threshold for sensory stimulation and heightened sensitivity to those stimuli.

Individuals with high anxiety exhibit alterations in executive functioning (Ristic & Landry, 2015) which may be similar to individuals with sensory processing differences, for example those with attention deficit disorder (Huang et al., 2016; Shimizu, Bueno, & Miranda) and people with CS (Berryman et al., 2013). Executive functioning is processed via the medial (mPFC), ventral and dorso-lateral (DLPFC) prefrontal cortices and includes, among many functions, making meaning of sensory input by the DLPFC, (Ristic & Landry, 2015; Stein, 1998; Stein, Stanford, & Rowland, 2009) which may extend to interpretation bias towards stimuli perceived as threatening.

When compared with low trait anxiety subjects, those with high trait anxiety exhibit the following sensory processing and behavioural response differences (M. Eysenck & Derakshan, 2011; Ristic & Landry, 2015).

Reduced inhibition of stimulus distraction

Inhibition of stimulus distraction is similar to sensory gating, whereby the CNS filters out, or inhibits, the perception of sensory stimuli when these are not considered relevant, important or threatening (Davies et al., 2009; Legrain et al., 2011). The sensory processing function of inhibition is reduced in individuals with high trait anxiety causing them to be

much more susceptible to distraction by other stimuli (Ansari & Derakshan, 2011; Berggren & Derakshan, 2013; Eysenck et al., 2007). This loss of inhibition is comparable with loss of descending inhibitory control described in CS (Moseley & Butler, 2015) in which the condition pain modulation system is impaired in people with chronic musculoskeletal pain (Lewis, Rice, & McNair, 2012). Furthermore, cognitive loading further decreases the ability to inhibit irrelevant information in a high anxiety state making cognitive function much less efficient (Berggren et al., 2013), drawing similarities with diminished working memory capacity in people with CS (Berryman et al., 2013).

Reduced shifting function

Shifting function is the ability to switch focus of attention between tasks or stimuli, inhibiting focus of attention on one task or stimulus in favour of another and is diminished in those with high anxiety (Eysenck et al., 2007; Ristic & Landry, 2015). Loss of shifting function, coupled with distractibility above, may be comparable with observations of the hyper-vigilance of some individuals with CS, focusing their attention on the stimulus (Berggren & Derakshan, 2013; Cisler & Koster, 2010; Ristic & Landry, 2015).

Anxiety and Pain

One of the most well tested approaches to understanding anxiety and its influence on the central processing of stimuli is the Attention Control Theory (ACT), (Eysenck et al., 2007). The ACT is based on the observation that anxiety impairs control of attention on a task, which is a key executive function, increasing the allocation of attention on threat-related stimuli (and on deciding an appropriate response). A threat to a current goal, such as a task,

causes allocation of attention to detecting the source of the threat and formulating a behavioural response (Eysenck et al., 2007). ACT may relate to CS insomuch as attentional control is shifted to possibly innocuous stimuli that are interpreted as threatening (to goals such as daily functions) and which may be perceived as painful. How someone responds to the sensory stimuli and perceived physiological arousal may depend on the nature of their personality type.

Personality Types

In addition to the physiological responses to sensory stimuli and stressors, behavioural responses are likely to form an additional important contributory role and may be partly linked to the nature of individual personality types. Individuals with different personality types respond to anxiety-related sensations and feedback from their body in different ways (Eysenck, 1997). Weinberger (1979) described four personality types based on a combination of trait anxiety and defensiveness: High anxious (high anxiety, low defensiveness), defensive high anxious (high anxiety, high defensiveness), low anxious (low anxiety low defensiveness) and repressor (low anxiety, high defensiveness); (Weinberger et al., 1979).

It is known that defensive high anxious and high anxious individuals have a greater tendency to interpret stimuli as threatening (Franklin et al., 2014; Myers, 2010) compared with their low anxious counterparts. Attentional bias towards or away from stimuli varies between personality types also. One study found that extreme defensive high anxious individuals with chronic back pain showed an attentional bias towards threatening stimuli, whereas the extreme high anxious individuals did not (Franklin et al., 2016). Conversely, repressors tended to show avoidant behaviours away from threatening symptoms (Franklin et al.,

2016). Repressors are self-deceivers and tend to prefer not to think of sensory stimuli as threatening (Myers, 2010). The behavioural aspects of personality types may play a role in the development of CS. Figure 2 illustrates the completion of the proposed path to CS based on the interpretation and action behaviours of the different personality types, in response to the stressed state induced by stressors. It is proposed that the defensive high anxious and high anxious personality types may attend to the stressors and the stress-response feedback they experience from their body, interpret them as threatening and this in turn heightens the sensitivity to stimuli and pain. Conversely, repressors tend to be prone to ignore stimuli and bodily stress-responses, preferring not to think of them as threatening and therefore might be much less likely to become sensitised. Similarly, people low in trait anxiety (low anxious personality type), who tend not to respond to stressors with physiological arousal, are unlikely to become sensitised (figure 3).
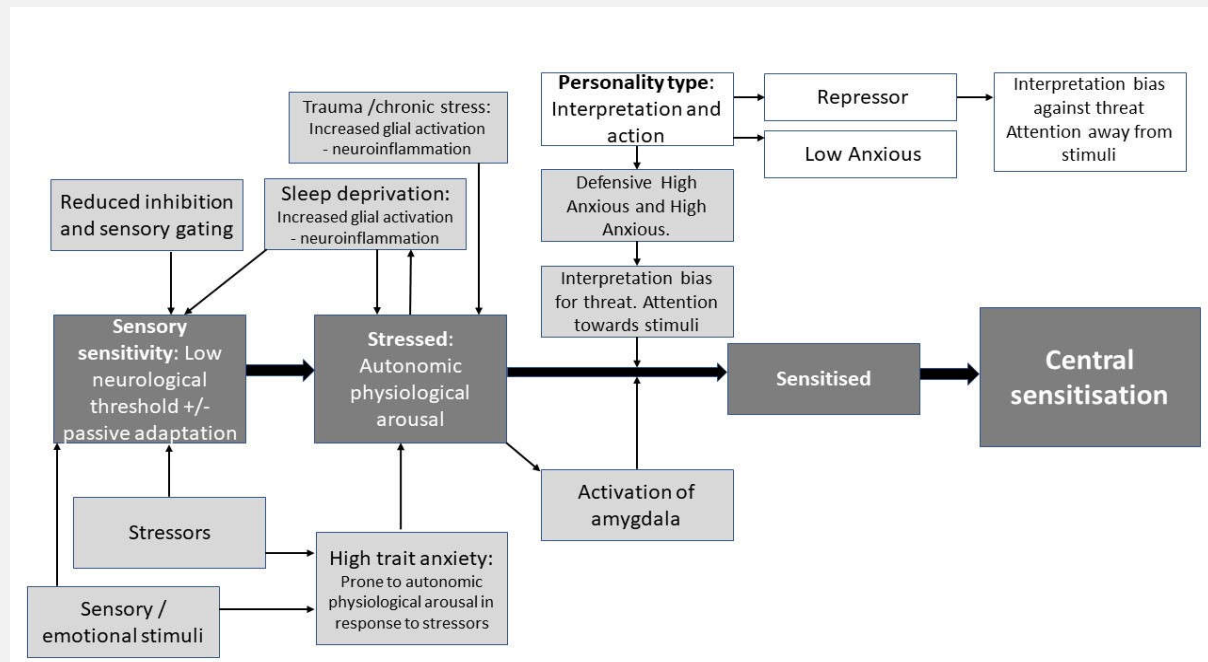
Figure 3: Schematic presentation of the completion of the proposed mechanism of central sensitization through sensory sensitivity to stressors and subsequent interpretation and action responses based on the nature of individual personality types.

Trait characteristics of sensory sensitivity and trait anxiety may determine various psychological reactions to pain, for example catastrophising and fear avoidance. However post-morbid responses to pain were beyond the scope of this review.

Clinical Implications

If individual trait characteristics can be identified at the acute stage of musculoskeletal pain, the clinician may be able to tailor management according to sensory needs and action and interpretation tendencies, to reduce the risk of the patient developing CS. Furthermore, if trait anxiety, personality types and trait sensory sensitivity characteristics can be identified as risk factors in the development of CS then preventative measures may be implemented accordingly.

Conclusion

To conclude, CS is a disease of the central nervous system which involves physiological sensory sensitivity (low neurological thresholds for sensory stimuli and proneness to physiological arousal to stressors) and these may be linked to pre-morbid trait sensory profiles and trait anxiety-related personality characteristics. A pattern of passive adaptive responses to over-stimulation according to trait sensory profiles, or attentional bias towards threatening stimuli, depending on personality types, may play a role in the development of

CS. Recommended areas for research include the following: 1) investigation of the relationships between CS, trait sensory profiles, trait anxiety and personality types; 2) consideration of trait sensory profiles and personality types when developing management interventions in CS pain populations. Understanding trait characteristics in the development of CS may help researchers and clinicians to identify individuals at risk of developing CS, thereby guiding early intervention and management accordingly.

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1.3 Conclusion to chapter 1

The narrative review (article 1) study postulates that relationships between aspects of sensory processing, anxiety and personality types are plausible and that trait characteristics related to these aspects may contribute to the development of   musculoskeletal CS pain. The next chapter investigates how much was already known specifically about factors which predict CS pain in musculoskeletal populations, measured from a pre-morbid baseline. The resultant systematic review will be presented, followed by the formulation of the research questions for the current thesis.

Chapter 2

What Are the Predictors for Altered Central Pain Modulation in Chronic Musculoskeletal Pain Populations: A Systematic Review

2.1 Introduction

The previous chapter put forward a reasoned proposal that people with central sensitisation (CS) pain may have pre-morbid trait characteristics relating to sensitivity, specifically trait sensory processing sensitivity and trait anxiety-related personality types. This was presented in a narrative review. The following chapter will attempt to determine the predictive factors of CS pain (altered central pain modulation) in chronic musculoskeletal pain disorders in a systematic review (article 2):

What are the Predictors of Altered Central Pain Processing in Chronic Musculoskeletal Pain Populations? A Systematic Review.

An article based on the following systematic review has been published in the Pain Physician Journal (Clark et al., 2017) and is presented below. Following the systematic review article, the research questions for the current thesis will be put forward. Below is the 'road map' (figure 4) to help orientate the reader through the thesis, indicating the stage at which the systematic review is presented.
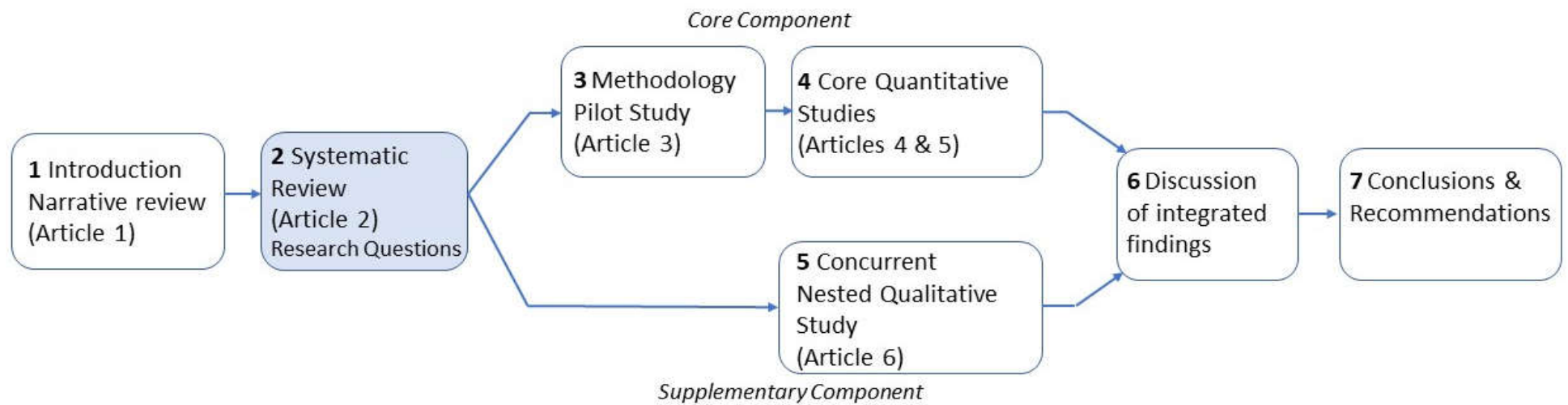
Figure 4: Roadmap through the current thesis: systematic review and research questions

The systematic review article will now be presented which examined the existing literature for predictive factors for central sensitisation (altered central pain modulation) in chronic musculoskeletal pain populations.

2.2 Article 2: What are the predictors for altered central pain modulation in chronic musculoskeletal pain populations? A systematic review

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Abstract

Background: Altered central pain modulation is the predominant pain mechanism in a proportion of chronic musculoskeletal pain disorders and is associated with poor outcomes. Although existing studies predict poor outcomes such as persistent pain and disability, to date there is little consensus on what factors specifically predict altered central pain modulation.

Objectives: To review the existing literature on the predictive factors specifically for altered central pain modulation in musculoskeletal pain populations.

Study Design: This is a Systematic Review in accordance with supplemented PRISMA guidelines.

Methods: A systematic search was performed by two mutually blinded reviewers. Relevant articles were screened by title and abstract from Medline, Embase, PubMed, CINAHL and Web of Science electronic databases. Alternative sources were also sought to locate missed potential articles. Eligibility included studies published in English; adults aged 18 to 65; musculoskeletal pain; baseline measurements taken at the pre-morbid or acute stage; > 3-month follow-up time after pain onset and primary outcome measures specific to altered central pain modulation. Studies were excluded where there were concurrent diseases; non-predictive studies. Risk of Bias was assessed using the QUIPS tool. Study design, demographics, musculoskeletal region, inclusion / exclusion criteria, measurement timelines, predictor and primary outcome measures and results were extracted. Data was synthesized qualitatively, and strength of evidence was scored using the GRADE scoring system.

Results: Nine eligible articles were located, in various musculoskeletal populations (whiplash, n=2; widespread pain, n=5; temporomandibular disorder, n=2). Moderate evidence was found for two predictive factors of altered central pain modulation: 1) high sensory sensitivity (using genetic testing or quantitative sensory tests), 2) psychological factors (somatisation and poor self-expectation of recovery), at a pre-morbid or acute stage baseline.

Limitations: At the times of the article publications, the current definitions and clinical guidelines for identifying altered central pain modulation were not yet available. Careful

interpretation of the information provided using current knowledge and published guidelines was necessary to extract information specific to altered central pain modulation in some of the studies, avoiding unwarranted assumptions.

Conclusion and Implications: Premorbid and acute stage high sensory sensitivity and/or somatization are the strongest predictors of altered central pain modulation in chronic musculoskeletal pain to date. This is the first systematic review specifically targeting altered central pain modulation as the primary outcome in musculoskeletal pain populations. Early identification of people at risk of developing chronic pain with altered central pain modulation may guide clinicians in appropriate management, diminishing the burden of persistent pain on patients and heath care providers alike.

Systematic Review Registration no.: PROSPERO 2015:CRD42015032394.

Introduction

Chronic pain is experienced when, subsequent to the subacute phase of healing, pain persists beyond the expected healing time frame, leading to poor outcomes. Existing studies have investigated predictors of poor outcomes associated with musculoskeletal pain including disability (Sterling et al., 2006; Walton et al., 2011), and failure to return to work (Iles et al., 2008; Iles et al., 2009). However, there remains little consensus, probably due to the heterogeneity of outcomes studied and, moreover, the heterogeneity of pain mechanisms. Hence, the transition from acute musculoskeletal pain to chronic pain is currently difficult to predict.

Common to a significant proportion of chronic musculoskeletal pain populations is the phenomenon of sensitisation of the central nervous system pain pathways, i.e. altered central pain modulation. Altered central pain modulation manifests as a predominantly non-nociceptive, non-neuropathic pain mechanism (Nijs et al., 2014; Smart et al., 2012) and is defined as a dysregulation of the central nervous system causing neuronal hyper-excitability, characterised by generalised hypersensitivity of the somatosensory system to both noxious and non-noxious stimuli (Nijs et al., 2010; Smart et al., 2012). Altered central pain modulation involves impaired modulatory mechanisms within the central nervous system whereby nociceptive pathways are less inhibited and nociceptive facilitatory pathways enhanced, resulting in augmentation of nociceptive transmission (Baert et al., 2015).

Poor outcomes such as disability are not necessarily an indication of altered central pain modulation *per se*, despite being commonly associated with each other (Ferrari, 2010; Sterling et al., 2003). Disability may be the result of psychological factors that may not be predominantly a result of altered central pain modulation, such as fear avoidance (Vlaeyen & Linton, 2000). Similarly, poor outcomes such as chronic pain may or may not be an indication of altered central pain modulation, depending on the predominant pain mechanism. It is proposed that the phenomenon of altered central pain modulation should be investigated specifically in the development of poor outcomes.

A strong clinical predictor of altered central pain modulation is "disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors" (Smart et al., 2012) (p.342). Altered central pain modulation is associated with many non-specific chronic musculoskeletal pain conditions and the aetiology is poorly understood. It is considered by some that altered central pain modulation is a disease in itself rather than a disease of the particular presenting musculoskeletal condition (Mogil, 2012). From a clinical perspective, identifying predictors of altered central pain modulation may help to sub-classify "at-risk" patients at baseline after acute musculoskeletal pain onset. Appropriate management could then be prioritised accordingly to minimise the risk of altered central pain modulation and poor outcomes.

Therefore, the objective of the current study was to systematically evaluate the current available literature to identify predictors of altered central pain modulation in adults with general musculoskeletal pain conditions, measured at a pre-morbid or acute stage baseline and followed up at least 3 months later. Furthermore, if data allow, predictors for altered

central pain modulation specifically in patients with non-specific low back pain might be identified as a second objective.

The scope of the current review follows the type of model intended to inform clinicians' therapeutic decision making, in accordance with Moons (Moons, 2014). It intends to focus on prognostic studies designed to predict a future health outcome (altered central pain modulation) as opposed to diagnostic predictor models or models designed to identify suspected existing disease (Moons, 2014).

Methods

The review protocol was registered prior to commencement of the search with PROSPERO, protocol no.: PROSPERO 2015: CRD42015032394. The methods used in the current study follow the guidelines published in the PRISMA Statement for systematic reviews (David et al., 2009). This is supplemented by methodological guidelines specific to systematic reviews of prognostic studies by Dretzke (2014) and Moons (2014) and their respective colleagues.

Search strategy

The following electronic databases were searched from their inception up to March 2016: EMBASE (via Ovid), Medline (via Ovid), CINAHL (EBSCO), Scopus, Web of Science (via Web of Knowledge) and Google Scholar. Reference lists of the eligible studies were hand searched and 31 other researchers in the field were contacted by email by JC in order to identify any missed, potentially important studies.

A pilot search was carried out to test preliminary search terms identified from related literature. With a view to finding studies detailing prognostic indicators which predict altered central pain modulation, the search term "Prognos*" was piloted. This was with the intention of capturing terms such as prognosis / prognostic indicators / prognostic factors / poor prognosis and was initially focused on low back pain (LBP) populations. However, it became clear that the studies with chronic LBP and prognos* were generally looking at the natural course of LBP or the response to management regarding whether or not they would return to work. Therefore, the pilot search was altered to acute low back pain AND prognos* because this would potentially yield prognostic indicators for a poor outcome in acute LBP. However, poor outcome in acute LBP can lead to various outcomes such as disability or persistent pain, which are not specific to altered central pain modulation. Therefore, specific terms for the outcome measures of altered central pain modulation had to be developed, with the assistance of examples drawn from other review studies in altered central pain modulation (Malfliet et al., 2015; Roussel et al., 2013).

The term predict* was chosen because statistically logistic regression models are used to find predictors (Field, 2009). Dretzke (2014) advises the use of both prognosis- and predictor-related terms, without filters, so as to minimise loss of relevant studies.

The term "central sensitisation" was also piloted. It became clear that there are two spellings, English and American, the latter using "z", as in "sensitization." Both spellings had to be included. No word filters were applied to the search strategy.

Subsequently, the systematic search was conducted to locate studies relevant to three key subject areas of the research question: 1) central sensitisation pain due to altered central pain modulation, 2) predictors and 3) musculoskeletal pain known to be associated with altered central pain modulation (Yunus, 2008), using the tested search terms. Keywords or database specific search terms (e.g. MeSH, subject terms, subject headings, and CINAHL headings) or a combination of both were used. The Boolean operators "OR" and "AND" were used to combine search terms within and between each of the subject areas. No time limits were applied to any of the databases. No filters were used in the search strategies, as recommended by Dretzke et al., (2014). Only full text studies reported in English were to be included. The systematic search was carried out independently by JC and PG. The search terms are detailed in table 2.

Table 2: Search Terms

Target Population: Musculoskeletal pain	("low back pain" OR backache OR lumbago OR "ache, low back" OR "Low* back pain" OR "neck pain" OR "cervical pain*" OR cervicalgia OR cervicodynia OR "temporomandibular pain*" OR "widespread pain*" OR "musculoskeletal pain" OR "shoulder pain" OR whiplash)
	And:
Target condition: Central sensitisation pain; altered central pain modulation	("Central pain" OR "central sensitisation" OR "central sensitization" OR "central sensitivity" OR "central hypersensitivity" OR "endogenous analgesia" OR "descending nociceptive inhibition" OR "descending facilitation" OR "nociceptive facilitation" OR "central pain modulation")
	And:
Methodology: prospective predictive cohort studies using regression analysis	(inception OR prognos* OR predict* OR prospective OR cohort OR longitudinal OR "follow-up" OR "follow up study" OR Risk)

The review included only predictive or prognostic studies where baseline predictive factor measurements were taken pre-morbidly or at the acute stage of musculoskeletal pain onset. The primary outcome measurements were those that indicate a likelihood of the pain mechanism being specific to altered central pain modulation, measured at least 3 months after the initial acute pain onset. Longitudinal data were used in logistic regression models of analysis to identify predictors of altered central pain modulation.

Although prognostic longitudinal cohort studies using logistic regression models of analysis were expected in the search, it was agreed at the outset not to restrict the search to those only using logistic regression models of analysis. This decision was made in anticipation of a small number of studies eligible for inclusion to avoid unnecessary exclusion. It was proposed, *a priori,* that authors of potentially relevant studies could be contacted for permission to re-run their data through a logistic regression analysis if necessary and if possible.

Of critical importance to this review was the primary outcomes specific to altered central pain modulation. An anticipated potential difficulty was the lack of a single gold standard measurement tool for the determination of altered central pain modulation. Quantitative sensory testing (QST) is an acceptable measurement procedure for sensory hypersensitivity (Shy et al., 2003), a manifestation of altered central pain modulation. Another acceptable measure of altered central pain modulation is the Central Sensitisation Inventory (CSI) questionnaire (Mayer et al., 2012) validated in 2013 by (Neblett et al., 2013). The CSI gives a score that indicates the likelihood of symptoms being attributed to altered central pain

modulation. More recent clinical guidelines have been available detailing how to clinically identify altered central pain modulation (Nijs et al., 2014; Smart, et al., 2012). Outcome measurements paralleling any of these guidelines were anticipated as being acceptable in the search process, especially for studies published before 2012, which did not use QST as the primary outcome measure.

Table 3: Eligibility Criteria for study screening

Inclusion Criteria	Exclusion criteria
Prognostic longitudinal studies	Non-musculoskeletal pain populations
Participants - Adult (age 18-65)	People aged under 18 or over 65;
Recruited pre-morbidly or at the acute pain onset with follow-up at least 3 months after pain onset.	Specific pathologies; post-surgical pain studies;
Musculoskeletal pain (known to be associated with altered central pain modulation)	Rheumatoid arthritis or any other rheumatic, neurological, oncological or internal disease.
Measuring an outcome of altered central pain modulation according to clinical guidelines (if described) or using QST	Functional outcomes not specific to altered central pain modulation such as return to work or disability-only outcomes.

Study selection

Studies were screened according to titles and then by abstracts, based on the inclusion and exclusion criteria listed in table 3. All studies were independently screened by two reviewers (JC/PG) before collaboration on the screening. In the case of disagreement, a third reviewer was available for consultation (GY). Discussion between reviewers enabled a consensus to be reached regarding the eligibility of the final studies for inclusion.

Risk of bias (quality) assessment

At the study level, the QUIPS (Quality in Prognostic Studies; Hayden et al., 2013) risk of bias tool for prognostic studies was used to assess the quality of each study. This was tailored to the requirements of the review and supplemented by recommendations from the CHARMS (Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies) checklist (Moons, 2014). The final seven-part risk of bias check list was used to grade each study with an overall score of low, moderate, or high risk of bias, according to the QUIPS grading guidelines. The risk of bias grades were taken into consideration when evaluating the strength of findings in each predictive study.

Overall quality of evidence and strength of recommendation was determined using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria (Schunemann et al., 2008). The final GRADE score incorporated the 4 categories, quality, consistency, directness and effect size. Evidence quality was based on the overall GRADE scores for each comparison and graded: high (at least 4 points overall), moderate (3 points), low (2 points), or very low (1 or less).

JC and PG independently extracted results from the included studies. A data extraction form was agreed between the two reviewers prior to extraction based on the required information and research question. Authors were contacted directly by email in the event of data queries.

The data extracted were: Study Design; Characteristics of participants (number /age/sex/ musculoskeletal pain condition); Recruitment setting; Inclusion / exclusion criteria   ; Baseline time point since injury; Primary outcome measure; Predictive factor measures; Follow-up time points; Main findings. The main findings varied in their summary measures. Given the small number of studies and the variation in predictors and outcome measures across the selection, statistical pooling of data was not feasible. Instead, findings were synthesised qualitatively.

Results

The initial search yield was n=2,368 hits from the databases and n=13 from additional sources (figure 5). After removal of duplicates, n=171 articles were selected from the initial hits. Screening of the titles, using the inclusion and exclusion criteria reduced the yield to n=107. Further screening by abstract reduced the yield to n=36. N=1 article was excluded as it could not be retrieved (Murphy & Cornish, 1984). Further exclusions were made based on non-English language reporting (n=2), primary outcomes not specific to altered central pain modulation (n=22), too short a follow-up time (n=1), subjects being above age 65 (n=1) and only associations being calculated (n=1). The total number of full articles selected was n=9. Full text articles were screened by JC and PG and there was no disagreement requiring

consultation with the third reviewer (GY). Based on the research question, the inclusion and exclusion criteria and clinical knowledge of altered central pain modulation, it was agreed by consensus that the n=9 studies meeting study eligibility were: (Diatchenko et al., 2005; Ferrari, 2010; Gupta et al., 2007; Harkness et al., 2004; Markkula et al., 2016; McBeth et al., 2001; Slade et al., 2014; Sterling et al., 2003; Wynne-Jones et al., 2006)

One corresponding author was contacted in order to clarify a reporting error – the study reported that high tender point counts significantly predict WP but quoted a non-significant p value of 0.157 (Gupta et al., 2007). It was confirmed by the author as a typographical error in the article and corrected as p=0.042. The study demographics are summarised in table 4.

Figure 5: PRISMA flowchart describing the selection of articles.

Identification

Records identified through database searches
(N = 2,368)

Additional records identified through other sources
(n = 13)

Records after duplicates removed
(n = 1,227)

Screening

Records screened by title
(n = 171)

Records excluded
(n = 64)

Eligibility

Records screened by abstract (n = 107)

Records excluded
(n = 71)

Full-text articles assessed for eligibility
(n = 36)

Full-text articles excluded, (1 article not located, 2 in foreign language, 21 outcome not altered central pain modulation-specific, 1 only associations calculated, 1 age range >65, 1 short f/u time)

Included

Final number of studies included
(n = 9)

Table 4: Study Demographics

Study	Age (years)	Male / female	Setting
McBeth et al. 2001	Range = 18-64	Male n=608, Female n=796.	Random population sample, UK
Sterling et al. 2003	Mean = 36.27(SD+/- 12.69) Controls: mean = 40.1 (SD+/- 13.6 years)	Male n=24, Female n=56, 20 controls 8 males, 12 females,	Hospital accident and emergency departments, primary care practices (medical and physiotherapy) and media advertisements
Harkness et al. 2004	Median = 23	Male Approx. 1/3	12 diverse occupational settings
Diatchenko et al. 2005	Range = 18-34	Females n=202	Setting not mentioned ? population study implied
Wynne-Jones et al. 2006	Median = 41 yrs. [IQR= 33–50]	Female = 51%	UK based vehicle insurance co.
Gupta et al. 2007	25–39 n=66 (28.6%) 40–49 n=54 (23.4%) 50–65 n=111 (48%)	Male n=71 (30.7%) Female n=160 (69.3%)	Three population-based primary care registers covering two socio-demographically mixed suburban areas
Ferrari 2010	Mean = 37.5 (SD+/-13)	Male n=32, Female n=37	Single primary care walk-in clinic in Canada
Slade et al. 2014	Range = 18-44	Not stated	OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) research clinic USA
Markkula et al. 2016	Mean = 27.7 (SD± 7.3)	Male = 46.2% Female = 53.8%.	Finnish Twin Cohort, Finland

Table 5: Summary of Study Characteristics

Study	Study Design	Condition	Inclusion / exclusion criteria	Base-line time point	Predictors	Primary outcome measure	Follow-up	Results as presented in study
McBeth et al. 2001	Population based prospective study	WP	Included if free of WP pre-morbidly and showed evidence of somatisation	Pre-morbid	ACR criteria for WP Somatising Q'aires: somatic symptoms checklist Illness Attitudes Scale General health Questionnaire Fatigue questionnaire All described and valid	ACR criteria for WP	12 months	Illness Behaviour Scale and Somatic Symptom scores most strongly predicted new onset chronic WP at 12 months. Strong relationships between baseline test scores and subsequent risk of chronic WP (odds ratio for the Somatic Symptom Checklist 3.3; odds ratio for the Illness Behaviour subscale of the Illness Attitude Scales 9.0). All 95% confidence intervals excluded unity. These associations were independent of baseline pain status.
Sterling et al. 2003	Prospective cohort	Whiplash	Quebec Task Force Classification of WAD II or III Exclusion: WAD IV, experienced concussion, LOC or head injury, previous history of whiplash, neck pain/ headaches that required treatment.	Within 1 month	Thermal (hot, cold) pain thresholds Brachial plexus provocation test (BPPT) Sympathetic vasoconstrictor reflex GHQ-28 10 cm VAS scale	Neck disability index (NDI) (PPT's also measured at FU.)	ALL PF's measured at 2, 3 and 6 months post-injury NDI at 6 months	3 groups – Recovered, Mild, Moderate to Severe Pain and Disability at 6 months: PPT's and TPT's lower at baseline for "Moderate to Severe" group and remained low. Other groups had higher baseline thresholds and recovered to normal by 6 months. Psychological distress not found to be a predictor of altered central pain modulation. No CI's & OR's
Harkness et al. 2004	Prospective cohort	WP	Newly employed workers Subjects free of WP selected for F/u.	premorbid	Detailed questionnaire information on: Mechanical exposure Posture Physical environment PsychoSoc risk factors	Pain status questionnaire based on ACR 1990 criteria	12 and 24 months	Those who pulled heavy weights had an 80% increased, but not statistically significant, risk of symptom onset compared with those who did not perform these activities. Those who squatted for >15 minutes (OR 2.0 95%CI: 1.1-3.6) and those who thought their work was monotonous or boring (OR 1.9 95% CI: 1.1–3.2) had a significantly increased approximately double) odds of developing new-onset WP in 2 years.
Diatchenko et al. 2005	3 year prospective longitudinal	TMD	TMD free at baseline, no exclusion criteria	Pre-morbid	COMT genotyping for pain sensitivity PPT's Ischaemic pain thresholds	TMD with QST high sensitivity	3 monthly interviews and annual physical examinations for up to 3 years to identify new onset TMD	From n=170, n=15 new onset TMD were detected; in whom COMT genotypes for HPS were significantly more prevalent than the APS and LPS haplotypes. HPS haplotypes (and associated pain sensitivity in QST) predict new onset TMD. The incidence density ratio of 2.3 was significant (95% CI: 1.1–4.8), suggesting that the HPS and/or APS haplotypes represent significant risk factors for TMD onset.
Wynne- Jones et al. 2006	Prospective longitudinal	WP	Inclusion: UK residents, fluent in English. Excluded if reported WP in the period 1 month pre-MVA.	Median 23 days post MVA	General Health Q'aire Illness Attitude Q'aire Rate general health (excellent to poor) Somatic Symptom check list Primary care visit count in 1 year period pre MVA Collision specific factor Q'aire Symptom severity Q'aire VAS pain scale	WP (ACR 1990 criteria)	12 months	54 (7.8%) reported new WP. Few collision-specific factors predicted the onset of WP. In contrast, post-collision physical symptoms (rate ratio 2.5, 95% confidence interval 1.2–5.1), pre-collision health-seeking behaviour (RR 3.6, 95% CI 1.6–7.9), pre-collision somatization (RR 1.7, 95% CI 0.99–2.8), and perceived initial injury severity (RR 1.7, 95% CI 0.9–3.3), in addition to older age (RR 3.3, 95% CI 1.5–7.1), were all independently predictive of new onset WP. In combination, these factors accounted for about a 20-fold difference in the risk of new onset WP.
Gupta et al. 2007	Prospective longitudinal	WP	Included if free of WP but who showed evidence of somatising behaviour.	Pre-morbid	Somatic symptom score Illness behaviour score Total pain threshold Tender point count (ACR 1990 criteria)	WP (ACR 1990 criteria)	15 months	In people who show somatising behaviour a high pre-morbid tender point count is associated with the onset of new WP (OR 4.1, 95% CI: 1.1 -15.,), a low pain threshold at baseline is not.
Ferrari 2010	Prospective Longitudinal with	Whiplash neck injury following motor	Included: WAD Gd 1 or 2, they were seated within the interior of a car,	Within 7 days of onset	Recovery expectation questionnaire Age	BPPT (1- angle of elbow flexion & 2- 10cm VAS)	3 months	Those who expect 'never to get better' or 'don't know' have a much higher likelihood of developing at least one sign of central sensitisation 3 months later.

	consecutive recruitment	vehicle accident	truck, sports/utility vehicle, or van in a collision (any of rear, frontal or side impact) No LOC Age 18+ Within 7 days accident Excluded: #'s,neuro signs, (i.e. WAD gd 3 – 4) prev WAD, non trauma pain Non MVA		Gender Initial Whiplash Disability Questionnaire score			
Slade et al. 2014	Nested Case control study using longitudinal data from prospective cohort study.	TMD	Included: English language fluency, intention to live in the area > 2 years. <5 HA's pcm for previous 3 months, no prior TMD symptoms / treatment, absence of 13 specific health conditions. Excluded: orofacial pain >5 days in past 30 days and/or evoked pain in >=3 muscle locations or =>1 TMJ.	Pre-morbid	PPT's Interval between visits Study site Gender Race ethnicity	TMD and PPT's	Up to 5 years	Pre-morbid PPT's measurements not useful in predicting the course of TMD (whether TMD will be transient vs persistent) but do provide insight into the mechanisms of altered central pain modulation in generalized pain in recent onset TMD.
Markkula et al. 2016	Prospective longitudinal	WP	Included if no pain nor exclusion criteria reported in 1975 and 1981. Excluded if had rheumatic diseases, malignancies, Subjects with: missing data on regional pain in 1975 & 1981;WP & likely FM in 1975 & 1981; reported frequent use of analgaesialtered central pain modulation in 1975 or 1981.	Pre-morbid In 1975	FM Q'aire, medical record data. Questions based on other predictive study results on: Regional pain Headaches Migraine Zygosity (by validated twin q'aire.) Sleep Weight BMI Smoking Physical activity leisure-time activity.	WP or FM using ACR 1990 criteria for FM	6 and 15 years: T1: 1981, T2: 1990.	The strongest non-genetic predictor was frequent headache (OR 8.6, CI 95 % 3.8–19.2), followed by persistent back pain (OR 4.7, CI 95 % 3.3–6.7) and persistent neck pain (OR 3.3, CI 95 % 1.8–6.0).

All the studies were prospective longitudinal cohort studies (table 5). All investigated prognostic factors with an outcome measure related to altered central pain modulation.

Baseline measurements of predictors were taken pre-morbidly by the majority of studies (Diatchenko et al., 2005; Gupta et al., 2007; Harkness et al., 2004; Markkula et al., 2016; McBeth et al., 2001; Slade et al., 2014) and at the acute stage of the pain in the other studies (Ferrari, 2010; Sterling et al., 2003; Wynne-Jones et al., 2006), so that it was likely that baseline predictors were measured before the onset of altered central pain modulation. Follow-up measurements were all taken at time points beyond the normal healing time frame, ranging from 3 months (Apkarian et al., 2013; Diatchenko et al., 2005) to 6 months (Sterling et al., 2003), 12 months (McBeth et al., 2001; Wynne-Jones et al., 2006), 15 months (Gupta et al., 2007), 24 months (Harkness et al., 2004), 5 years (Slade et al., 2014) and 15 years (Markkula et al., 2016).

Predictors varied widely across studies and can be grouped according to sensory sensitivity, psychological and other factors. Six studies (Diatchenko et al., 2005; Gupta et al., 2007; Markkula et al., 2016; McBeth et al., 2001; Slade et al., 2014; Sterling et al., 2003) used sensory sensitivity at baseline as a predictive factor of altered central pain modulation. Diatchenko and colleagues (2005) specifically used a genetic marker for sensitivity, unlike the others which included quantitative sensory testing (QST) or the American College of Rheumatology (ACR, 1990) criteria as predictors. Psychological measures included Somatising Symptoms Checklist (Gupta et al., 2007; McBeth et al., 2001) and Illness

Attitudes Scale (McBeth et al., 2001; Wynne-Jones et al., 2006), Illness Behaviour Score (Gupta et al., 2007), Recovery Expectation Questionnaire (Ferrari, 2010), perception of premorbid general health including psychological distress, using the General Health Questionnaire (McBeth et al., 2001; Sterling et al., 2003; Wynne-Jones et al., 2006) and work-related psychosocial risk factors (Harkness et al., 2004). Work related physical factors (Harkness et al., 2004) and collision-specific factors (Wynne-Jones et al., 2006) were also tested as predictors.

Risk of Bias Assessment

All studies were judged as low risk of bias (ROB; table 6). The study by Diatchenko and colleagues (2005) initially presented as high ROB. It was written in a style relevant to its background of genetics and according to the journal requirements in which it was published and in order to review it fairly, the supporting information was obtained from the journal website

Table 6: Risk of Bias summary for methodological quality.

Study	Study participation (QUIPS)	Target Population (CHARMS)	Study attrition /complete follow up (QUIPS)	Prognostic Factor Measure (QUIPS)	Outcome measurement (QUIPS)	Study confounding (QUIPS)	Statistical analysis and reporting (QUIPS)	Overall Statement of Risk of Bias
	Data related to outcome may be different for participants and eligible non-participants	Description of source of participants and inclusion and exclusion criteria.	Data related to outcome may be different for completing and non-completing participants	The measurement of the PF may be different for different levels of the outcome of interest	Measurement of the outcome may be different related to the baseline level	Outcome may be distorted by another factor related to outcome	Reported results may be spurious or biased related to analysis or reporting	Based on number of low, moderate and high ratings
McBeth et al., 2001	L	L	L	L	L	L	L	Low
Sterling et al., 2003	H	L	L	L	L	M	L	Low
Harkness et al., 2004	L	L	H	L	L	L	L	Low
Diatchenko et al., 2005	L	L	H	L	L	L	L	Low
Wynne-Jones et al., 2006	L	L	H	L	L	L	L	Low
Gupta et al., 2007	L	L	L	L	L	L	L	Low
Ferrari, 2010	L	L	L	L	H	L	M	Low
Slade et al., 2014	M	L	H	L	M	L	L	Low
Markkula et al., 2016	L	L	L	L	L	L	L	Low

L= low risk of bias; M = moderate risk of bias; H = High risk of bias; QUIPS = Quality in Prognostic Studies;
CHARMS = Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies

Three main groups of predictors were identified across the studies as: 1) sensory sensitivity factors, 2) psychological factors, and 3) other factors (Table 7). According to the groups, there might be a higher risk of the patient developing altered central pain modulation, if:

1) High sensory sensitivity can be identified at baseline using QST or the ACR guidelines for tender point counts or genetic testing for sensory sensitivity;

2) Somatisation, poor illness attitudes and negative expectation of recovery can be identified at baseline, (Somatisation Checklist; Illness Attitudes questionnaire; Expectation of Recovery questionnaire);

3) Pre-morbid frequent headaches were apparent.

Table 7: Clinical interpretation of results

Author	Grouped Results	Quality of evidence and strength of recommendation (GRADE score)
Sensory Hypersensitivity at baseline		
Sterling et al., (2003)	Higher sensory sensitivity (using QST) within 4 weeks of a whiplash injury is a predictor of altered central pain modulation (low PPT) at 6 months, associated with moderate to severe pain and disability and poor recovery. High sensory sensitivity at the acute stage is apparent in all individuals who experienced a whiplash injury, but sensory sensitivity is 1) less elevated at baseline and 2) returns to normal, in those who do not develop altered central pain modulation at 6 months, compared with those who do.	
Diatchenko et al., (2005)	Genetic sensitivity to pain, associated with pre-morbid pain sensitivity to QST is a predictor of altered central pain modulation (TMD with low PPT's and ischaemic pain thresholds). In this study group, healthy individuals with genetic markers for sensitivity (COMT genotyping for HPS haplotypes) developed TMD with altered central pain modulation.	Moderate
Gupta et al., (2007)	A high pre-morbid tender point count is a predictor of altered central pain modulation (WP). In healthy pain-free individuals who show somatising behaviour (Somatisation Check list), PPT's taken at all 16 points are summed to make a total PPT score. Of those PPT's, the ones measuring <4kg/cm² are counted as tender points and totalled up per participant.	

Slade et al., (2014)	After the onset of TMD, pre-morbid low PPT's are a predictor of persistent pain and altered central pain modulation (low PPT).	
Psychological factors		
McBeth et al., (2001)	In a healthy population, those who show evidence of somatisation before pain onset are more likely to experience altered central pain modulation in the form of WP within 12 months of showing somatisation.	Moderate
Wynne- Jones et al., (2006)	A tendency towards somatisation and health seeking behaviour pre-morbidly (Somatisation check list and GHQ), increased perception of initial injury severity (Illness attitudes questionnaire) severity of initial symptoms (symptom severity questionnaire) and older age all predict altered central pain modulation (WP) after a whiplash injury.	
Ferrari, (2010)	Responses of [I expect] 'never to get better' or 'don't know' on the Recovery Expectation questionnaire are predictors of altered central pain modulation (BPPT with VAS) after whiplash by 3 months.	
Other factors		
Markkula et al., (2016)	In a healthy population, pre-morbid frequent headache, followed by subsequent persistent regional back or neck pain are predictors of altered central pain modulation (WP).	NA

NA= not applicable

None of the studies selected were specific to low back pain, therefore predictors of altered central pain modulation in low back pain could not be determined.

Discussion

This study set out to 1) identify predictors of altered central pain modulation in adults with general musculoskeletal pain conditions and secondly, if data were to allow, 2) determine predictors for NSCLBP. We found nine high quality articles and identified three groups of predictors of altered central pain modulation, two with a moderate strength of evidence 1) sensory sensitivity factors, 2) psychological factors and one which only included one study 3) other factors.

Some overlapping themes were found, for example, across all studies the musculoskeletal pain conditions were limited to whiplash, temporomandibular disorder (TMD) and widespread pain (WP). Similarly, sensory sensitivity tests were limited to QST, the ACR guidelines (1990; Wolfe et al.) and COMT (catecholamine-O-methyltransferase) genetic testing. There was more variation across psychological measures, although the Somatisation Checklist and GHQ were used three times, enabling some qualitative comparisons. In this review, we did not find any articles that had studied the predictors of altered central pain modulation in NSLBP.

Due to the relatively new concept of altered central pain modulation in the last 15 years there has been little consensus as to what predictors lead to altered central pain modulation. It is therefore perhaps not surprising that many of the predictors tested varied widely as researchers attempt to narrow down the possibilities. The heterogeneity of predictors and of outcome measures made grouping of factors and outcomes for comparisons broad and prevented meta-analysis of the results.

Definitions of altered central pain modulation

One challenge during this review was a lack of definition for altered central pain modulation. At the time of publication of many of the studies, there was a lack of clinical guidelines on how to identify altered central pain modulation in patients. Altered central pain modulation was not directly defined but could be inferred. Some of the studies used the ACR guidelines (1990) as a validated measure of WP (McBeth et al., 2001; Harkness et al., 2004; Wynn-Jones et al., 2006; Gupta et al., 2007; Markkula et al., 2016). Although the full ACR guidelines provide diagnostic criteria for identifying fibromyalgia, a section of the

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guidelines specifically identify WP. WP is indicative of altered central pain modulation (Nijs et al., 2014) and is an appropriate primary outcome measure for altered central pain modulation to be included in the current review.

The musculoskeletal pain disorders studied also allowed for inference of altered central pain modulation: Whiplash grade 1 or 2 (Sterling et al., 2003; Ferrari, 2010), WP (McBeth et al., 2001; Harkness et al., 2004; Wynn-Jones et al., 2006; Gupta et al., 2007; Markkula et al., 2016) and TMD (Diatchenko et al, 2005; Slade et al., 2014). These musculoskeletal pain disorders, when chronic, have been described as being closely associated with altered central pain modulation (Mayer et al., 2012; Yunus, 2008; Kindler, 2010) increasing the likelihood that the study populations in the current review contain a proportion presenting with altered central pain modulation at follow-up.

Quantitative Sensory Testing (QST) was used in four studies and included PPT (Sterling et al., 2003; Diatchenko et al., 2005; Ferrari, 2010; Slade et al, 2014); Temperature Pain Thresholds (TPT; Sterling et al., 2003) and the Brachial Plexus Provocation Test (BPPT; Sterling et al.,2003; Ferrari, 2010). Whilst PPT's are a valid measure of altered central pain modulation (Shy et al., 2003), BPPT, although associated, has not been validated specifically for measuring altered central pain modulation in Ferrari (2010). Despite this, the BPPT has been accepted for use by some authors as a test to indicate central hypersensitivity in whiplash associated disorders (Sterling, 2008), enabling these two studies (Sterling et al., 2003; Ferrari, 2010) to be eligible for inclusion into the current review.

Should baseline measures be taken pre-morbidly or during the acute stage?

In the current study, it was assumed *a priori* that taking baseline measurements in the acute stage of injury precedes the onset of altered central pain modulation. Sterling and colleagues (2003) argue that acute stage measures may not accurately reflect pre-morbid sensory sensitivity as alterations in central pain modulation may have already taken place. However, it could be argued acute-stage sensitivity measures do give an indication of pre-morbid sensitivity status, because those who developed altered central pain modulation showed higher sensitivity at baseline than the rest of the acute-stage cohort and remained higher at follow-up.

Pre-morbid baseline measures were taken in the population-based studies reported in the current review, with the advantage that the predictors were clearly taken prior to the development of altered central pain modulation symptoms. As well as the disadvantage of longer periods needed to reach post-morbid follow-up, longer time frames may introduce confounders based on demographic and time-dependent co-morbidities. Wynne-Jones and colleagues (2006) possibly attempted to overcome this by measuring baseline pre-morbid predictors retrospectively using questionnaires around the time of the whiplash (acute stage). While this is commendable, a drawback might have been participant recall bias.

Negative results

Gupta et al., (2007) and Slade et al., (2014) both found pre-morbid PPT's not to be predictive of new onset altered central pain modulation-related musculoskeletal pain. The study by Gupta et al., (2007) was underpowered and did not find a significant change from baseline PPT's in order to predict first onset WP within 15 months. This may also have been

related to the group being an already–at–risk group, with somatization as an inclusion criterium. These participants may have already had lower PPT's than a healthy population, making differences more difficult to detect.

Although Slade et al., (2014) specifically sought to find predictors of new onset TMD with altered central pain modulation, their results did show that at follow-up, participants with a lower baseline PPT tended to sensitise more vigorously, developing TMD with even lower PPT's post-morbidly. Those with PPT's closer to normal pre-morbidly and who experienced TMD did not develop persistent symptoms and altered central pain modulation but instead made a full recovery. Therefore, it may be interpreted that individuals with pre-morbid low PPT's may be at greater risk of developing persistent pain with altered central pain modulation, in a TMD population. This may be generalizable to other altered central pain modulation populations such as whiplash, based on the work of Sterling and colleagues (2003). Sterling (2003) measured baseline PPT's within the acute stage of whiplash injury and found that those with lower baseline PPT's developed persistent pain with altered central pain modulation by 6 months.

There may be a difference between insidious onsets of WP or TMD versus traumatic onset of pain following a motor vehicle accident (MVA). Unfortunately, the three studies (Sterling et al., 2003; Ferrari, 2010; Wynne-Jones et al., 2006) where the baseline was during the acute stage following a MVA, used different predictors of altered central pain modulation onset and therefore cannot be grouped to compare with studies including insidious pain onset.

Although sensory hyper-sensitivity has been measured as a predictor, other aspects of sensory processing alterations have not been evaluated, such as sensory hypo-sensitivity. Mailis-Gagnon and Nicholson (Mailis-Gagnon & Nicholson, 2010) have found sensory hypo-sensitivity to be a feature of a sub-group of fibromyalgia patients and these have not been used as predictors in prognostic studies to date. Measures of QST do not provide a full reflection of sensory alterations or differences because they only measure sensory hyper-sensitivity to particular stimuli.

Genetic markers for sensory sensitivity were discussed in two papers – Markkula et al., (2016) with regard to twins and Diatchenko et al., (2005) with regard to COMT haplotypes. Both studies discuss the likelihood of genetic predisposition to altered central pain modulation, either insidiously or after the first onset of musculoskeletal pain. It may be proposed, on the basis of the current findings, that pre-morbid trait sensory sensitivity and psychological characteristics such as coping styles, possibly of partly genetic origin, may predispose to altered central pain modulation, either insidiously or once regional pain is experienced.

Psychological predisposition

Ferrari (2010) used a one-question questionnaire as a predictor in which expectation of recovery predicted altered central pain modulation in a whiplash group. This is a psychological variable and no baseline physical examination was performed to assess for altered central pain modulation for longitudinal comparison. Three studies (Gupta et al., 2007, Wynne-Jones et al., 2006 and McBeth et al., 2004) found that a tendency towards

somatisation pre-morbidly was a predictor of altered central pain modulation. Somatisation is said to be a measure of distress and anxiety, manifesting as physical symptoms (Kroenke et al., 1998). Pre-morbid anxiety was not assessed in any of the studies; it may be useful to assess for pre-morbid trait anxiety characteristics in future studies. Distress is a measure of coping styles, none of which were assessed as predictors in any of the studies in the current review. Trait anxiety and coping styles may be an important element in the development of altered central pain modulation based on somatisation being a predictor in the current review

Predisposition requires a trigger before altered central pain modulation develops

It is suggested that if a person is predisposed to altered central pain modulation, there requires a trigger, such as an injury or trauma, to start the transition to altered central pain modulation (Diatchenko et al., 2007; Markkula et al., 2016). This echoes the observations by Latremoliere and Woolf (Latremoliere & Woolf, 2009) that it is not known why some people tend to sensitise more vigorously after an injury. Markkula and colleagues (2016) found that if there was initially some regional pain (back or neck) or headaches, this predicted the transition to altered central pain modulation in the form of WP. What is unknown from Markkula et al., (2016) is whether the regional pain was predominantly nociceptive, which might be an important distinction to make in predicting altered central pain modulation.

Methodological Strengths

The strengths of this review are based around the methodological rigour and the use of altered central pain modulation-specific inclusion / exclusion criteria. Two independent

reviewers carried out the searches and a third reviewer was available for discussion. Search terms were piloted on advice from previous authors on searching for prognostic or predictive studies.

Methodological guidelines were followed according to more than one source (Moher et al., 2009, Dretzke et al., 2014 and Moons, 2014). The search strategy included relevant databases without filter limitations, extensive hand searching and the contacting of a large number of pain researchers in order to include any potential studies. *A priori* registration of the review was done.

Valid risk of bias and data extraction tools were used (Hayden et al., 2013; Moons et al., 2014) and strict inclusion / exclusion criteria were developed from current guidelines and literature specific to altered central pain modulation enabling close adherence to the research question.

Methodological Limitations

Only papers published in English were included, to the exclusion of two in German. One paper could not be retrieved. Altered central pain modulation had to be inferred due to the lack of definitions available at the times of publication. Interpretation of the reporting of each study where altered central pain modulation was only inferred presented as a challenge at review level. This careful interpretation was done in order to extract altered central pain modulation-specific information and, despite adhering closely to current altered central pain modulation guidelines, may present as a limitation. A further limitation may be that one eligible study from 1984 could not be retrieved and two were excluded based on being in a non-English language.

Conclusion

Nine studies were included in the review to identify predictors of altered central pain modulation in adults with general musculoskeletal pain conditions. We found moderate strength of evidence to suggest that sensory hypersensitivity and somatisation pre-morbidly, or higher sensory sensitivity and low expectation of recovery at the acute stage of pain are predictors of altered central pain modulation in some musculoskeletal pain conditions. The implications for this review are that pre-morbid traits of sensory sensitivity and anxiety (somatisation) might play a role in the development of altered central pain modulation. Further investigations into pre-morbid characteristics of individuals with altered central pain modulation is warranted. This may help identify risk factors likely to predispose a person with acute musculoskeletal pain to the development of chronic pain with altered central pain modulation.

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2.3 Discussion

The results of the systematic review show that there is a paucity of studies which specifically set out to investigate the predictive factors for CS pain in musculoskeletal populations and to date there have been no further publications with this aim. The challenge when undertaking this systematic review was to find articles which were specifically able to predict CS pain. Articles which used the term 'chronic pain' as an outcome measure and/or measured pain at outcome using a numeric pain scale or visual analogue scale were insufficiently clear as to which chronic pain mechanism was being predicted. However, use of the then-recently published clinical guidelines on the classification of CS pain, together with a working knowledge of CS pain (JC), enabled CS to be inferred in cases where CS was not stated as being the primary outcome measure.

A further challenge in the review process was in determining the quality of evidence, based on two combined risk of bias (ROB) tools, in which some of the studies presented with a medium or high ROB. In Sterling et al., (2003), no demographic information was provided about the potential participants who were excluded (high ROB), nor in Slade et al., (2014). However, Slade et al., (2014) did provide the number of participants excluded and provided reasons why (medium ROB). Four studies carried a high ROB for study attrition (Harkness et al., (2004), Diatchenko et al., (2005), Wynne-Jones et al., (2006) and Slade et al., (2014)), based on there being no information reported regarding the differences between participants who completed the study at follow-up and those who did not. Furthermore, in Slade et al (2014) N=3,258 recruited into the larger longitudinal cohort study of which

N=456 were drawn for *their current* nested control study. 273 completed all 3 visits, so that 57% completed, leaving a 43% attrition rate. For the outcome measurements, it was important that the outcomes were a valid measure for identifying CS. In Ferrari (2010), the brachial plexus provocation test (BPPV) had not been validated as a test of CS. Therefore, a high ROB was recorded for Ferrari (2010). Similarly, in Slade et al., (2014) the outcome measure was a test for TMD, which is associated with CS in other literature (Yunus, 2008) but in and of itself is not a validate way of testing for CS, warranting a medium ROB score. Sterling et al., (2003) carried a medium ROB score for study confounding based on there being a high likelihood of concurrent nociceptive pain from soft tissue injury incurred during the whiplash injuries. Finally, there was one study who did not report the full linear regression statistics (Ferrari, 2010) creating a medium ROB for statistical analysis and reporting.

It was clear from the review, that pre-morbid sensitivity (measured using quantitative sensory testing or genetic markers) was predictive of CS, and some psychological factors, however, no studies had used sensory profiles or trait-anxiety related personality types to predict CS pain. Therefore, before a longitudinal predictive study could be undertaken using sensory profiles and trait anxiety-related measures in people with CS pain, some preliminary work was considered necessary. The ground work needed was to observe trait sensory profiles and anxiety-related characteristics in a group of centrally sensitised people with CS from a non-specific chronic low back pain (NSCLBP) population and their inter-relationships. The reason for choosing a NSCLBP population was because there is a rising prevalence of people with chronic low back pain with increasing frequency of presentation to health care providers (Freburger et al., 2009) including physiotherapy.

2.3.1 The research questions

As discussed in chapter 1, it was hypothesised that physiological arousal would be more likely in individuals with NSCLBP and pre-morbid high sensitivity and trait anxiety and that the outcome of CS pain would be partly dependent on the behavioural responses of the aroused individual with NSCLBP. In cognisance of this and the need for the aforementioned preliminary work, this thesis sets out to ask the following questions in two components (which will be described in more detail in chapter 3):

The core component:

- What trait characteristics of sensory profiles, trait anxiety and personality types can be observed in people with CS pain, in a NSCLBP population?

- What are the relationships between these characteristics and the extent of CS symptoms?

The supplementary component:

- How do the pre-morbid contexts in which CS pain developed relate to trait sensitivity and anxiety-related characteristics in a sub-group of the core component participants?

- Can the existence of the observed characteristics in the core component be confirmed as likely to have existed pre-morbidly?

2.4 Conclusion

Chapter 2 has presented the systematic literature review to establish the existing level of published knowledge on predictors of CS in musculoskeletal populations, which were pre-morbid baseline sensitivity, psychological factors and the existence of recurrent headaches. This confirmed the likelihood of trait pre-morbid sensory sensitivity, however, none of the studies had investigated sensory profiles nor trait anxiety measures in musculoskeletal populations including NSCLBP. The research questions have been stated for the current thesis in a study population of people with NSCLBP and predominant CS pain. The next chapter will outline the development of the mixed methods study followed by the pilot study testing of the quantitative component of the current mixed methods study.

Chapter 3

Developing and piloting the design: Mixed Methods

3.1. Introduction

The following chapter will outline the philosophical considerations underpinning the current study and the reasons why a mixed methods study design was chosen to answer the research questions. First, the theoretical perspectives underpinning the study will be discussed, including the epistemological and ontological positions and the research paradigm. This will be followed by an introduction to the mixed methods methodology and implementation of a pilot study. The presentation of the pilot study article (article3) will be included, which has been accepted for publication to the *Journal of Bodywork and Movement Therapies*. The pilot study process tested the concept plausibility and informed the refinement of the methods which will be discussed in the conclusion of the current chapter. Below is the 'road map' to assist the reader in orientation through the thesis and to indicate the position of the pilot study in the process (figure 6).
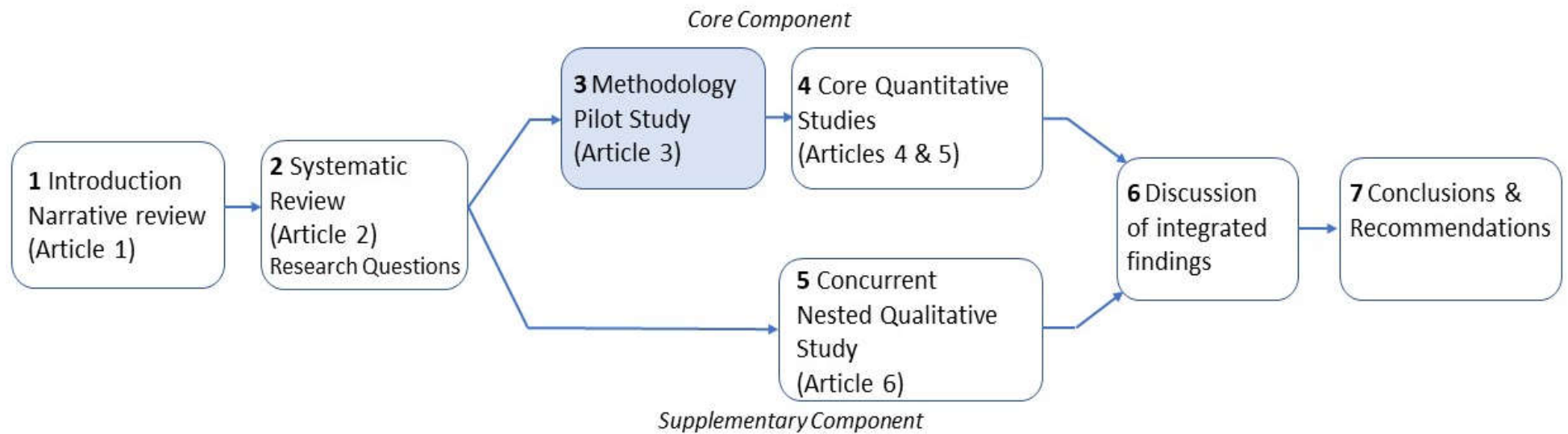
Figure 6: Roadmap through the current thesis: Pilot study.

3.2 Theoretical Perspectives

The theoretical perspective explores the set of assumptions that underpin the research study, based on the epistemological and ontological beliefs of the researcher. Along with the nature of the research question, the researcher's epistemological and ontological assumptions determine the decisions regarding the choice of methods for data collection and analysis (Tashakkori & Teddlie, 2010). These will be discussed in relation to the current study as follows:

3.2.1 Epistemology and Ontology

Epistomology is the knowledge or ideas around how we can know about a reality (Tashakkori & Teddlie, 2010). The two extreme epistemological positions are that knowledge can be gained objectively about how the world 'really is' or knowledge can be subjectively produced by individual knower based on their perceptions and experiences of the world (Tashakkori & Teddlie, 2010). However, these dichotomies may be unhelpful in social research and are often seen as incompatible with regard to combining opposing epistemological positions into one (mixed methods) study (Bryman, 2008).

The design of the current research study was justified through the epistemological assumptions that knowledge can be gained through both means - objectively, through observational measurements and quantitative analysis, and subjectively, through understanding the experiences of participants and interpretive analysis of data.

Furthermore, the objective findings found in participant responses to questionnaires might be influenced by subjective perspectives, experiences and motivations of both the researched individuals and the researcher (Tashakkori & Teddlie, 2010).

The ontological question is, what is the nature of reality and what can be known about it? (Guba & Lincoln, 1994). In social research the reality being studied is social characteristics and behavioural actions (Bryman, 2008) and these are either caused or motivated (A Tashakkori & Teddlie, 2010). Ontological positions of causation and motivation form two potentially opposing philosophical view-points:

Mechanistic ontology holds the view-point that reality is based on a world in which there are deterministic relationships between causes and effects and assumes that all social phenomena can be reduced to physical or natural phenomena (Tashakkori & Teddlie, 2010). In the designing of the current study there was an underlying mechanistic ontological assumption that central sensitisation (CS) pain mechanisms would have causes whereby certain factors would lead to CS pain in non-specific chronic low back pain (NSCLBP) population, by causality. However, as the literature was being explored in preparation for the current study, it became clearer that the outcome of CS pain in people with NSCLBP may be dependent on multiple and variable behavioural factors, in line with the view-point of social ontology.

Social ontology says that the world is a world of meaning and interpretation (Tashakkori & Teddlie, 2010). The social ontology view would not necessarily deny a world in which there is cause and effect but would interpret actions as being motivated by meaning, rather than caused mechanically (Tashakkori & Teddlie, 2010). It was considered that an understanding

of the intentions and reasons behind the responses of individuals to sensory stimulation would greatly enhance the understanding of the outcome of CS pain in a NSCLBP population.

3.2.2 The Post-positivist paradigm

Post-positivism states that knowledge can be objectively found but absolute truth can never be found in social science, evidence is imperfect and fallible and new hypotheses develop from rejected hypotheses (Creswell, 2009). In the current study, the theory that personal characteristics of sensory sensitivity and trait anxiety might be causative factors in the extent of CS symptoms in people with NSCLBP and CS is to be tested. The testing, however, will be done with the expectation of the emergence of other possible aetiological factors, based around behavioural motivations and responses to sensations associated with pain, for further testing. Further testing may involve adjustment of the hypothesis according to the findings in the current study, in line with research practice underpinned by a post-positive world view (Creswell, 2009). Post-positivism attempts to harness quantitative methodology within a more complex research design and is said to be "more cautious concerning strong and one-sided interpretations and restrained regarding the too extensive (or obsessive) use of (quantitative) data and methods", (Adam, 2014; p. 5).

To best achieve the over-arching objectives of the current thesis and based on the post-positivist philosophical position of the primary researcher, a mixed methods design was chosen.

3.3 Mixed Method Design

The nature of the current research questions (see section 2.3.1) meant that there were parts of the question that could not be answered using quantitative strategies (Tashakkori & Creswell, 2007), specifically - how the contexts in which CS pain developed might contribute to the outcome. The systematic literature review (article 2) concluded that, among other predictors, baseline genetic markers for sensory sensitivity were predictive of CS pain, suggesting an objective component to pre-morbid sensory sensitivity. Philosophically, this would suggest that there is an element of sensory sensitivity that is 'real' and exists independently of how they are interpreted by participants and researchers. However, sensory sensitivity is also anticipated to be a product of life experiences and the interpretation of sensory perceptions by the participants.

A mixed methods design was implemented to investigate the overarching thesis objectives stated in chapter 1 which were to: "investigate the trait sensory processing and anxiety-related characteristics of people with non-specific chronic low back pain (NSCLBP) and central sensitisation (CS) and to explore how these might relate to CS symptoms and the context of lived experiences before the development of pain."

The design includes a primary quantitative design using data collection through questionnaires and quantitative statistical analysis, and a concurrent nested qualitative design using semi-structured interviews and thematic analysis of the data. The quantitative 'theoretical drive' was anticipated to inform the methods of data collection and analysis in both study components (Morse, 2010). Figure 7 shows an overview of the design whereby

the 'core' component is the quantitative (QUAN) method, supplemented by the concurrent

nested qualitative (*qual*) design (Morse, 2010).
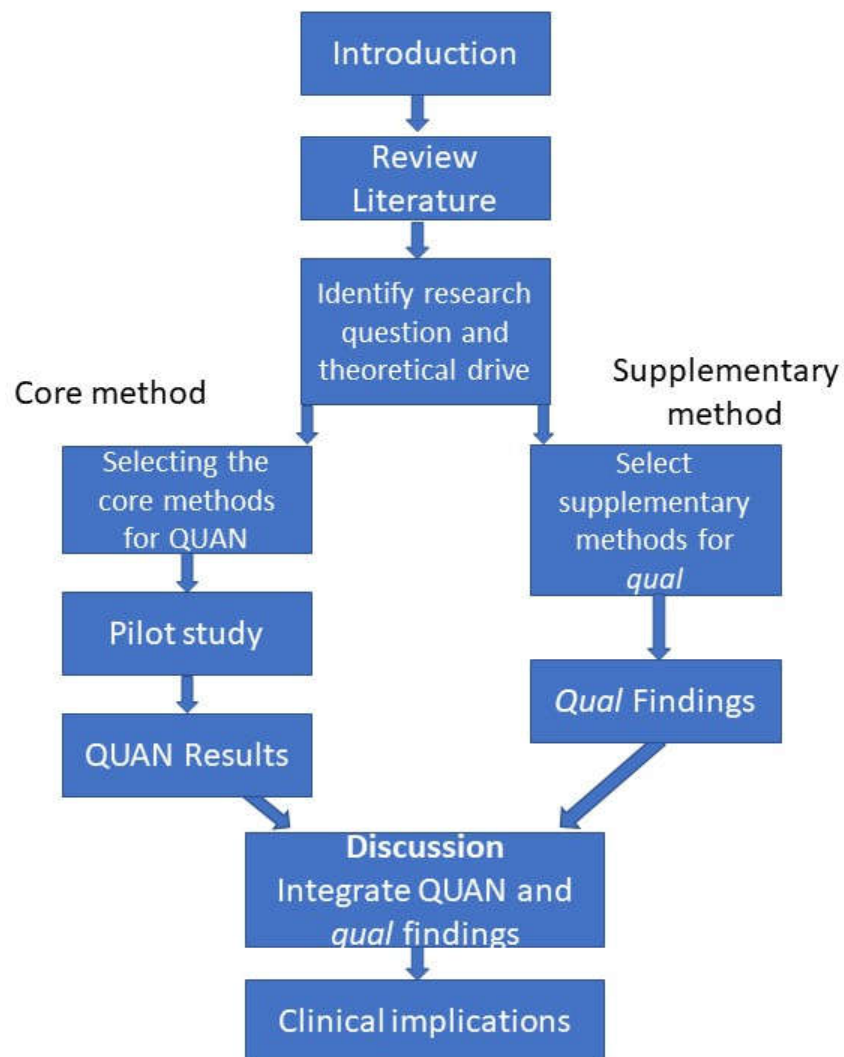
Figure 7: Overview of the mixed methods study design whereby the 'core' component is the quantitative method (QUAN) in the left column, supplemented by the concurrent nested qualitative design (qual) in the right column. (Adapted from Morse, (2010)).

A core quantitative design was implemented to investigate the research questions in core component (see section 2.3.1). A supplementary qualitative design was implemented to investigate the research questions in the supplementary component (see section 2.3.1). The supplementary qualitative design did not need to be sequential for two main reasons – it was not necessary to collect all the quantitative data and analyse it in preparation for purposive sampling for the supplementary study. Secondly, a sequential design would have been logistically unrealistic due to the anticipated time needed to recruit the quantitative sample which carried strict selection criteria. Concurrent mixed method data collection strategies have been used by others to address different types of research questions within the overarching research aim, and in many cases the same individuals provide both qualitative and quantitative data so that the data can be more easily compared (Driscoll, 2007).

3.4.1 Pilot study

The next section of the chapter will address the testing of the quantitative element which was the core component of the mixed methods study which investigated trait anxiety and sensory processing profile characteristics in patients with non-specific chronic low back pain and central sensitisation, through a pilot study (article 3). A research report based on article 3 has been accepted for publication into the Journal of Body Works and Movement Therapies (Clarke at al*; in press*). The appendices contain documents used in the pilot study and the main quantitative studies (chapter 4) including ethics documentation (appendix 3a), health care providers introductory letter (appendix 3b), participant information sheet (appendix 3c), participant questionnaire consent form (appendix 3d), questionnaire front sheet with opportunity for participant consent for subsequent contact regarding an interview (appendix 3e) and ethics committee approval correspondence from Ireland, England and New Zealand (appendix 3f, 3g, 3h). The questionnaires utilised in the pilot study (article 3) and in both quantitative studies in articles 4 and 5, are included in the appendices as follows: Central Sensitisation Inventory (appendix 3i), State Trait Anxiety Inventory (appendix 3j), Marlowe Crowne Social Desirability Scale (appendix 3k), Adolescent / Adult Sensory Profile (appendix 3l) and the Leeds Assessment for Neuropathic Signs and Symptoms (LANSS short-form; appendix 3m).

Article 3: Trait anxiety and sensory processing profile characteristics in patients with non-specific chronic low back pain and central sensitisation - A pilot observational study

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Abstract

Introduction: People with non-specific chronic low back pain (NSCLBP) and central sensitisation (CS) exhibit sensory processing alterations, somatosensory hypersensitivity and differences in the brain's emotional networks. The concept that CS relates to pre-morbid trait sensory processing and anxiety characteristics is unknown.

The aims of this pilot observational study were to test concept plausibility in a NSCLBP population with central sensitisation by investigating:

1) the range of Central Sensitisation Inventory scores, to determine the extent of symptoms of central sensitisation, 2) whether there are identifiable patient characteristics of trait anxiety and trait sensory profile differences; and 3) whether potential relationships exist between trait anxiety, trait sensory profiles and the extent of symptoms of central sensitisation.

Methods: People with NSCLBP and CS were recruited from physiotherapy outpatient clinics in New Zealand and the United Kingdom. Outcomes included the Central Sensitisation Inventory (CSI), Adolescent/Adult Sensory Profile and the State/Trait Anxiety Inventory (trait

section) with the Marlow Crown Sociable Desirability Scale. Descriptive and non-parametric tests for correlation were used to analyse the data, p=<0.05.

Results: Of the 21 people recruited, 16 (76.2%) had CSI scores ≥40 in association with 1) an abnormally high prevalence of extreme scores of a) high trait Sensory Sensitive, Sensation Avoiding and Low Registration sensory profiles and b) low trait Sensation Seeking profile, 2) high trait personality types and 3) minimal low trait anxiety. Moderate correlations were identified between trait sensory profiles and 1) CS pain (Sensory Sensitive R= 0.57, p<0.01, CI= 0.07 to 0.88, p<0.01, Sensation Seeking R= -0.47, p<.05, CI= -0.72 to -0.02) and 2) trait anxiety (Sensory sensitive: R=0.65, p<.01, CI= 0.27 to 0.91) and Low Registration (R=.49, p<.05, CI= 0.03 to 0.84). The CSI scores moderately correlated with trait anxiety (R= 0.63, p<0.01, CI= 0.22 to 0.86).

Conclusion: These results provide concept plausibility that the extent of CS pain in people with NSCLBP might be associated with pre-morbid trait personality types and abnormal trait sensory processing profiles. A larger study to confirm the findings is warranted.

Key words: Central sensitisation pain; Chronic low back pain; Sensory processing profiles; Trait Anxiety

Introduction

Chronic low back pain is a significant health problem as well as an economic burden worldwide (Manchikanti et al., 2009). A proportion of people with non-specific chronic low back pain experience pain arising from a predominantly central sensitisation pain mechanism (Nijs et al., 2015) and this is associated with sensory processing alterations (Wand et al., 2011). In recent years, there has been considerable growth in the

understanding of pain mechanisms, now broadly classified into three groups: nociceptive pain, neuropathic pain and central sensitisation pain (Nijs et al., 2014). Symptoms resulting from central sensitisation (CS) tend to be disproportional to the extent of tissue pathology (Nijs et al., 2010; Smart et al., 2012), and may even be experienced in the absence of tissue pathology (Moseley & Butler, 2015). Pain associated with central sensitisation results from an augmentation of responsiveness of central neurons to input from unimodal and polymodal receptors (Mayer et al., 2012), characterised by generalised hypersensitivity of the somatosensory system (Nijs et al., 2010). Central sensitisation involves facilitation of peripheral stimulus processing and alterations in descending inhibitory control of nociceptive input to the brain (Woolf, 2011).

Central sensitisation is considered to be a dominant mechanism common to many chronic musculoskeletal pain conditions including a proportion of people with non-specific chronic low back pain (NSCLBP). Central sensitisation is regarded as the pain mechanism most difficult to treat (Latremoliere & Woolf, 2009), which may be partly due to the paucity of evidence underpinning its aetiology.

In addition to sensitisation of the central nervous system, people with predominant CS pain exhibit cortical disinhibition and neurological disruption resulting in sensory processing alterations (Moseley & Flor, 2012). Patients with NSCLBP exhibit these sensory processing alterations (Wand et al., 2010; Wand et al., 2013) and differences in the brain's neural activation networks compared with recovered back pain patients (Erpelding et al., 2012); (Mansour et al., 2013). It could be assumed that sensory processing alterations such as

sensory hypersensitivity develop simultaneously with CS pain; an alternative hypothesis, however, is that these alterations were present pre-morbidly.

A recent review found that pre-morbid sensory sensitivity and psychological factors may have predisposed individuals to CS in some chronic musculoskeletal pain populations (Clark et al. 2017). The hypothesis underpinning this study, therefore is that pre-morbid sensory sensitivity and psychological factors may be related to individual trait characteristics, such as trait sensory sensitivity and trait anxiety.

Trait sensory sensitivity forms a component of individual trait sensory profiles (Brown et al., 2001); (Engel-Yeger & Dunn, 2011c). Trait sensory profiles are a measurement of individual neural thresholds and behavioural responses to sensory stimulation and can be used to identify individual differences in sensory processing function (Dunn, 1997); (Brown et al., 2001).

Sensory processing is the registering, modulating and organising of sensory information from the environment (Brown et al., 2001) and creating an appropriate response output (Davies et al., 2009). Sensory input is received from cutaneous tactile receptors, muscle spindles and golgi tendon organs, mechanoreceptors, the vestibular apparatus, the auditory, olfactory, gustatory and visual systems (Davies et al., 2009) and cerebral efferent connections including connections from emotional and psychological networks (Aron et al., 2012). Key components of sensory processing are the neural thresholds for sensory reception (sensory sensitivity) and the behavioural response to sensory stimulation, which vary between individuals based on trait sensory profile characteristics (Dunn, 1997).

The range of neural thresholds for receiving sensory information sits on a continuum from high threshold [hypo-sensitive] to low threshold [hyper-sensitive],(Dunn & Brown, 1997; Dunn, 2001). Cross sectional studies of healthy (non-pain) populations show a normal distribution curve of sensory sensitivity from high to low neural thresholds (Brown et al., 2001). The behavioural response to received sensory stimuli, dependant on neural thresholds, is on a continuum ranging between passive and active (Brown et al., 2001). The response continuum is associated with how an individual adapts to sensory input, either actively or passively, by increasing or decreasing input as necessary, in order to function comfortably.

According to Brown et al., (2001) some people have high sensory thresholds as a trait characteristic, in association with sensory hypo-sensitivity. Similarly, sensory hypo-sensitivity to some sensory stimuli has been found in some people with chronic limb pain (Moseley et al., 2008) and non-specific chronic low back pain (Moseley et al., 2008; Wand et al., 2010). It is possible, therefore, that some of the sensory processing alterations observed in these chronic pain populations may involve trait sensory hypo-sensitivity. People with trait sensory hypo-sensitivity may not score as highly on the Central Sensitisation Inventory (CSI, score<40) yet still exhibit a predominantly non-nociceptive, non-neuropathic pain mechanism, inferring a central sensitisation pain mechanism and this was taken into consideration in the development of   the methods for this study.

High trait anxiety is associated with high trait sensory sensitivity (Engel-Yeger & Dunn, 2011c), and central sensitisation, including those with NSCLBP (Franklin et al., 2014). A common link between anxiety and sensory sensitivity is the low threshold of sensitivity to stimuli (Ristic & Landry, 2015). Those with anxiety and high sensory sensitivity exhibit physiological differences involving impaired inhibitory control mechanisms and impaired

cognitive function (Ansari & Derakshan, 2011b), similar to people with central sensitisation (Latremoliere & Woolf, 2009; Nijs et al., 2010; Berryman et al., 2013). Therefore, identification of trait anxiety and sensory profile characteristics might help understand the development of central sensitisation in patients with NSCLBP and in turn help clinicians sub-classify patients who are at risk of developing central sensitisation.

The aims of this pilot observational study were to test concept plausibility in a NSCLBP population with central sensitisation by investigating:

1) the range of Central Sensitisation Inventory scores, to determine the extent of symptoms of central sensitisation, across the group,

2) whether there are identifiable patient characteristics of trait anxiety and trait sensory profile differences; and

3) whether potential relationships exist between trait anxiety, trait sensory profiles and the extent of symptoms of central sensitisation.

Methods

This research is presented according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Vandenbroucke et al., 2007).

Design

A cross sectional observational study design was implemented (Robson & Colin, 2002). Ethical approval was obtained from Manchester Metropolitan University, UK (ref:1205) and permission was given from the Northern Y Ethics Committee, New Zealand.

Sample

A sample size of n=20, approximately 10% of the predicted sample required for the full study was calculated (Thabane 2004). Sample size was calculated based on 9 variables (4

sensory profile scores, 4 personality types and the CSI score variables) and 20 participants

per variable, as recommended for a correlation study (Field, 2009).

Patients with NSCLBP were recruited from physiotherapy clinics in New Zealand and the

United Kingdom between July 2014 and March 2015.

Inclusion and exclusion criteria (Table 8) were derived from the literature (Nijs et al., 2014)

and were chosen to select people with NSCLBP exhibiting a predominantly central

sensitisation pain mechanism. Allowing for the possibility that some people with a

predominantly non-nociceptive, non-neuropathic pain mechanism may have a trait sensory

hypo-sensitivity profile (Brown et al., 2001), the Central Sensitisation Inventory was not

used as a screening tool for inclusion. Instead, the range of CSI scores across the group was

investigated as part of the study.

Table 8: Inclusion and exclusion criteria given to all healthcare providers involved in participant recruitment.

Inclusion Criteria
Aged 18-64 years inclusive.   Reported low back pain most days for more than 6 months.   No clear diagnosis as to the specific source of the pain (such as malignancy/ infection/ inflammatory disease like ankylosing spondylitis etc.) and where anti-inflammatory (NSAID) medication had been used these had not been found to be significantly helpful for the pain.   Pain disproportionate to the current extent of the injury or pathology (i.e. moderate to high pain intensity, unexpected after the normal tissue healing time-frame.)   Pain in variable areas around the back +/- other body parts and that was not always in the same place, with a pain distribution that was not neuro-anatomically logical.
Exclusion criteria
Pain that is predominantly neuropathic in origin (determined using the S-LANSS neuropathic pain score)

> Pain that is predominantly nociceptive in origin (clear aggravating / easing factors and responds well to NSAIDs if used)
>
> Pregnancy and/or having given birth in the past 12 months
>
> Spinal surgery within the last 12 months
>
> Any rheumatic disease, neurological disease, cardiac, respiratory, metabolic or endocrine disorder

All participants satisfying the inclusion criteria received a participant information sheet from their clinician. Consent was obtained at a subsequent visit by the same clinician. Participants were asked to complete four questionnaires. The time required to complete the questionnaires was approximately 15 minutes and participants were given the option of completing them at home or at the clinic. For omitted or ambiguously answered questions participants were contacted by telephone by a third-party administrator to clarify responses.

Outcome Measures

The Central Sensitisation Inventory (CSI)

The CSI (Mayer et al., 2012; Neblett et al., 2013) measures the extent to which the person's symptoms are likely to be attributable to central sensitisation. This is a two-part questionnaire: Part A has 25 symptom related items scored on a Likert scale (0-4, score range 0-100) and Part B lists 10 conditions known to be related to central sensitivity syndromes (scored 0-1, range 0-10). The CSI has been shown to be valid and reliable with a test-retest reliability of 0.82 and Chronbach's Alpha of 0.88 (Mayer et al., 2012), sensitivity of 81% and specificity of 75% (Neblett et al., 2013). Neblett categorised the CSI scores into clinically relevant symptom severity attributable to central sensitisation, whereby 0-20 is

sub-clinical, 21-40 is mild, 41-50 is moderate, 51-60 is severe and 61-100 is extreme (Neblett et al., 2016).

The Adolescent / Adult Sensory Profile questionnaire (AASP)

The AASP measures a component of sensory processing function (Brown & Dunn, 2002) and identifies trait sensory sensitivity profiles. For healthy function, an individual requires an optimum level of sensory stimuli and feedback, without which function might be compromised (Dunn, 1997). Insufficient or excessive sensory stimuli require behavioural adaptation in order to maintain optimum sensory stimulation and feedback.

The AASP assesses the sensory profiles of adolescents and adults based on Dunn's original model of sensory processing (Dunn, 1997). The AASP combines the sensory thresholds with behavioural response continua and provides a summary score for each sensory profile.

These sensory profiles are: Sensory Sensitive (SSv), Sensation Avoiding (SAv), Low Registration (LR) and Sensation Seeking (SSk), summarised in Table 9. The AASP is a 60-item questionnaire and uses a Likert scale of responses ranging from: 'much less than most', 'less than most', 'similar to most', 'more than most' and 'much more than most- people', scored 1 to 5 respectively. Questions related to each of the four sensory profiles are sorted into the profile columns and the sum total for each profile is calculated accordingly. Normal score values for each profile have been established in a healthy population (N= 495; Brown and Dunn, 2002), and acceptable reliability was found for each sensory profile with coefficient alphas of: SSv = 0.81; Sav = 0.66; LR = 0.82 and SSk = 0.79 (Brown and Dunn, 2002). The coefficient alpha in 615 adult patients ranged from 0.66-0.82, consisting of psychology and occupational therapy students from a large mid-west university in the United States. Factor

analysis for all four profiles is supportive of Dunn's original sensory profile model (Dunn, 1997).

Table 9: Sensory Profiles identified by the Adult / Adolescent Sensory Profile Questionnaire (Adapted from Brown and Dunn, 2002).

	Behavioural response	
Stimulus Threshold	Active Behavioural Response	Passive Behavioural Response
High	Sensory Seeker (SSk)	Low Registration (LR)
Low	Sensation Avoiding (SAv)	Sensory Sensitive (SSv)

The State-Trait Anxiety Inventory (STAI-T)

The STAI-T (Spielberger, 1983), measures a patient's trait anxiety. Trait anxiety is an enduring, relatively stable character trait and is an indicator of the likelihood of the patient responding to perceived threats with (transient) state anxiety. The STAI-T is a 20-item questionnaire, scored 0-80 using a 1-4 point Likert scale with answers ranging from "almost never" to "almost always". Internal consistency coefficients range from 0.86 to 0.95 and test-retest reliability coefficients range from 0.65 to 0.75 over a 2-month interval (Spielberger 1983).

The Marlowe Crowne Social Desirability Scale (MCSDS)

 The MCSDS (Crowne & Marlowe, 1960) measures defensiveness / social desirability and may be used in conjunction with the STAI-T to identify a coping style or personality type. It is

useful when using self-report measures for data collection as it identifies people who are more likely to under-report socially undesirable information about themselves (Myers, 2010; Reynolds, 1982). High scorers in defensiveness might under-report levels of anxiety or sensory sensitivity and so the MCSDS was included in the current study.

The Short Form version, (Strahan and Gerbasi, 1972), is a validated 10-item questionnaire answered by "true" or "false", scored 0-10. An internal consistency alpha coefficient has been reported as 0.66 (Reynolds, 1982) and a correlation coefficient of r = 0.90 (p < 0.001) was reported between the 10 item MCSDS and the original 33 item MCSDS (Crowne & Marlowe, 1960). The Short form 10 item MCSDS was therefore chosen and deemed more time efficient for the participants' usage.

The four personality types identified using the MCSDS combined with the STAI-T (Weinberger, 1979; Eysenck, 1997) were: High Anxious (HA), Defensive High Anxious (DHA), Low Anxious (LA), and Repressor (Rep), summarised in table 10.

Table 10: Personality types identified by combining the Trait section of the State-Trait Anxiety Inventory, (Spielberger, 1983) *and the Marlowe-Crowne Social Desirability Scale (Crowne and Marlowe, 1960)*

| | | Social Desirability / Defensiveness | |
		High	Low
Trait Anxiety	High	Defensive High Anxious (DHA)	High Anxious (HA)
	Low	Repressor (Rep)	Low Anxious (LA)

All data were analysed using IBM SPSS Statistics version 22 (Corp., 2013). Means (SD) were used to describe the range of CSI scores in NSCLBP patients. To determine whether there are identifiable patient characteristics of trait anxiety and trait sensory profile differences in the sample, the prevalence of participants with extreme sensory profile scores was investigated in different sub-groups: High and low CSI scorers and the four personality types. The primary outcome measure chosen was the sensory profile scores, trait sensory hypersensitivity being the key outcome of interest.

As the data were ordinal, Spearman's correlation coefficient test was used to determine relationships between CSI scores, patient characteristics of trait anxiety and trait sensory profile scores. Significance was set at 0.05.

Results

Demographics

Of the 22 patients invited to participate the total number included in the study was 21 (n=16 females, n=5 males). One patient did not complete the questionnaires and could not be contacted. Mean age was 43 years (range 20-64). No one refused to participate, as the questionnaires were part of usual care in the physiotherapy clinics.

Range of Scores on the Central Sensitisation Inventory

The CSI scores were normally distributed (Shapiro Wilk test p=0.35) and ranged from 3 to 92 across the group. N=16 out of 21 (76%) participants scored 40 or more, which is the cut-off, indicating that their symptoms were attributable to central sensitisation (Neblett et al.,

2013; Fig. 8). In this NSCLBP population, the scores range from sub-clinical to severe in

accordance with the clinically relevant severity levels stipulated by Neblett et al., (2016).
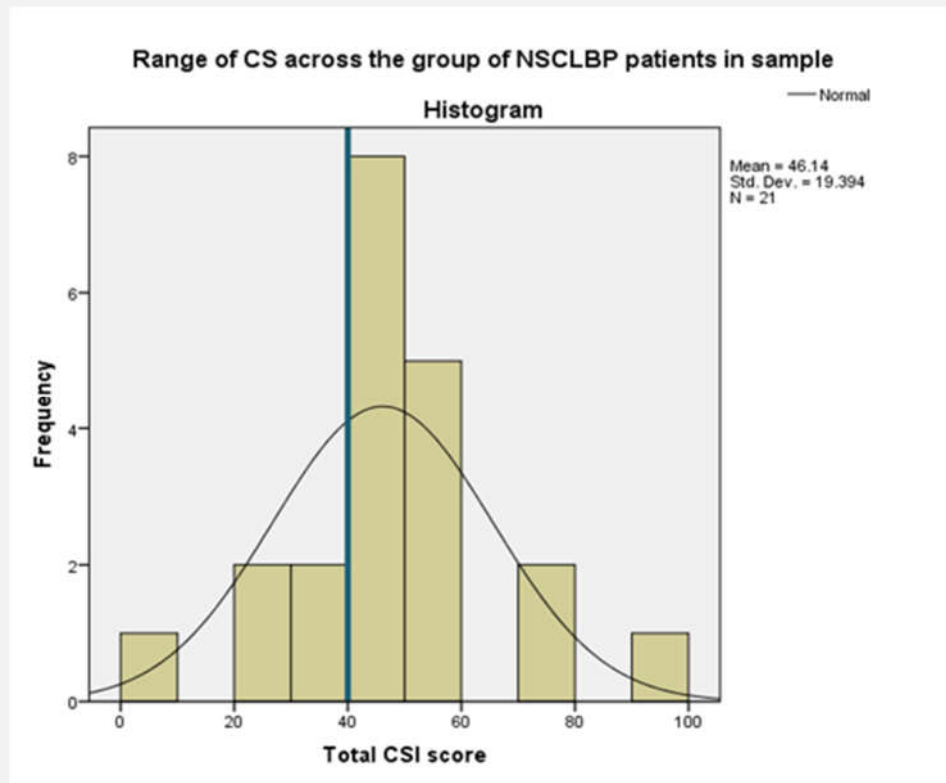
Figure 8: Range of central sensitisation inventory scores of NSCLP patients (>=40 shows greater likelihood that symptoms are attributable to central sensitisation).

Identification of differences in trait sensory profiles and anxiety characteristics

The prevalence of extreme (± 1SD) sensory hypersensitivity profile scores (SAv and SSv) was

calculated for both the high (≥40) CSI scoring, and the low (<40) CSI scoring groups. The

prevalence normal (within 1 SD) and extreme (± 1SD) scores for each sensory profile in the

healthy population (Brown & Dunn, 2002), was used as a reference to calculate the extreme

scores in the sample population (Table 4). The results are as follows:

1) Trait sensory hyper-sensitivity profiles in the high CSI scoring group.

The highly sensitised group (n=16 [76%] with CSI scores >=40) showed a higher prevalence of extreme scores for high trait sensory hyper-sensitivity profiles, SAv = 43% (Table 11) and SSv = 62% (Table 12). This is higher than 16% reported in the non-sensitised healthy population (Brown and Dunn, 2002). We interpreted this as meaning that participants with high CSI scores have high trait sensory hyper-sensitivity and either actively avoid excess stimulation (SAv) or passively receive excess stimulation (SSv) more or much more than most. One participant scored lower in SAv (Table 10) meaning they were trait sensory hyper-sensitive, but actively avoided excess stimulation less than others.

2) Sensory hypo-sensitivity in the high CSI scoring group.

The highly sensitised group (n=16 [76%] with CSI scores ≥40;) showed a higher prevalence of extreme scores for trait sensory hypo-sensitivity profiles, (-1 SD) SSk = 31% (Table 13), and (+1 SD) LR = 31% (Table 14). We interpreted this as meaning that those with high CSI scores have high trait sensory hypo-sensitivity and either actively seek stimulation (SSk) less, or much less than most, or respond passively to being under-stimulated more, or much more, than most (LR).

3) Sensory hyper-sensitivity in the low CSI scoring group.

Out of participants with a CSI score of <40 (n=5 [24%]), no-one had an extreme SAv score (Table 11). One participant had a SSv score of -1 ±SD (Table 12). All other participants scored within normal range of trait sensory hyper-sensitivity, reflecting the healthy population.

4) Sensory hypo-sensitivity in the low CSI scoring group.

Out of participants with a CSI score of <40 (n=5, [24%]), 40% had high extreme scores (+1 SD) in SSk (Table 13) and 60% had low extreme scores (-1SD) in LR (Table 14). Both of which are considerably greater than the 16% prevalence found in a healthy non-sensitised population (Brown and Dunn, 2002). We interpreted this as meaning that the low CSI scoring group shows trait sensory hypo-sensitivity, and they either actively seek sensation to compensate more, or much more, than most (SSk), and they miss some sensory information but less than most (LR; Brown and Dunn, 2002).

Table 11: Prevalence of Extreme Sensation Avoiding scores in high and low CSI scoring groups.

		Sensation Avoiding (SAv)		
		-1SD	68%	+1SD
CSI >=40 N=16	Range	44-45	45-53	54-55
	n=	1	8	7
	Prevalence (%)	6	50	43
CSI <40 N=5	Range Mean 32 +-SD 34	28	28-36	36
	n=	0	5	0
	Prevalence (%)	0	100	0

CSI = Central Sensitisation Inventory. SD = Standard Deviation

Table 12: Prevalence of Extreme Sensory Sensitive scores in the high and low CSI scoring groups.

		Sensory Sensitive (SSv)		
		-1SD	68%	+1SD
CSI >=40 N=16	Range (Mean 42 +-SD7)	32-34	35-49	50-53
	n=	0	6	10
	Prevalence (%)	0	38	62
CSI<40 N=5	Range (mean 30+-SD5)	23-24	25-35	35
	n=	1	4	0
	Prevalence (%)	20	80	0

CSI = Central Sensitisation Inventory. SD = Standard Deviation

Table 13: Prevalence of extreme Sensation Seeking scores in high and low CSI scoring groups.

| | | Sensation Seeking (SSk) | | |
		-1SD	68%	+1SD
CSI >=40 N=16	Range (mean 46 +- SD8)	25-37	38-52	53-56
	n=	5	11	0
	Prevalence (%)	31	69	0
CSI<40 N=5	Range (mean 56 +- SD8)	47	48-64	56-68
	N=	0	3	2
	Prevalence (%)	0	60	40

CSI = Central Sensitisation Inventory. SD = Standard Deviation

Table 14: Prevalence of extreme Low Registration scores in high and low CSI scoring groups.

| | | Low Registration (LR) | | |
		-1SD	68%	+1SD
CSI>=40 N=16	Range (mean 32 +- SD7)	18-24	25-39	40-47
	n=	2	9	5
	Prevalence (%)	13	56	31
CSI<40 N=5	Range (mean 24 +- SD6)	18	18-30	31-34
	n=	3	2	0
	Prevalence (%)	60	40	0

CSI = Central Sensitisation Inventory. SD = Standard Deviation

Sensory Profiles in people with different personality types.

Using the same strategy for calculating prevalence using the known prevalence of

individuals with normal and extreme scores for each sensory profile in the healthy

population (Brown and Dunn, 2002), the participants were grouped according to their

personality type. Results show that:

1) there were no participants with the trait personality type of Low Anxiety;

2) there was a greater prevalence of higher extreme SAv scores in those with a Defensive High Anxious (29%), High Anxious (75%) and Repressor (20%) personality type, compared with those in the healthy population (16%) (Table 15);

3) there was a greater prevalence of higher extreme Sensory Sensitivity scores in those with a Defensive High Anxious (57%), High Anxious (75%) and Repressor (30%) personality type, compared with those in the healthy population (16%) (Table 16);

4) there was a greater prevalence of lower extreme Sensation Seeking scores in those with a Defensive High Anxious (29%) and High Anxious (25%) personality type compared with those in the healthy population (16%), and the Repressor group showed a comparable distribution (20% in the higher and lower extremes; Table 17);

5) there was a higher prevalence of extreme Low Registration scores in those with a High Anxious (75%) personality type, and the Repressor group show a greater prevalence of lower extreme scores for LR (20%), compared with those in the healthy population (16%) (Table 18).

Table 15: Prevalence of extreme Sensation Avoiding scores in each personality type group.

| | | Sensation Avoiding (SAv) | | |
		-1SD	*68%*	*+1SD*
DHA (STAI >=39, MC>5) *N=7*	*Range*	*26-28*	*29-46*	*47-53*
	n=	*1*	*4*	*2*
	Prevalence (%)	*14*	*57*	*29*
HA (STAI >=39, MC<=5) *N=4*	*Range*	*30-33*	*34-55*	*55-55*
	n=	*0*	*1*	*3*
	Prevalence (%)	*0*	*25*	*75%*
Rep (STAI <39, MC>5) *N=10*	*Range*	*28*	*28-44*	*45-52*
	n=	*0*	*8*	*2*
	Prevalence (%)	*0*	*80*	*20*

DHA=Defensive High Anxious; HA=High Anxious; Rep=Repressor.

Table 16: Prevalence of extreme Sensory Sensitive scores in each personality type group.

		Sensory Sensitive (SSv)		
		-1SD	*68%*	*+1SD*
DHA (STAI >=39, MC>5) N=7	Range	32	33-49	49-52
	n=	0	3	4
	Prevalence (%)	0	43	57
HA (STAI >=39, MC<=5) N=4	Range	41	41-51	52-53
	n=	0	1	3
	Prevalence (%)	0	25	75
Rep (STAI <39, MC>5) N=10	Range	23-27	28-42	43-44
	n=	1	6	3
	Prevalence (%)	10	60	30

DHA=Defensive High Anxious; HA=High Anxious; Rep=Repressor.

Table 17: Prevalence of extreme sensation Seeking scores in each personality type group.

		Sensation Seeking (SSk)		
		-1SD	*68%*	*+1SD*
DHA (STAI >=39, MC>5) N=7	Range	42	43-51	51-53
	n=	2	5	0
	Prevalence (%)	29	71	0
HA (STAI >=39, MC<=5) N=4	Range	25-31	32-58	53
	N=	1	3	0
	Prevalence (%)	25	75	0
Rep (STAI <39, MC>5) N=10	Range	34-40	41-61	62-68
	N=	2	6	2
	Prevalence (%)	20	60	20

DHA=Defensive High Anxious; HA=High Anxious; Rep=Repressor

Table 18: Prevalence of extreme Low Registration scores in each personality type group.

		Low Registration (LR)		
		-1SD	*68%*	*+1SD*
DHA (STAI >=39, MC>5) N=7	Range	18-23	24-38	38
	n=	1	5	1
	Prevalence (%)	14	72	14
HA (STAI >=39, MC<=5) N=4	Range	32-33	33-45	46-47
	n=	0	1	3
	Prevalence (%)	0	25	75
Rep (STAI <39, MC>5) N=10	Range	18-19	20-34	35-40
	n=	4	5	1
	Prevalence (%)	40	50	10

DHA=Defensive High Anxious; HA=High Anxious; Rep=Repressor.

The concept that trait hyper-sensitivity, sensory profiles might correlate with high trait personality types and high levels of central sensitisation was explored. Results of the correlation studies showed that trait anxiety was found to moderately correlate with trait sensory profiles: A moderate positive correlation was found between trait anxiety and sensory profiles 1) SSv (R=0.65, p<.01, CI= 0.27 to 0.91) and 2) LR (R=.49, p<.05, CI= 0.03 to 0.84). A moderate negative correlation was found between trait anxiety and the sensory profile SSk (R= -0.47, p<.05, CI= -0.73 to -0.02). No correlation was found between trait anxiety and the SA profile.

A moderate positive correlation was found between the CSI and the sensory profile SSv (R= 0.57, p<0.01, CI= 0.07 to 0.88). A moderate negative correlation was found between the CSI and the sensory profile SSk (R= -0.53 p<.05, CI= -0.76 to -0.21). No correlation was found between the CSI and the sensory profiles LR or the SAv. The CSI scores were also found to moderately correlate with trait anxiety (STAI-T scores; R= 0.627, p<0.01, CI= 0.223 to 0.861); (Table 19).

Table 19: Correlations between Sensory Profiles and 1) CSI and 2) Trait Anxiety (STAI-T) scores.

	Sensory Sensitive	*Sensation Avoiding*	*Sensation Seeking*	*Low Registration*
CSI Scores	*R= 0.57, p<0.01, (CI= 0.07 to 0.88)*	*None*	*R= -0.53 p<.05, (CI= -0.76 to -0.21)*	*None*
STAI-T Scores	*R=0.65, p<.01, (CI= 0.27 to 0.91)*	*None*	*R= -0.47, p<.05, (CI= -0.73 to -0.02)*	*R=0.49, p<.05, (CI= 0.03 to 0.84)*

Discussion

The aims of this pilot observational study were to test concept plausibility in a NSCLBP population with central sensitisation by investigating 1) the range of Central Sensitisation Inventory scores, to determine the extent of symptoms of central sensitisation, across the group, 2) whether there are identifiable patient characteristics of trait anxiety and trait sensory profile differences; and 3) whether potential relationships exist between trait anxiety, trait sensory profiles and the extent of symptoms of central sensitisation.

In order to investigate CSI scores, participants with NSCLBP were selected based on their pain mechanisms being predominantly non-neuropathic and non-nociceptive. This is in line with the current classification algorithm for identifying central sensitisation, which identifies pain most likely to be related to changes in central pain processing mechanisms, to the exclusion of primarily nociceptive and neuropathic pain (Nijs et al., 2014).

Not all the participants scored ≥40 on the CSI, suggesting that not all were highly sensitised. This raises the question as to whether there may be central sensitisation mechanisms that do not exhibit high sensitisation, or generalised hypersensitivity, whereby centrally sensitised participants score <40 on the CSI. Alternatively, it is possible that some participants were more prone to under-reporting information about themselves on the CSI, characteristic of the defensiveness in their Repressor trait personality type. A larger study might determine whether individuals who score low on the CSI, despite being recruited for their clinical presentation of central sensitisation, also exhibit extreme scores for the Repressor personality type.

Of the participants with high levels of sensitisation (CSI ≥40) there was a greater prevalence of higher extreme scores for SAv and SSv and lower extreme scores for SSk. This was also

reflected in the moderate positive correlations between the CSI scores and the SSv profile scores and moderate negative correlation between the CSI and the SSk profile scores.

On face value, one might expect increased sensory sensitivity and Sensation Avoiding and reduced sensation seeking behaviours in individuals with central sensitisation, perhaps in association with fear avoidance and in response to pain. However, trait measures propose that trait characteristics are likely to have been present pre-morbidly and therefore these findings may not be an indication of behavioural responses to pain. Moreover, a sub-group of the highly sensitised participants (CSI ≥40) showed a greater prevalence of higher extreme scores for a sensory hypo-sensitivity profile, LR, which is unexpected in a highly sensitised group. The LR sensory profile indicates trait hypo-sensitivity to some stimuli with a passive response, thereby not actively compensating for a lack of stimulation. This observation might link with the observations of other authors regarding sensory hypo-sensitivity in NSCLBP. (Wand et al., 2010; Wand et al., 2013) reported sensory hypo-sensitivity in the perception of tactile stimuli and a tendency to sensory mislocalisation in patients with NSCLBP, suggestive of possible hypo-sensitivity sensory profiles. These results may challenge the current thinking that central sensitisation always involves sensory hyper-sensitivity. Importantly, this pilot might indicate that there are discrepancies between normal trait sensory sensitivity profiles and those with NSCLBP and central sensitisation.

The prevalence of extreme sensory profile scores in the low CSI group (n=5) are similar to the healthy control group, further supporting our idea that the extreme scores are abnormal and represent a subgroup within the NSCLBP population.

Our results also show that anxiety and personality types might be related to central sensitisation. We found that participants with central sensitisation exhibited a form of high trait anxiety sub-typing (DHA; n=6; HA, n=4; Rep, n=6). Although Repressors typically score low in self-report trait anxiety, they have been shown to present with the same high state anxiety physiological changes as HA and DHA in the face of threatening stimuli (Myers, 2010). Our results suggest that Rep might undergo similar physiological changes associated with high anxiety in association with high levels of central sensitisation, physiologically linking them with HA and DHA individuals.

No participants were of a low anxious trait personality type. This is in agreement with other studies showing low trait anxiety is not associated with high sensitivity to sensory stimuli (Eysenck & Byrne, 1992; Derakshan & Eysenck, 2009; Ansari & Derakshan, 2011a). However, high anxiety and central sensitisation have in common a low threshold to various sensory stimuli, which might account for the high CSI scoring group containing all three trait personality types that demonstrate the physiological characteristics of high anxiety sensitivity.

A moderate correlation was found between trait anxiety and central sensitisation. This may have been a stronger correlation if the Repressor group were excluded from the calculation. In a larger study, it might be possible to select cases excluding the Rep group and correlate anxiety scores reported by the DHA and HA groups versus the whole group anxiety scores, and the CSI scores.

Interestingly, we found a positive correlation between LR sensory profile and trait anxiety. This was a somewhat unexpected result from a shared physiological mechanism perspective, in so much as high anxiety (Derakshan et al., 2007) and central sensitisation (Nijs et al., 2010, 2014) are both associated with high sensory sensitivity. This is in contrast to the LR sensory profile which is characterised by low sensory sensitivity. This suggests that trait sensory hyper-sensitivity may not be a key factor in linking anxiety with sensory sensitivity and central sensitisation, using a hypothesis of shared physiological mechanisms of hypersensitivity. Instead, there might be wider aspects of sensory processing involved in central sensitisation, perhaps involving sensory perception, and is yet to be understood. Individuals with LR sensory profiles might be a new group of individuals susceptible to central sensitisation but who may not be generally trait hyper-sensitive.

The eligibility criteria allowed accurate identification of participants most likely to have predominantly central sensitisation, in line with other studies (Nijs et al., 2010; Smart et al., 2012). Despite this, 76% showed clinically relevant levels of central sensitisation. Either the validity of the CSI is to be questioned, particularly in light of self-reporting by Rep personality type characteristics, or the presence of low and sub-clinical levels of central sensitisation (Neblett et al, 2017), in the absence of predominant nociceptive and neuropathic pain, must be considered. To avoid recruitment of patients with predominantly nociceptive or neuropathic pain mechanisms, a comprehensive education in clinical recognition of central sensitisation for the participating clinicians is critical.

Strengths and Limitations

The current study has demonstrated the plausibility of the concepts tested. The study methods were rigorous and reported according to STROBE guidelines (Vandenbroucke et al., 2007). They followed the current clinical recommendations for accurately identifying patients with predominantly central sensitisation, thereby limiting heterogeneity within the sample. Bias was limited through the recruitment of participants by multiple participating clinicians instead of just one principle investigator.

Recruitment was successful with n=21/22 (95%) of participants completing all questionnaires. There was 0.17% (4 out of 2,415 questions) of missing data during completion of the questionnaires. After contacting the participants, 100% of questions were completed allowing for a full data set. No information was available from participating clinicians as to how many potential participants refused to participate. The study recruited more female than male participants, which may also present as a limitation.

The small sample size, although appropriate for a pilot study design, presents as a limitation in terms of the strength of the results. However, the concept of relationships existing between sensory processing profiles, personality types and central sensitisation has been found to be satisfactorily plausible and lays the foundation for a much larger study. Although the questionnaires claim to measure trait characteristics, validation of the questionnaires longitudinally for stability, and construct validity in specific chronic pain populations would be of value. Despite this, the current study obtained cross-sectional data, which the questionnaires have been validated for. The success of the pilot study has laid the foundation for a much larger investigation into trait characteristics behind the development of central sensitisation.

If trait characteristics contribute to the risk factors that predispose to the development of central sensitisation, clinicians will be ultimately equipped to identify at-risk patients and administer appropriate management from baseline for these individuals, saving resources for clinicians, health care providers and patients alike.

Conclusion

This is the first study to investigate the concept that trait anxiety and sensory profile characteristics are related to the development of   central sensitisation in people with NSCLBP. High trait sensory hyper-sensitivity and high trait personality types are associated with central sensitisation in people with NSCLBP. This information can be assessed at baseline and may help clinicians identify those at risk of developing central sensitisation informing appropriate management and early preventative interventions. A rigorous methodology is in place to study these relationships further.

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3.4.2 Discussion

The pilot study process was successful in identifying areas for improvement for the main study. This was further assisted by constructive feedback from the journal reviewers. The following changes were concluded for the main quantitative study:

1. The pilot study recruitment experience revealed that some clinicians felt strongly that they were able to diagnose specific pathology in most chronic back pain patients. Furthermore, some were unaware of the clinical classification of CS pain. It was planned that a clear explanation of the nature of NSCLBP and CS was included for every participating health care provider in order to minimise the risk of recruiting outside of the strict inclusion criteria.

2. It was not clear whether the intake of medications may have affected the results. It was planned to record the medications taken by each participant at the time of recruitment.

3. It was decided that the use of the original article term 'anxiety sub-type' would be changed to 'personality type' for the current thesis. Personality type had initially represented a more objective, mechanistic philosophical viewpoint whereby the neuro-physiological mechanisms for trait anxiety was anticipated to be related to those of sensory sensitivity. However, on reflection after the pilot study it was considered more appropriate to use the same terminology as the original authors of the personality types (Weinberger et al., 1979) as the interpretation of the behaviours of each personality type appears to follow a more subjective philosophical view-point.

4. Numbers were too low in the pilot study to perform regression analyses. However, it was anticipated that because there were positive correlations found between sensory profiles, trait anxiety and CSI scores, that there may be some predictive relationships there also. Furthermore, because the prevalence of extreme sensory profile scores was an indication of differences between healthy populations and a NSCLBP population with CS, extreme personality types should be included in a similar way, if possible, in the analyses in the main study.

Limitations

It should be acknowledged that there are additional methodological limitations not covered in the pilot study published article (article 3). These include a lack of information in relation to the demographic profiles of participants. This lack of information meant that it was unclear as to how representative the study sample was of the general population of individuals with NSCLBP and CS. Furthermore, no demographic information was acquired regarding the patients who refused to participate so that it remains unclear what

differences there may have been between the participants and those who refused to participate.

A further limitation is in the difficulty in the way CS can be identified in participants. As yet there remains no gold standard for identification of CS. The pilot study utilised clinical recommendations as a way of identifying participants with a predominant CS pain mechanism. Other ways to identify CS which were not used in the current study are different forms of quantitative sensory testing (QST) and fMRI studies. Quantitative sensory tests are a way to test the excitability of different pain pathways and involves different modalities and techniques including pressure, temperature and electrical pain thresholds, conditioned pain modulation, temporal summation tests and imaging (Arendt-Nielsen et al., (2018). Due to logistical restrictions, none of these additional CS assessment methods were utilised in the current studies (articles 3-5). Most of the pilot study participants (85%, n = 18/21) were assessed for inclusion by the primary investigator (JC). A thorough working knowledge of CS in clinical populations meant that the clinical guidelines for assessing CS were well understood and therefore there was confidence that at least 85% of the pilot study participants did present with a predominant CS pain presentation. Furthermore, the pilot study revealed that some participants showed a hypo-sensitive sensory profile, although it was not identified as to which specific senses were hypo-sensitive. It remains unclear, therefore, as to how QST may be impacted by sensory hypo-sensitivity in some of the senses and whether QST would be associated with CS symptoms in people with sensory hypo-sensitivity profiles. To date there is no evidence to show that QST and CSI scores are related, and this may be one of the reasons as to why there remains no gold standard for measuring CS.

The acceptance letter from the Journal of Bodywork and Movement Therapies is included (appendix 3n).

3.5 Conclusion

Following the success of the pilot study and implementation of changes, the core component quantitative studies (see sections 2.3) were implemented. Chapter 4 will present the core component quantitative study protocol. This will be followed by the research articles (articles 4 and 5) written up for publication relating to the core component quantitative studies. The subsequent chapter (chapter 5) will present the qualitative methodological decisions and the research findings from the qualitative study for the supplementary component (see sections 2.3) written for publication (article 6). Appendices will include additional information as directed. The findings of the qualitative study will be integrated with the quantitative study results and discussed in the final chapter (chapter 7).

Chapter 4

What characteristics of trait sensory profiles, trait anxiety and personality types, and their relationships to the extent of CS symptoms, can be observed in people with CS pain, in a NSCLBP population?

4.1 Introduction

The previous chapter discussed the reasoning process behind the development of the mixed methods research design, and the quantitative methods for the core component which were tested in a pilot observational study. In this chapter, the core component (see section 2.3.1) of the thesis is presented which consists of two quantitative studies. Then the two quantitative study articles are presented (articles 4 and 5). Articles 4 and 5 contain the details of the methodological processes and results, which are discussed.

The following two quantitative studies aim to address the research questions put forward in the core component of the thesis (see section 2.3.1) which were to identify trait sensory profile, trait anxiety and personality type characteristics in a NSCLBP population with CS pain and to investigate the relationships between these and the extent of CS symptoms. These two studies (articles 4 and 5) have been published according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Von Elm et al.,

2007) (appendix 4a). The first of the two studies has been submitted to The Journal of Pain (appendix 4b) and is reported in article 4, entitled:

The Extent of Central Sensitisation Symptoms can be Predicted by Trait Sensory Profiles, Trait Anxiety and Extreme Personality Type in People with Non-specific Chronic Low Back Pain.

A secondary analysis was performed which compared the prevalence of 1) extreme scores in each sensory profile and 2) non-extreme and extreme personality types, between the low- and high-CSI scoring subgroups (CSI: central sensitisation inventory). This study has been submitted to the Clinical Journal of Pain (appendix 4c) and is reported in article 5, entitled:

Prevalence of Extreme Trait Sensory Profiles and Personality types in Non-specific Chronic Low Back Pain with Predominant Central Sensitization: Secondary analysis of an international study.

Some methodological issues relating these two studies will be discussed after the presentation of the two articles (articles 4 and 5). Chapter will 5 will then present the supplementary (qualitative study) component (see section 2.3.1) of the current mixed methods thesis and the combined results and findings will be discussed in chapter 6. The 'road map' below may help orientate the reader and indicates the position of the core component quantitative studies in the thesis (figure 9).
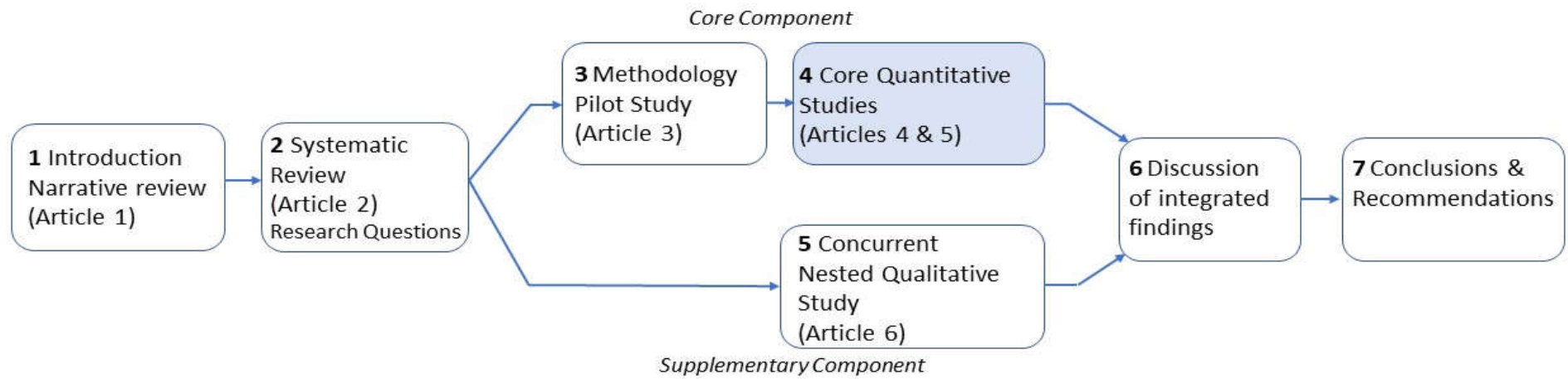
Figure 9: Roadmap through the current thesis: core component quantitative studies.

Here, the first of the two core component quantitative studies is presented.

4.2 Article 4: The Extent of Central Sensitisation Symptoms can be Predicted by Trait Sensory Profiles, Trait Anxiety and Extreme Personality Type in People with Non-specific Chronic Low Back Pain.

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Background and Aims: People with non-specific chronic low back pain (NSCLBP) and central sensitisation (CS) can exhibit sensitivity-related trait characteristics which may play a role in the development of CS. The aims of this study were to investigate 1) relationships between four trait sensory profiles, trait anxiety and CS symptoms, and 2) the predictive capacity of the sensory profiles, trait anxiety and personality types on CS symptoms, in people with NSCLBP and CS.

Methods: Cross sectional observational study; adults (N = 165, n = 39 male; mean age = 45 +-12 SD) from physiotherapy outpatient clinics in New Zealand, Ireland and England.

Inclusion: NSCLBP, aged 18 to 64, predominant CS pain, without specific pathology.

Outcome measures: 1) Central Sensitisation Inventory (CSI), 2) Adolescent/Adult Sensory

Profile, 3) State/Trait Anxiety Inventory, 4) Marlowe Crowne Social Desirability Scale. Parametric and non-parametric correlation statistics and regression analyses were used.

Results: Positive correlations were found between CSI scores and Sensory Sensitive (r = 0.63; CI = 0.53 – 0.71), Sensation Avoiding (r = 0.48; CI = 0.40 – 0.59), Low Registration (r = 0.54; CI = 0.42 – 0.64) profiles and trait anxiety (r = 0.46; CI = 0.31 – 0.60).

CSI score increases could be predicted by: Sensory Sensitive, Low Registration and trait anxiety scores (F (3, 55.19), p < 0.001 with R^2 = 0.507) and extreme defensive high anxious personality type (F (3, 2.82), p < 0.001 with R^2 = 0.14).

Conclusion: Trait sensory profiles and anxiety characteristics may play a role in the development of CS in people with NSCLBP, warranting further investigation.

Introduction

Central Sensitisation as a predominant pain mechanism is found in many musculoskeletal pain conditions (Arendt-Nielsen et al., 2018; Clauw, 2015; Yunus, 2008). Central sensitisation (CS) is defined as a dysregulation of the central nervous system causing neuronal hyper-excitability, characterized by generalized hypersensitivity of the somatosensory system to both noxious and non-noxious stimuli (Mayer et al., 2012; Neblett et al., 2013; Nijs et al., 2010). A musculoskeletal pain population commonly subject to CS pain is the non-specific chronic low back pain population (NSCLBP),(Roussel, 2013, Clauw, 2015) NSCLBP has enormous impact on both the society (Apkarian et al., 2012) and the individual. For this reason, a NSCLBP population with predominantly CS pain was targeted for this study.

To date there is limited evidence to identify the factors and mechanisms that contribute towards the development of CS in musculoskeletal pain. People with CS pain (Nijs et al., 2010; Wolfe et al., 2010), high trait anxious individuals (Ansari & Derakshan, 2011b; Eysenck & Byrne, 1992) and people with high trait sensory sensitivity (Ansari & Derakshan, 2011b; Brown et al., 2001) all experience a heightened sensitivity to sensory stimuli in the form of physiological arousal. This may be due to shared physiological mechanisms, involving low neurological thresholds to sensory stimuli. Sensory stimulation can be excessive in people with low neurological thresholds, or insufficient in people with high neurological thresholds for sensory stimulation, and the resulting discomfort can be modulated by an adaptive behavioural response (Brown et al., 2001). The behavioural responses described by Brown et al., (2001) can be active to restore comfort, or passive in which discomfort continues. Furthermore, sensory discomfort may lead to physiological arousal as a response to stressors (Gomez et al., 2017). People with high trait anxiety are prone to have heightened sensitivity to stressors and respond with physiological arousal (Spielberger, 1983; Ansari & Derakshan, 2011b). An individual's personality type can determine the way in which they respond to stressors and the associated physiological arousal.

Weinberger et al. (1979) proposed four personality types that will respond to stressors differently. These four personality types (Weinberger et al., 1979) are determined by levels of trait anxiety and defensiveness: High Anxious (high anxiety, low defensiveness), Defensive High Anxious (high anxiety, high defensiveness), Low Anxious (low anxiety, low defensiveness), and Repressor (low anxiety, high defensiveness). Eysenck (Eysenck, 1997) proposed that these individuals possess cognitive biases which could influence their perception of, and response to, physiological arousal by attending to or from, and interpreting for or against, threat. Physiological arousal to stressors may relate to

heightened sensitivity to bodily sensations including pain. Therefore, trait characteristics involving sensory sensitivities and associated behavioural responses were anticipated to relate to CS.

The objectives of this study were to investigate 1) the relationships between the four trait sensory profiles, the extent of CS symptoms and trait anxiety, and 2) the ability of the trait sensory profiles, trait anxiety scores and personality types to predict the extent of CS symptoms, across a group of people with predominantly CS pain in a NSCLBP population.

Methods

This study is presented according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Von Elm et al., 2007).

Design

An international cross-sectional observational study design (Robson & Colin, 2002) across a group of people with NSCLBP and CS was used in 3 countries and 2 continents. Ethical approval (ref:1205) was given by Manchester Metropolitan University, UK, the Research and Development departments of the participating hospitals (IRAS REC no.:15/NW/0378) in England and Ireland and permission was obtained from the Northern Y Ethics Committee, New Zealand.

Sample

The required sample size was determined based on a mean sample size calculated from three suggested methods: 1) For a regression analysis, with a power of 80% and alpha (α) set at 0.05, a value of $R^2 \geq 0.23$ can be detected with n = 50 participants (Thabane, 2004), where n = 50 must make up the smallest variable, which was anticipated to be around 26% (Franklin, Holmes, Smith, & Fowler, 2016) (n = 192); 2) a minimum of 15 to 20 participants per variable is recommended for regression analyses (Thabane, 2004) and 10 to 15

participants per variable for correlation analysis (Field, 2009) with 9 variables, (n = 180); 3) For multiple correlation n > 50 + $m8$, where m is the number of variables, for a moderate effect size (Thabane, 2004) (minimum n = 122). Using these 3 suggested sample sizes, a mean sample size was derived: n = 165. A post-hoc power analysis confirmed that the sample size in the current study was sufficient for meaningful results (13 per variable), (Rigby, 1998).

Recruitment

People from clinical populations with non-specific chronic low back pain (NSCLBP) were recruited. Recruitment was dependent on meeting the strict inclusion criteria for primarily CS pain, and to the exclusion of neuropathic and nociceptive primary pain presentations (Smart et al., 2012). The inclusion and exclusion criteria are listed in Table 20.

Recruitment took place from physiotherapy outpatient and pain clinics in the United Kingdom, New Zealand and Ireland between July 2015 and March 2017.

Table 20: Inclusion and exclusion criteria given to all healthcare providers involved in participant recruitment.

Inclusion Criteria
Aged 18-64 years inclusive
Reported low back pain most days for more than 6 months
No clear diagnosis as to the specific source of the pain (such as malignancy/ infection/ inflammatory disease like ankylosing spondylitis etc.) and where anti-inflammatory (NSAID) medication had been used these had not been found to be significantly helpful for the pain
Pain disproportionate to the current extent of the injury or pathology
Pain in variable areas around the back +/- other body parts and that was not always in the same place, with a pain distribution that was not neuro-anatomically logical
Pain which is unpredictable in its aggravation and easing factors and responses to previous treatments.

Exclusion criteria
Pain that is predominantly neuropathic in origin (determined using the S-LANSS neuropathic pain score)
Pain that is predominantly nociceptive in origin (clear aggravating / easing factors and responds well to NSAIDs if used)
Pregnancy and/or having given birth in the past 12 months
Spinal surgery within the last 12 months
Any rheumatic disease, neurological disease, cardiac, respiratory, metabolic or endocrine disorder

All participants satisfying the inclusion criteria were given a participant information sheet by their health care provider. Consent was obtained at their subsequent visit to the clinic by the same health care provider. Participants were asked to complete the study questionnaires with the option of completing them at home or at the clinic. No monetary compensation was offered to them and no incentives were made, to avoid coercion. It was made clear to all potential participants that any subsequent health care they may receive would not be affected. For ambiguously answered or omitted questions, participants were contacted where possible by a third-party administrator by telephone, thereby reducing the risk of any primary-researcher influence, to clarify responses.

Outcome Measures

Central Sensitisation Inventory (CSI)

The CSI (Mayer et al., 2012; Neblett et al., 2013) measures the extent to which an individual's symptoms are likely to be attributable to CS. Part A of this two-part questionnaire has 25 symptom related items. These items are scored on a Likert scale (0-4, score range 0-100, where 100 is maximum central sensitisation symptoms). The CSI has been shown to be valid and reliable (Mayer et al., 2012) with a test-retest reliability of 0.82

and Cronbach's alpha of 0.88, sensitivity of 81% and specificity of 75% (Neblett et al., 2013). CSI scores are classified into symptom severity levels of clinical relevance, such that 0-20 is sub-clinical, 21-40 is mild, 41-50 is moderate, 51-60 is severe and 61-100 is extreme (Neblett, 2017) Part B lists 10 central sensitivity syndromes and asks if any have been diagnosed by a doctor (yes / no; score range 0-10).

Adolescent / Adult Sensory Profile questionnaire (AASP)

The AASP (Brown & Dunn, 2002) is a 60-item questionnaire which identifies trait sensory sensitivity profiles which are based on Dunn's original model of sensory processing (Dunn, 1997). The AASP combines the neurological thresholds to sensory stimuli with adaptive behavioural response continua to sensory stimulation. A summary score is calculated for each sensory profile as follows: Sensory Sensitive (low neurological threshold, passive adaptive response), Sensation Avoiding (low threshold, active response), Low Registration (high neurological threshold, passive adaptive response) and Sensation Seeking (high threshold, active response), summarised in table 21. Items are scored 1-5 using a Likert scale based on frequency of sensory-related experiences from "almost never" to "almost always" respectively. Scores in each profile range from: 'much less than most', 'less than most', 'similar to most', 'more than most' and 'much more than most - people'. Normal values and standard deviation values have been established in a healthy population (N= 495; Brown & Dunn, 2002). Acceptable reliability was found for each sensory profile with coefficient alphas of: Sensory Sensitive = 0.81; Sensation Avoiding = 0.66; Low Registration = 0.82 and Sensation Seeking = 0.79 (Brown & Dunn, 2002). The coefficient alpha in a larger group of 615 healthy adults ranged from 0.66-0.82. Factor analysis for all four sensory profiles is supportive of Dunn's original sensory profile model (Dunn, 1997).

Table 21: Sensory Profiles identified by the Adult / Adolescent Sensory Profile Questionnaire (Adapted from Brown and Dunn, 2002).

	Behavioural response	
Stimulus Threshold	**Active**	**Passive**
High	Sensory Seeker	Low Registration
Low	Sensation Avoiding	Sensory Sensitive

The populations for which the AASP has been validated include people with sensory processing disorders such as autism spectrum disorder and specific learning difficulties. Two concurrent longitudinal validation studies to validate the use of the AASP in musculoskeletal pain populations with predominantly CS pain are being undertaken, in the Dutch and English languages. Preliminary results on the Dutch version of the AASP in people with musculoskeletal pain with CS show good internal consistency (Cronbach's alpha 0.91) and individually the Cronbach's alpha for the four sensory profiles: Low Registration 0.91; Sensation Seeking 0.90; Sensory Sensitive 0.92 and for Sensation Avoiding 0.92. Furthermore, the test-retest reliability was considered excellent for all four sensory profiles with the intra-class correlation coefficients as: Low Registration 0.83, 95% CI 0.73 to 0.89; Sensation Seeking 0.82, 95% CI 0.72 to 0.89; Sensory Sensitive 0.85, 95% CI 0.77 to 0.91 and Sensation Avoiding 0.84, 95% CI 0.75 to 0.90 (Gräper et al., *unpublished*).

State-Trait Anxiety Inventory (STAI)

The STAI (Trait section; Spielberger, 1983) measures a person's trait anxiety. Trait anxiety is an enduring, relatively stable character trait and is an indicator of the likelihood of the person responding to perceived threats with (transient) state anxiety. Trait anxiety is associated with sensitivity to sensory stimuli (Ansari & Derakshan, 2011b). The STAI (trait section) is a 20-item questionnaire, scored 0-80 (where 80 is maximum trait anxiety) using a 1- to 4-point Likert scale with answers ranging from 'not at all' to 'very much so'. Internal consistency coefficients range from 0.86 to 0.95 and test-retest reliability coefficients range from 0.65 to 0.75 over a 2-month interval.

Marlowe Crowne Social Desirability Scale (MCSDS)

The MCSDS (Crowne & Marlowe, 1960) measures defensiveness / social desirability and may be used in conjunction with the STAI-T to identify a personality type (Weinberger et al., 1979). The Short Form version (Strahan & Gerbasi, 1972) of the MCSDS was used. It is a 10-item questionnaire answered by "true" or "false" responses and scored from 0-10. An internal consistency alpha coefficient has been reported as 0.66 and a correlation coefficient of $r = 0.90$ ($p < 0.001$) (Reynolds, 1982) between the 10 item MCSDS and the original 33 item MCSDS (Crowne & Marlowe, 1960). The short form version was therefore chosen for its time-logistic advantage.

The four personality types were identified using mean STAI and MCSDS scores from normative data, similar to the use of normative data for cut-off scores by other authors (Lewis et al., 2012). The method of identification of the four personality types using scores above (high) and below (low) a cut-off score on the trait anxiety and defensiveness measures has been used previously (Jensen, 1987; Myers, 2010). For the current study the STAI mean and standard deviations were calculated from four different healthy population studies (Kendall & Sheldrick, 2000; Spielberger, 1983): STAI mean = 39, (SD = 10)., whereby < 39 = low anxious and ≥ 39 = high anxious. MCSDS normative data was drawn from a previous healthy population study (Johnson & Fendrich, 2002) which found a MCSDS mean of 5.4 (mode = 5), whereby ≤ 5 = low defensiveness and > 5 = high defensiveness. In line with the method used to identify extreme scores in the AASP, that is - scores above or below one standard deviation (SD) from the mean normative scores from healthy populations, sub-groups of extreme personality types were also identified for comparison. The identification and sub-grouping of personality types are summarised in table 22.

Table 22: Illustration of how the personality types were identified and grouped from the State-Trait Anxiety Inventory (STAI) and Marlowe Crowne Social Desirability Scale (MCSDS) scores for the whole group of study participants with non-specific low back pain and CS, and the extreme personality type sub-groups.

	High Anxious	Defensive High Anxious	Repressor	Low Anxious
STAI and MC splits across: Whole group, n = (% of whole group)	STAI ≥ 39 MC ≤ 5 43 (26%)	STAI ≥ 39 MC > 5 75 (45%)	STAI < 39 MC > 5 41 (25%)	STAI <39 MC ≤ 5 6 (4%)
Extreme sub-groups n = (% of whole group)	STAI ≥ 49 MC ≤ 4 23 (14%)	STAI ≥ 49 MC ≥ 8 19 (12%)	STAI ≥ 29 MC ≥ 8 8 (5%)	STAI ≤ 29 MC ≤ 4 0 (0%)

STAI – State Trait Anxiety Inventory score; MC – Marlowe Crowne Social Desirability Scale score

Data Management

After the completion of the questionnaires had been checked, the questionnaires were pseudo-anonymised by removing the front page with identifiable information on it. The questionnaires were each allocated a research number for identification and the front sheets filed separately with the corresponding number noted on them. Any missing data items were entered using the individual participant's mean score of the measure in question.

Analysis

All data were analysed using IBM SPSS Statistics version 22 (Corp., 2013). Descriptive statistics were used to describe the demographics of the group. Tests for normality were undertaken for each variable scale, using the Shapiro Wilks test. Normally distributed variables were analysed using Pearson's correlation statistics and non-normally distributed variables were analysed using Spearman's Rho correlation statistics. These preliminary tests are detailed in table 23. The primary outcome was the AASP sensory profile measure.

Table 23: Results of the Shapiro-Wilkes tests for normality and the correlation statistical model chosen for testing relationships between sensory profile scores and 1) CS symptoms (CSI) and 2) anxiety (STAI).

Data set	Normally distributed	Not normally distributed	Correlation statistical model used against the CSI	Correlation statistical model used against the STAI
CSI scores	P = 0.535		---------------------	Spearman's Rho
STAI scores		P = 0.02	Spearman's Rho	---------------------
Sensory sensitive	P = 0.78		Pearson's	Spearman's Rho
Sensation Avoiding		P = 0.04	Spearman's Rho	Spearman's Rho
Low Registration	P = 0.238		Pearson's	Spearman's Rho
Sensation seeking	P = 0.172		Pearson's	Spearman's Rho

CSI – Central Sensitisation Inventory; STAI = State Trait Anxiety Inventory

Results were adjusted with the removal of the repressor personality types for comparison.

A hierarchical logistic regression model was used to calculate the capacity in which the trait sensory profile scores and trait anxiety scores might predict CSI scores (indicated by the

beta (β) values). The most likely predictors were identified from the correlation analyses. After checking for multicollinearity, using a multiple correlation analysis between the identified variables where r must not be more than 0.9 (Field, 2009), a step-forward analysis was used to find out the individual contribution of each predictor. Using the hierarchical method, the CSI as the independent variable was entered at the first stage with the Sensory Sensitive profile scores, followed by the Low Registration profiles and STAI scores in the second stage, as the dependent variables. R values represent the multiple correlation coefficient between predictors and outcome and R^2 values represent the variability accounted for in the outcome by the predictors. The second regression analysis using block entry (Field, 2009) included the dependent variable CSI score and independent variables personality type. Each personality type, determined by two combined scale measures, were transformed into categorical data using dummy variables (Field, 2009). The low anxious variable was assigned as the baseline group and compared with the more prevalent personality types. 95% confidence intervals were calculated using bootstrapping method (N=1000).

Results
Demographics
Data were collected from 8 sources in New Zealand (n = 82), 3 sources in England (n = 36) and two in Ireland (n = 47). A total of 165 participants were recruited, 126 of whom were female. The age of the participants ranged from 18 to 64 (mean 45, +/-12 SD). The study group also consisted of people with extreme scores (+/- 1 SD) of one or more of the following sensory profiles: 1) high trait Sensory Sensitivity (n = 91; 55%), Sensation Avoiding (n = 72; 44%) and Low Registration (n = 60; 36%), and 2) low trait Sensation Seeking (n = 62;

38%) sensory profiles. The proportions of personality types across the whole study group were as follows: Defensive high anxious, n = 75, 45%, (extreme sub-group n = 19; 12%), high anxious n = 43, 26% (extreme sub-group n = 23; 14%) and repressor n = 41, 25% (extreme sub-group n = 8; 5%). Part B of the CSI showed a median score of 2 concurrent sensory sensitivity diagnoses (mean 2.25, SD 1.8).

Associations between Trait Sensory Sensitivity, Trait Anxiety and the Central Sensitisation Inventory Scores

Associations were observed between the primary outcome of the sensory profile scores (AASP) and 1) the CSI scores and 2) the STAI scores. A further association was observed between the CSI and the STAI scores. Figure 10 illustrates each bivariate correlation statistical analysis between a) the primary outcome of the Adolescent / Adult Sensory Profile scores and 1) the extent of CS symptoms (CSI scores) and 2) the extent of trait anxiety (STAI score); and b) between the STAI and CSI scores.
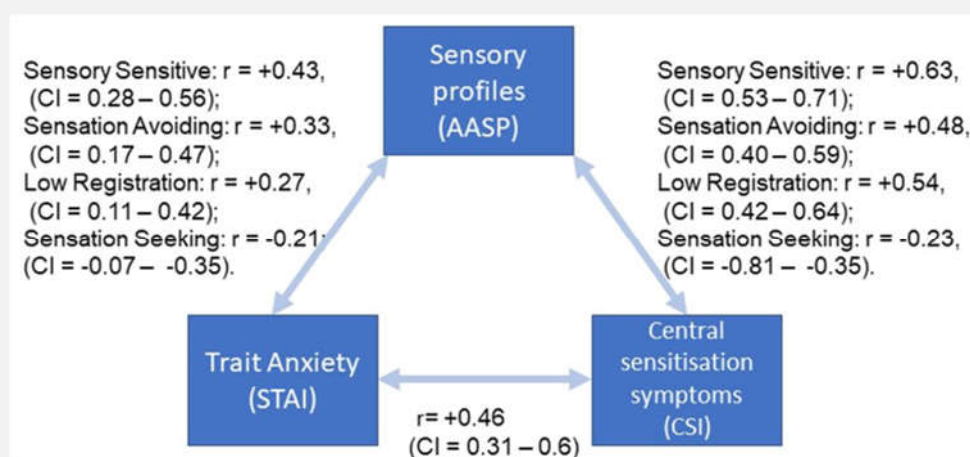
Figure 10: Diagram to illustrate the correlation statistical analyses between a) the primary outcome of the Adolescent / Adult Sensory Profile scores and 1) the extent of CS symptoms (CSI scores) and 2) the extent of trait anxiety (STAI score); and b) between the STAI and CSI scores, (p < 0.01).

AASP = Adolescent / Adult Sensory Profile quadrant scores; STAI = State-Trait Anxiety Inventory scores; CSI = Central Sensitisation Inventory scores.

Relationships between Trait Sensory Profile and Central Sensitisation Inventory Scores

Moderate positive correlations were found between the Central Sensitisation Inventory scores and the trait sensory profiles of Sensory Sensitivity, Sensation Avoiding and Low Registration. A weak negative correlation was found between the Central Sensitisation Inventory scores and the trait sensory profile of Sensation Seeking, $p < 0.01$. These relationships are summarised in figure 10.

Relationships between the Trait Sensory Profiles and Trait Anxiety Scores

The results of the correlations between trait anxiety (STAI scores) and the trait sensory profile scores showed the following: A moderate positive correlation with Sensory Sensitive, Sensation Avoiding and Low Registration and a weak negative correlation with Sensation Seeking; $p < 0.01$. These relationships are shown in figure 10.

Relationships between Trait Anxiety and the Central Sensitisation Inventory Scores

The results showed that there is a moderately positive correlation between trait anxiety scores and CSI scores among people with NSCLBP. Repressors tend to under report their anxiety on the STAI (Myers, 2010) and this has been recognised as a problem in research by previous authors where self-report measures are utilised (Eysenck, 1997). It was considered possible, therefore, that a stronger correlation might be found if the repressor group was excluded. A secondary analysis was performed in which the correlation was recalculated

after exclusion of the repressor personality type group, resulting in a similar relationship of (r = 0.44, CI = 0.27 – 0.58; p = 0.01) between STAI and CSI scores.

Regression analysis

Trait anxiety

The first regression analysis tested whether CSI scores could be predicted by any of the trait sensory profile scores, and/or trait anxiety scores. The predictors of CSI scores, identified from the correlation analyses, were most likely to be the Sensory Sensitive and Low Registration sensory profile scores and the STAI scores.

Tests for multicollinearity between the CSI and Sensory Sensitive, Low Registration and STAI scores showed that there was no multicollinearity between the predictors ($p < 0.001$; Table 7). The model summary showed R = 0.628 for step 1 and R = 0.712 for step 2. $R^2 = 0.394$ whereby the Sensory Sensitive profile score accounts for 39.4% of variability in the CSI scores. $R^2 = 0.498$ for step 2 whereby, in conjunction with the STAI and Low Registration scores, the Sensory Sensitive score accounts for 50.7% variability in the CSI scores. Adjusted R^2 scores were comparable to R^2 with 0.003% and 0.009% difference for steps 1 and 2 respectively, showing cross validity to be good (P<0.001). The Durbin Watson score to check the assumption of independent errors was acceptable at 1.834. Table 24 shows the model summary indicating the R, R^2 and adjusted R^2 values.

Table 24: R, R^2 and adjusted R^2 values, where r is the correlation coefficient between the CSI and the Sensory Sensitive, Low Registration and STAI score predictor variables, at step 1 and step 2 of the hierarchical regression model. (The percentage variability in CSI scores accounted for by the predictor(s) is indicated for each step with the R^2 values.) P<0.001.

Model of CSI scores and:	R	R^2	Adjusted R^2
Step 1, Sensory Sensitive scores	0.628	0.394 (39.4% variability in CSI)	0.391
Step 2, Sensory Sensitive, Low Registration & STAI scores.	0.712	0.507 (50.7% variability in CSI)	0.498

Table 25 shows the unstandardized (B and standard error) and standardised (Beta)

coefficients of the regression model, including the SD for each variable.

Table 25: Coefficients of the CSI versus Sensory Sensitive, Low Registration and trait anxiety Regression Model showing unstandardized (B and standard error) and standardised coefficients (Beta). P<0.001.

Model	B	Standard Error	Beta (p<0.001)
Step 1, CSI (constant) Sensory Sensitive	14.241 0.84	3.58 0.08	0.62
Step 2, CSI (constant) Sensory Sensitive Low Registration STAI scores.	0.54 0.49 0.37 0.32	3.96 0.09 0.10 0.07	0.37 0.25 0.27

NB: R^2 = .394 step 1 (p<.001); change in R^2= .113 for step 2.

Personality type

The second regression analysis was to investigate whether CSI scores could be predicted by

personality type. No relationships were found between the whole-group (inclusive of the

extreme sub-group) personality types and CSI scores. Therefore, extreme personality type

sub-groups were isolated, and the analysis repeated. Extreme sub-groups of personality

types were entered by block entry into the model. The Durbin Watson score to check the

assumption of independent errors was acceptable at 2.12. Extreme personality types accounted for 14% of variance in CSI scores which, according to the ANOVA, was significant (p = 0.048). The extreme defensive high anxious personality type contributed to increases in CSI scores the most (p = 0.05), whereas the high anxious and repressor personalities did not contribute, (table 26).

Table 26: *Coefficients of the regression analysis between CSI scores and personality type dummy variables, with low anxious as the baseline dummy variable, showing unstandardized (B and standard error) and standardised coefficients (Beta).*

Dummy Variable	B	Standard Error	beta	P=
Constant	46.50	5.73	-	
Defensive high anxious	13.34	6.58	0.43	0.05
High anxious	9.98	6.44	0.34	0.13
Repressor	-1.13	7.58	-0.03	0.88

R^2 = 0.14.

Discussion

This is the first study to identify inter-relationships between the extent of CS symptoms and 1) trait sensory hyper- and hypo-sensitivity; 2) trait anxiety and 3) personality type, in people with NSCLBP. This is also the first study to demonstrate the capacity of trait sensory hyper- and hypo-sensitivity, trait anxiety and the defensive high anxious personality type to predict the extent of CS symptoms in people with NSCLBP. Interpretation of the correlation analyses shows that the greater the extent of symptoms of CS in people with NSCLBP, a) the higher the extent of trait sensory hyper-sensitivity: (Sensory Sensitivity and Sensation Avoiding) and b) trait sensory hypo-sensitivity: Low Registration with a passive adaptive

response to sensory under-stimulation. Also, the greater the extent of CS symptoms the lesser the tendency to respond to sensory under-stimulation with an active compensatory response (Sensation Seeking profile). In addition, the results of the correlation statistics show that in the current study the more trait anxious the participants were, the more they showed trait sensory hyper-sensitivity (Sensory Sensitive and Sensation Avoiding respectively) and less so, trait sensory hypo-sensitivity with passive adaptive reposes (Low Registration). This is similar to (Engel-Yeger & Dunn, 2011c) in which trait anxiety was found to correlate positively with sensory sensitivity, sensation avoiding and low registration profile scores in healthy adult populations. This similarity adds validity to the stability of trait measures over time, strengthening the assumption that post-morbid scores in trait characteristics may not be confounded considerably by pain.

The Sensory Sensitive, Sensation Avoidant and Low Registration profiles have been positively correlated with pain catastrophising (using the pain catastrophising scale) in another study, although the correlations were weak, possibly due to the respondents being healthy (Engel-Yeger & Dunn, 2011b). The correlation found between trait anxiety and the Sensation Avoiding profile (low neurological threshold, active adaptive response) in people with NSCLBP may link with fear avoidance as a response to symptoms. The Sensation Avoiding profile has been found to be predictive of state anxiety in healthy adults (Engel-Yeger & Dunn, 2011c) suggestive of a possible tendency to reactive responses to pain. However, because Sensation Avoiding is a trait characteristic it is less likely to be a reactive behaviour to symptoms in people with NSCLBP, but behavioural responses learned from pre-morbid years. The findings of a concurrent nested qualitative study showed that emotional and physical sensory sensitivities had been present in the lives of the participants with NSCLBP pre-morbidly; [*Thesis article 6*, *submitted*]. The qualitative findings provide

support for the assertion that these were trait characteristics that had been present prior to the onset of low back pain and CS, and not limited to reactive responses to symptoms, in people with NSCLBP.

Regression analysis in the current study found trait anxiety to be a predictor of CSI scores in people with NSCLBP, reflective of the tendency of high trait anxious individuals to react to threats with state anxiety. State anxiety is a stress response and chronic stress has been identified in animal work as an activator of glial cells in the central nervous system which may be associated with neuroinflammation and subsequent CS onset or aggravation (Nijs et al., 2017).

The current study showed a prevalence of 12% in the extreme sub-group of defensive high anxious participants and whilst dominant, was on the verge of significance (p=0.05). This is similar to 13% found among a group of target shooters and hockey players with low back pain (Franklin et al., 2014); and less than a group of people with chronic low back pain where CS pain was not specified (26%), (Franklin et al., 2016). The difference between the prevalence of defensive high anxious participants in the current study and in the latter study (Franklin et al., 2016) may have been due to the latter having a much lower cut-off score (STAI ≥ 42, as opposed to STAI ≥ 49 in the current study) for identification of extreme defensive high anxious individuals, making the prevalence greater. Extreme defensive high anxious individuals tend to respond to the physiological arousal associated with stressors with vigilance towards the stimuli, interpretation of the stimuli as threatening (Eysenck, 1997; Franklin et al., 2016; Franklin et al., 2014) and persistence in their seeking of multiple medical interventions for their chronic low back pain significantly more so than the other

three personality types (Franklin et al., 2014). This may explain why the factor of extreme defensive high anxious personality type contributes, in part, to the prediction of symptoms of CS.

Repressors personality type show a bias by rapidly attending to threat-related stimuli (vigilance) and then actively avoid negative affect by shifting their attention away from the stimuli (avoidance) (Derakshan et al., 2007). Repressors may be vigilant towards somatic symptoms of CS but rapidly shift their attention away and avoid them (Myers, 2010). Associations between the Sensation Avoiding profile and the repressor personality type, in people with NSCLBP require further investigation.

Both the sensory profiles with the passive behavioural response to over- or under-stimulation predict the extent of CS symptoms (Sensory Sensitive and Low Registration) in people with NSCLBP. Self-efficacy has been found to be low in chronic back pain populations (Woby et al., 2007) which may link with passive adaptive behaviours seen in the current study.

The clinical implications for these profiles are that if individuals present with NSCLBP and they are found to have high trait sensory hyper-sensitivity and / or low registration profiles, high trait anxiety or an extreme defensive high anxious personality type, their symptoms are likely to be related to CS pain rather than nociceptive pain. Management may require education about sensory requirements and responses to stressors and this warrants further investigation.

The results of the regression analysis provide ground work for a longitudinal study to test for trait Sensory Sensitivity and Low Registration sensory profiles, trait anxiety and the

extreme defensive high anxious personality type as predictors of CS pain from a pre-pain or acute pain baseline in people with NSCLBP. This would enable clinicians to identify patients at risk of CS.

Strengths and limitations

Strengths include the rigorous methodology used in the current study were and which were reported according to the STROBE guidelines (Vandenbroucke et al., 2007). The methods followed the current clinical guidelines for identifying people with predominantly CS pain (Smart et al., 2012; Nijs et al., 2015), thereby increasing homogeneity within the sample. Selection bias was limited and external validity was facilitated by ensuring participants were recruited by multiple participating health care providers, rather than just one principle investigator, and across three countries and two continents.

Limitations included information not being available from participating clinicians as to how many potential participants refused to participate as refusals were not recorded. Furthermore, no record was made as to which variables contained missing data although these were very few and were spread across the outcome measures. The study recruited more female than male participants, which may present as a limitation, or may be reflective of females with chronic pain tending to seek treatment more than males (Cornally & McCarthy, 2011).

The current study obtained cross-sectional data, for which the AASP questionnaire has previously been validated (Brown & Dunn, 2002).

Conclusion

This is the first study to demonstrate that trait characteristics of trait sensory hyper-sensitivity and trait anxiety are positively associated with the extent of CS symptoms, and that Sensory Sensitivity and Low Registration sensory profile scores, trait anxiety scores and the defensive high anxious personality type have some capacity to predict the extent of CS symptoms in people with NSCLBP. Further studies to investigate relationships between 1) sensory profiles and personality types and 2) specifically the Sensation Avoiding sensory profile and the Repressor personality type in people with NSCLBP would be of value to better understand sensory hypo-sensitivity in CS. Longitudinal predictive studies from a pre-morbid or acute pain stage baseline to test trait characteristics of the Sensory Sensitive and Low Registration sensory profiles and trait anxiety as predictors of CS pain in people with NSCLBP are recommended. If predictive factors in the development of CS pain can be identified, "at risk" people can be targeted at baseline with appropriate management to reduce the risk of CS, which in turn will reduce the burden of NSCLBP on society.

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Here, the second of the two core component quantitative studies is presented.

4.3 Article 5: Prevalence of Extreme Trait Sensory Profiles and Personality types in Non-specific Chronic Low Back Pain with Predominant Central Sensitisation: Secondary analysis of an international observational study.

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Abstract

Objectives: Individuals with non-specific chronic low back pain (NSCLBP) and central sensitisation (CS) exhibit sensory hypersensitivity which may be related to pre-existing trait

characteristics. The objectives of this study were to observe 1) the range of Central Sensitisation Inventory (CSI) scores in a NSCLBP population with predominantly CS pain, and 2) the prevalence of four personality types and extreme scores of four trait sensory profiles in high and low CSI scoring sub-groups.

Methods: An international cross-sectional observational study was undertaken. Adults (n=165; mean age = 45$\pm$12 SD) were recruited from physiotherapy clinics. Inclusion: NSCLBP, aged 18 to 64, predominant CS pain without specific pathology. Outcome measures: CSI, Adolescent/Adult Sensory Profile, State/Trait Anxiety Inventory, and Marlowe Crowne Sociable Desirability Scale; Descriptive and comparative statistics were used.

Results: CSI scores ranged from 19 – 79 (mean = 50). There was a high prevalence of extreme 1) trait sensory hyper- and hypo-sensitivity profile scores ($p < 0.001$) and defensive high anxious personality ($p < 0.01$) in the high CSI (CSI $\geq$40; 78%) sub-group and 2) trait sensory hypo-sensitivity profile scores ($p < 0.01$) and repressor personality ($p < 0.01$) in the low CSI sub-group (CSI <40; 22%).

Discussion: These results are the first to demonstrate extreme sensory profiles and personality types in people with NSCLBP and predominant CS. A sub-group who report low levels of CS symptoms may have a hypo-sensitive sensory profile and repressor personality type. Further study is required to investigate the extent to which these trait characteristics may predict CS symptoms in people with NSCLBP.

Introduction

Chronic musculoskeletal pain is often characterised by the pain mechanism of central

sensitisation whereby pain is experienced by the individual even when there is no or

minimal pathology present (Moseley & Butler, 2015), due to hypersensitivity of the nervous

system to stimuli (sensory hypersensitivity). Central sensitisation (CS) is defined as a

dysregulation of the central nervous system causing neuronal hyper-excitability,

characterized by generalized hypersensitivity of the somatosensory system to both noxious

and non-noxious stimuli (Nijs et al., 2010; Mayer et al., 2012; Neblett et al., 2013). A

population prone to CS is a sub-group of people with non-specific chronic low back pain

(NSCLBP); (Nijs et al., 2015; Yunus, 2007), a condition having tremendous impact on society

(Apkarian et al., 2012).

A recent systematic review (Clark et al., 2017) of predictors of CS in adults with

musculoskeletal pain found evidence to suggest that the presence of sensory hyper-

sensitivity (tested using quantitative sensory testing) and somatisation (psychological

distress being reported in terms of physical symptoms) pre-morbidly, or at the acute stage

of pain, predict the development of CS at outcome (three or more months after pain onset).

Other than genetic testing (Diatchenko et al., 2005), none of the predictor studies measured

the participants' trait characteristics. Following the results of the systematic review, further

investigation into the role of trait characteristics of sensitivity was warranted. The question

is posited in this study as to what aspects of an individual's trait characteristics might

predispose them to the development of CS pain. Such aspects may include physiological and

behavioural characteristics of sensitivity to sensory stimuli, which, as trait characteristics,

may have been attributable to the individual prior to the development of CS pain and therefore may play an important role in its aetiology.

Physiological trait characteristics of sensitivity may include a lower neurological threshold to sensory stimuli than most people (Dunn, 1997), and/or a greater tendency toward physiological arousal in response to perceived threats, as part of characteristics related to high trait anxiety (Eysenck, 1997; Weinberger et al., 1979). Furthermore, behavioural characteristics may include active or passive adaptive responses to sensory stimulation or discomfort according to an individual's trait sensory profile (Brown et al., 2001; Dunn, 1997); or attention to, or avoidance of, sensory feedback according to the nature of the individual's personality type (Eysenck, 1997).

Dunn's (1997) trait sensory profile was designed to assess individual sensory preferences across five senses (auditory, visual, movement, touch, taste/small) and activity levels, giving a profile to illustrate the neurological thresholds to sensory stimulation (on a high to low continuum) and behavioural response to sensory discomfort (on a passive to active response continuum) (Dunn, 1997). For healthy function, it was proposed that an individual requires an optimum level of sensory stimuli and feedback, without which function might be compromised (Dunn, 1997, 2001). Insufficient or excessive sensory stimuli require an adaptive behavioural response to maintain optimum sensory stimulation and feedback. Studies using Dunn's trait sensory profile model have investigated sensory sensitivity and behavioural responses in other populations with sensory sensitivity differences, such as Asperger syndrome (Dunn et al., 2002), healthy adult populations with anxiety (Engel-Yeger & Dunn, 2011b, 2011c), and pain catastrophising behaviours in adults (Engel-Yeger & Dunn, 2011b).

Weinberger's four personality types (Weinberger et al., 1979) are determined by levels of defensiveness and trait anxiety: High Anxious (high anxiety, low defensiveness), Defensive High Anxious (high anxiety, high defensiveness), Low Anxious (low anxiety, low defensiveness), and Repressor (low anxiety, high defensiveness). It has been proposed that individuals with high trait anxiety personality types possess cognitive biases which would influence their perception of, and response to, sensory stimuli (Eysenck, 1997). These cognitive biases are 1) selective attentional bias (attention is drawn towards threatening stimuli), 2) interpretive bias (stimuli are interpreted as threatening) and 3) negative memory bias (recall of threatening situations more than neutral ones). The opposite is so for individuals with low trait anxiety personality types. Low (self-reported) anxiety-related personality types include the repressor personality which tends to avoid negative affect and avoid stimuli, believing they are not threatening (Eysenck, 1997; Myers, 2010). Conversely, individuals with the defensive high anxious personality type tend to selectively attend towards sensory stimuli and interpret them as threatening (Eysenck, 1997; Eysenck & Byrne, 1992). These individuals are significantly more likely to remain in the care system and utilise a variety of treatment options (Franklin et al., 2014).

For all these reasons it is anticipated that there would be a higher prevalence of defensive high anxious individuals, particularly in the extreme personality sub-groups, in a group of people with predominantly CS pain in a NSCLBP population. Furthermore, it is anticipated that there would be a high prevalence of extreme scores of sensory hyper-sensitivity profiles in people with predominantly CS pain in a NSCLBP group, based on the commonality

of sensitivity to sensory stimuli in people with CS and in people with sensory hyper-sensory profiles.

A recent pilot study (Clark et al. 2017 *in press*) investigating the trait sensory profiles and personality types of people with NSCLBP and predominantly CS pain found a sub-group of participants who self-reported low levels of CS symptoms, yet who were seeking treatment for pain. Low levels of CS symptoms were identified using the Central Sensitisation Inventory (CSI; Mayer et al., 2012) in which scores less than 40 are said to be below the cut-off score for clinically relevant CS (Neblett et al., 2013). Further study of these possible relationships is warranted as the pilot study used a small sample size and was exploratory in nature. The finding of a low CSI sub-group in the pilot study suggests some people with NSCLBP may experience a pain mechanism that is predominantly CS, but which may not involve extreme somatosensory hyper-sensitivity. Furthermore, self-reporting of symptoms, particularly under-reporting, can be related to individual characteristics of the repressor personality type (Eysenck, 1997; Myers, 2010).

The aims of this study were to investigate the prevalence of four personality types including extreme sub-groups, and extreme scores of four trait sensory profiles, in the low- (CSI < 40) and high- (CSI ≥ 40) CSI sub-groups, across a group of people with predominantly CS pain in a NSCLBP population.

Methods

This study is presented according to the Strengthening the Reporting of Observational

Studies in Epidemiology (STROBE) statement (Von Elm et al., 2007).

Design

This was an international cross-sectional observational study (Robson, 2002) of a NSCLBP

population with predominantly CS pain. Ethical approval was obtained from Manchester

Metropolitan University (ref:1205), participating hospitals in Ireland, the National Health

Service (NHS) in the United Kingdom (UK) (IRAS REC no.:15/NW/0378), and the Northern Y

Ethics Committee, New Zealand (NZ).

Sample

The sample size of n = 165 was calculated based on the requirements of the concurrent

primary study (Clark et al., *submitted*). This was done by taking the mean sample size of

three, each calculated using suggested sample size formulae (Field, 2009; Thabane, 2004),

with a power of 80% and alpha (α) set at 0.05. A post-hoc power analysis confirmed that the

sample size in the current study was sufficient (13 per variable), (Rigby and Vain, 1998).

Recruitment

Consecutive individuals with NSCLBP were identified by their clinician as being most likely to

be experiencing predominantly CS pain, based on their working knowledge of CS pain.

Recruitment was based on strict inclusion criteria for predominantly CS pain, and exclusion

of neuropathic and nociceptive primary pain presentations (Smart et al., 2012); (Table 27).

Recruitment took place from physiotherapy and pain outpatient clinics in NZ, UK and Ireland between July 2015 and March 2017.

Table 27: Inclusion and exclusion criteria given to all healthcare providers involved in participant recruitment.

Inclusion Criteria
- Aged 18-64 years inclusive   - Reported low back pain most days for more than 6 months   - No clear diagnosis as to the specific source of the pain (such as malignancy/ infection/ inflammatory disease like ankylosing spondylitis etc.) and where anti-inflammatory (NSAID) medication had been used these had not been found to be significantly helpful for the pain   - Pain disproportionate to the current extent of the injury or pathology   - Pain in variable areas around the back +/- other body parts and that was not always in the same place, with a pain distribution that was not neuro-anatomically logical   - Pain which is unpredictable in its aggravation and easing factors and responses to previous treatments.
Exclusion criteria
- Pain that is predominantly neuropathic in origin (determined using the S-LANSS neuropathic pain score)   - Pain that is predominantly nociceptive in origin (clear aggravating / easing factors and responds well to NSAIDs if used)   - Pregnancy and/or having given birth in the past 12 months   - Spinal surgery within the last 12 months   - Any inflammatory spondyloarthropathy, neurological disease, cardiac, respiratory, metabolic or endocrine disorder

Participants satisfying the inclusion criteria were provided with a participant information sheet. Consent was obtained at their subsequent visit to the clinic by the same clinician. Participants completed four self-assessed questionnaires supervised by the clinician. For omitted or ambiguously answered questions, participants were telephoned where possible

by an independent administrator to clarify responses, reducing the risk of any primary-researcher influence.

Outcome Measures

Central Sensitisation Inventory (CSI)

The CSI (Mayer et al., 2012) (Neblett et al., 2013) measures the extent to which the individual's symptoms are likely to be attributable to central sensitisation. Part A was utilised, which has 25 symptom related items scored on a Likert scale (0-4, score range 0-100). Part B was not used at it does not give specific information regarding the extent of CS symptoms relevant to the current study. The CSI has been shown to be valid and reliable (Mayer et al., 2012) with a test-retest reliability of 0.82 and Cronbach's Alpha of 0.88, sensitivity of 81% and specificity of 75% (Neblett et al., 2013). A cut off score of 40 was used to identify low and high CS symptoms (Neblett et al., 2017).

Adolescent / Adult Sensory Profile questionnaire (AASP)

The AASP is a 60-item questionnaire that measures two components of sensory processing function, neural thresholds to sensory stimulation and active or passive behavioural responses to sensory over- or under-stimulation (Brown & Dunn, 2002).

The AASP identifies four trait sensory profiles of adolescents and adults based on Dunn's original model of sensory processing (Dunn, 1997). The AASP combines the sensory thresholds with behavioural response continua to provide a summary score for each sensory profile: Sensory Sensitive (low neural threshold, passive adaptive response), Sensation Avoiding (low neural threshold, active adaptive response), Low Registration (high neural

threshold, passive adaptive response) and Sensation Seeking (high neural threshold, active adaptive response) (Table 28). Scores in each sensory profile item range from 1 to 5 based on a Likert scale of 'almost never' to 'almost always', respectively, with a total score for each profile of 75 on a scale from 'much less than normal' to 'much more than normal'. Normal values have previously been established in a healthy population (n= 495), aged between 18 and 65 years (Brown & Dunn, 2002). Internal reliability (coefficient alphas) for each sensory profile is 0.81 for Sensory Sensitive, 0.66 for Sensation Avoiding, 0.82 for Low Registration and 0.79 for Sensation Seeking (Brown & Dunn, 2002).

Table 28: Sensory profiles: Sensory Profiles identified by the Adult / Adolescent Sensory Profile Questionnaire (Adapted from Brown and Dunn, 2002).

		Adaptive behavioural response	
		Active	**Passive**
Stimulus Threshold	**High**	Sensation Seeking	Low Registration
	Low	Sensation Avoiding	Sensory Sensitive

State-Trait Anxiety Inventory (STAI)

The STAI (trait section; Spielberger, 1983), measures trait anxiety, an enduring, relatively stable characteristic indicating the likelihood of the person responding to perceived threats with increased state anxiety. Trait anxiety has been found to be associated with sensory sensitivity to stimuli (Ansari & Derakshan, 2011b). It is a self-assessed 20-item questionnaire, using a 1 to 4-point Likert scale with answers ranging from "not at all" to "very much so" respectively, with a maximum score of 80 (with higher scores indicating

higher trait anxiety). Internal consistency coefficients range from 0.86 to 0.95 and test-retest reliability coefficients range from 0.65 to 0.75 over a 2-month timeframe (Spielberger, 1983).

Marlowe Crowne Social Desirability Scale (MCSDS)

The MCSDS (Crowne & Marlowe, 1960) measures defensiveness / social desirability. The Short Form of the MCSDS was used (Strahan & Gerbasi, 1972) which is a 10-item self-reported questionnaire with "true" or "false" responses with a scale of 0-10 (with higher scores indicating greater defensiveness). (Reynolds, 1982) reported an internal consistency alpha coefficient of 0.66 and a correlation coefficient of r = 0.90 (p < 0.001) between the 10 item MCSDS and the original 33 item MCSDS (Crowne & Marlowe, 1960). The short form version was chosen in preference to the longer version for its time management advantage.

The MCSDS combined with the STAI-T indicate the personality type of the individual (Weinberger et al., 1979): Defensive high anxious (high trait anxiety, high defensiveness); high anxious (high trait anxiety, low defensiveness); repressor (low trait anxiety, high defensiveness); low anxious (low trait anxiety, low defensiveness) summarised in Table 29.

Table 29: Personality types identified by combining the Trait section of the State-Trait Anxiety Inventory, and the Marlowe-Crowne Social Desirability Scale (MCSDS).

		Social Desirability / Defensiveness	
		High	**Low**
Trait Anxiety	**High**	Defensive High Anxious	High Anxious
	Low	Repressor	Low Anxious

Data Management

Data were pseudo-anonymised prior to data analysis by removing the front page containing the identifiable information and allocated a research number.

Analysis

Data were analysed using IBM SPSS Statistics version 22 (Corp., 2013). The primary outcome measure was the CSI.

CSI score

Descriptive statistics were used to describe the demographics and the range of CSI scores across the study population. The high- and low- CSI sub-groups were identified using a cut-off score of ≥ 40 on the CSI (Neblett et al., 2013). The prevalence of extreme scores from each sensory profile in the high- and low- CSI sub-groups was calculated. Extreme scores were identified as one standard deviation either side the mean (±1SD). Prevalence was compared to healthy population data (Brown & Dunn, 2002) from the AASP User Manual. Chi Squared (χ^2) calculations were used to determine whether differences between the observed and expected calculations for each sensory profile were statistically significant ($p >$

0.05). Proportions of the four personality types were calculated in the two CSI sub-groups and chi squared calculations were used to establish any statistically significant proportional differences between the two sub-groups.

Personality type

The method chosen for splitting the STAI and MCSDS scores for identification of the four personality types in the current study was to reflect the same method used by Brown et al (Brown & Dunn, 2002) for identifying the four sensory profiles. Personality types were identified using a cut off score based on means and standard deviations identified in normative data (Johnson & Fendrich, 2002; Kendall & Sheldrick, 2000; Spielberger, 1983). Using normative data as a reference has been done by previous authors (Lewis et al., 2012). Other authors have also used a cut off score above and below which identified high or low anxiety and defensiveness scores respectively (Creswell & Chalder, 2001). Therefore, the four personalities were identified as follows: high anxious, STAI ≥ 39 and MCSDS ≤ 5; defensive high anxious, STAI ≥ 39 and MCSDS > 5; low anxious, STAI < 39 and MCSDS ≤ 5; and repressor, STAI < 39 and MCSDS > 5. Heterogeneity of personality types was tested using Levene's test. To identify extreme sub-groups within each personality type, extreme scores were calculated using the standard deviations from normative data for the STAI (Kendall & Sheldrick, 2000; Spielberger, 1983) and MCSDS (Lewis et al., 2012) scales as follows: STAI ≤29 for low anxious and ≥49 for high anxious and MCSDS ≤4, low defensiveness and MCSDS ≥8, high defensiveness. The independent t-test and effect sizes were used to test for differences in the mean trait anxiety scores between the high- and low-CSI sub-groups, in each personality type.

Results

Demographics

A total of n=165 participants were recruited (n = 39 male) from eight physiotherapy and

pain outpatient clinics in NZ (n = 82), three in England (n = 36) and two in Ireland (n = 47).

Age ranged from 18-64 years, (mean = 45 ±12). CSI scores were normally distributed and

ranged from 19 to 79, mean = 50 (95% CI 47.97 - 52.23).

Participants consisted of high CSI (CSI ≥ 40; n = 129) and low CSI (CSI < 40; n = 36) scoring sub-

groups, which was anticipated given the strict inclusion criteria aimed at recruiting only those

NSCLBP participants with predominantly CS pain.

A total of n=112 (68%) participants were taking one or more pain-related medication. (Table

30). Almost a third of the group were not taking any medication (n = 53, 32%).

Table 30: Mean Central Sensitisation Scores for each medication group used by the participants (N=165) with NSCLBP and CS pain.

Medication group	Participants (N=)	Mean CSI score (±SD)
Anti-convulsants	38	57 (14)
Antidepressants: SS(N)RI	24	55 (15)
Tricyclics	29	54 (10)
Analgaesics	48	53 (15)
Opioids	23	53 (14)
NSAIDs	37	50 (15)
Antispasmodics	8	49 (17)
Anti-anxiety (SARI)	7	49 (10)
No medication	53	44 (11)

Anti-anxiety: Serotonin Antagonist & Reuptake Inhibitors (SARI)
Non-steroidal anti-inflammatories
Antidepressants: Selective Serotonin (Norepinephrine) Reuptake Inhibitors SS(N)RI

Prevalence of extreme Sensory Profile (AASP) Scores: extreme high vs extreme low CSI sub-groups

The AASP provides a summary score for all four sensory profiles; these are presented in two groups based on sensory hyper- and hypo-sensitivity:

Sensory hyper-sensitivity group: Sensory Sensitive and Sensation Avoiding sensory profiles:

Participants identified in the high-CSI sub-group (CSI ≥ 40) had significantly more scores in the extreme high groups compared to the extreme low groups in both the Sensory Sensitive (67%; $\chi^2_{(2)}$ = 182.63, p < 0.001) and Sensation Avoiding profiles (53%; $\chi^2_{(2)}$ = 102.53, p < 0.001) (Tables 31 and 32).

Conversely, participants in the low-CSI sub-group (CSI < 40) showed no significant difference in prevalence of extreme scores (Sensation Avoiding: 11%, $\chi^2_{(2)}$ = 2.5 p > 0.05; Sensory Sensitive: 14%, $\chi^2_{(2)}$ = 5.72, p > 0.05).

Table 31: Prevalence of extreme sensory sensitivity scores in the low and high CSI Groups.

Sensory Sensitive Profile					
		Distribution of participants			P=
		>-1SD	≤±1SD	>+1SD	
CSI >=40 N=129	N=	3	40	86	P < 0.001
	Range	20-24	35-55	42-69	
	Mean (±SD)	22 (2)	45 (9.9)	51 (6.2)	
	Prevalence (%)	2	31	67	
CSI<40 N=36	N=	4	27	5	p > 0.05
	Mean (±SD)	22 (3.9)	34 (7)	47 (2.1)	
	Range	16-25	27-41	42-50	
	Prevalence (%)	8	78	14	

CSI = Central Sensitisation Inventory Score
SD = Standard Deviation

Table 32: Prevalence of extreme Sensation Avoiding scores in the low and high CSI groups.

Sensory Avoiding Profile					
		Distribution of participants			P=
		>-1SD	≤±1SD	>+1SD	
CSI >=40 N=129	N=	8	53	68	p < 0.001
	Range	18-26	31-53	42-70	
	Mean (±SD)	24 (2.4)	42 (11)	51 (6.8)	
	Prevalence (%)	6	41	53	
CSI <40 N=36	N=	5	27	4	p > 0.05
	Mean (±SD)	22 (2.8)	34(7)	49 (3.9)	
	Range	17-24	27-41	44-52	
	Prevalence (%)	14	75	11	

CSI = Central Sensitisation Inventory Score
SD = Standard Deviation

Sensory hypo-sensitivity - Sensation Seeking and Low Registration sensory profiles: In participants in the high-CSI sub-group (CSI>=40), low extreme scores for Sensation Seeking were significantly more prevalent (47%; $\chi^2_{(2)}$ = 71.83, p < 0.001). There was no significant difference in the prevalence of extreme scores in participants in the low-CSI sub-group (Table 33).

Table 33: Prevalence of extreme Sensation Seeking sensory profile scores in the low and high CSI groups.

Sensory Seeking Profile					
		Distribution of participants			P=
		>-1SD	≤±1SD	>+1SD	
CSI >=40 N=129	N=	61	58	10	p < 0.001
	Range	18-42	35-53	57-63	
	Mean (±SD)	36 (5.4)	44(9)	59 (1.9)	
	Prevalence (%)	47	45	8	
CSI <40 N=36	N=	7	26	3	p > 0.05
	Mean (±SD)	37 (3.3)	47(7)	60 (2.1)	
	Range	31-42	40-54	58-62	
	Prevalence (%)	20	72	8	

CSI = Central Sensitisation Inventory Score
SD = Standard Deviation

In participants in the high-CSI sub-group (CSI>=40), high extreme scores were significantly more prevalent in Low Registration sensory profiles (63%; $\chi^2_{(2)}$ = 165.07, $p < 0.001$); (Table 26). Unlike the other sensory profiles in the low CSI (CSI<40) sub-group, there was a significantly greater prevalence of both high (25%) and low (22%) extreme scores for the Low Registration sensory profile ($\chi^2_{(2)}$ = 9.12, $p < 0.05$). The Low Registration profile results are summarised in table 34.

Table 34: Prevalence of extreme Low Registration sensory profile scores in the low and high CSI groups.

Low Registration Profile					
		Distribution of participants			P=
		>-1SD	≤±1SD	>+1SD	
CSI >=40 N=129	N=	6	42	81	p < 0.001
	Range	17-22	29-47	36-60	
	Mean (±SD)	20 (2.1)	38(9)	44 (6.3)	
	Prevalence (%)	4	33	63	
CSI <40 N=36	N=	8	19	9	P < 0.05
	Mean (±SD)	21 (2.7)	30(8)	40 (4.6)	
	Range	15-23	22-38	36-50	
	Prevalence (%)	22	53	25	

CSI = Central Sensitisation Inventory Score
SD = Standard Deviation

Personality Types

Across the whole group of people with NSCLBP and CS, the largest proportion of individuals were: Defensive high anxious (n = 75, 45%) and high anxious (n = 43, 26%), then the repressor group (n = 41, 25%). The lowest proportion was the low anxious group (n = 6, 4%) none of whom were in the extreme score ranges (Table 9). The four personality type groups were significantly distinguishable from each other in their trait anxiety and defensiveness scores: STAI, $F_{(3,161)}$ = 10.19, $p = 0.00$ and MCSDS, $F_{(3,161)}$ = 3.51, $p = 0.017$.

The proportion of low and high CSI scores was 22% and 78% respectively (Table 9). There was a significantly greater prevalence of repressors in the low CSI sub-group ($\chi^2_{(1)}$ =12 P<0.01). There was no significant difference in the prevalence of people with the defensive high anxious and high anxious personality types between the low- and high-CSI sub-groups. Comparison of the expected and observed prevalence of extreme personality type sub-groups distributed between the low and high CSI groups showed a significant difference in only the extreme defensive high anxious personality type: 100% of these individuals scored over 40 on the CSI ($\chi^2_{(1)}$ = 21.7, p < 0.01). The proportional distribution and prevalence of personality types and extreme personality type sub-groups are illustrated in figure 11.

*Figure 11 The proportions and prevalence of personality types **including the extreme personality type sub-groups** within the low and high CSI sub-groups in the non-specific chronic low back pain population with central sensitisation.*
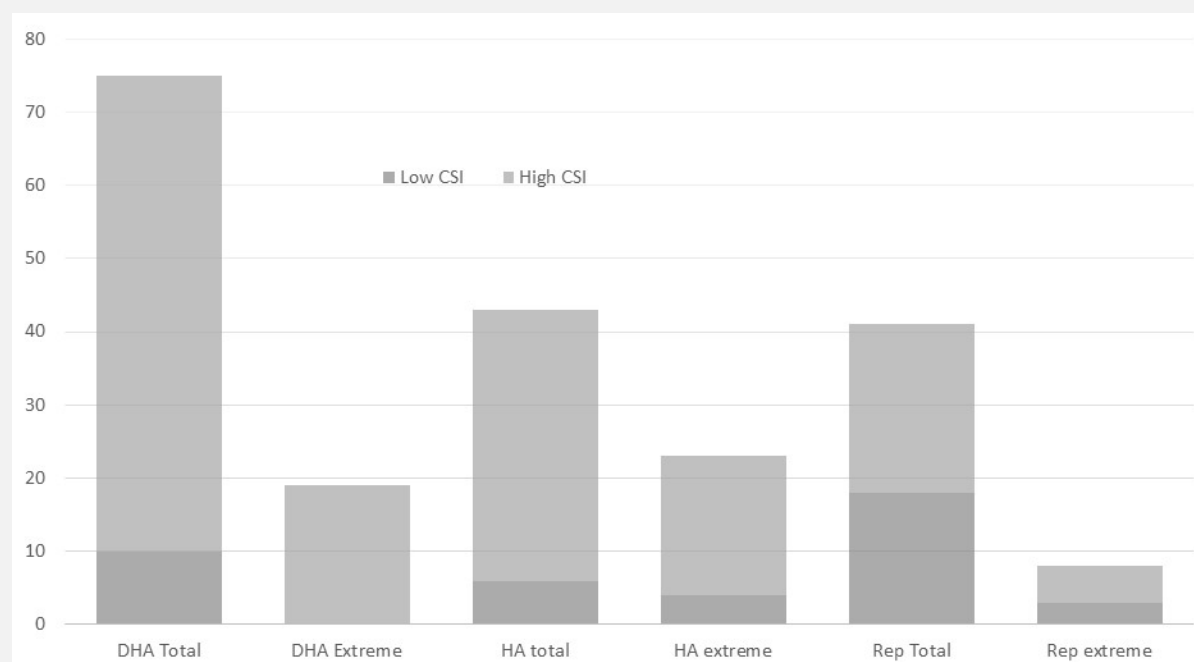
Furthermore, the defensive high anxious group had significantly higher levels of trait anxiety in the high- compared with the low-CSI sub-group (U = 3.0, p=0.000). There were no significant differences in the trait anxiety scores in the high anxious and repressor individuals, nor in defensiveness scores for all the personality types, between low- and high-CSI sub-groups.

Discussion

This is the first and largest study to observe the prevalence of low- and high-CSI sub-groups CSI scores in people with NSCLBP. It is also the first study to observe the prevalence of trait sensory profiles and personality types in this population.

Extreme trait sensory hypersensitivity profiles in people with high-CSI scores suggests that a significant number of people with NSCLBP and CS have a low neurological threshold for sensory stimulation and either a passive adaptive response to sensory over-stimulation (Sensory Sensitive), or an active adaptive response to sensory over-stimulation (Sensation Avoiding). The AASP claims to measure trait preferences (Brown & Dunn, 2002); trait sensory hyper-sensitivity profiles imply characteristics of sensory hypersensitivity are present pre-morbidly. Conceptually, this is similar, in terms of low sensory thresholds as part of a character trait, to a pre-morbid study in which genetic sensory sensitivity markers were identified (Diatchenko et al., 2005). The COMT (Catechol-O-Methyltransferase gene), partly responsible for trait sensory sensitivity, was found in people who developed a CS pain syndrome and was absent in those who did not. It is possible that genetic sensory sensitivity might be linked to trait sensory hypersensitivity profiles. The results of the current study are suggestive of pre-existing trait sensory sensitivity reflecting other work in which premorbid baseline sensory hyper-sensitivity has been found (using quantitative sensory testing) in people who later developed musculoskeletal CS pain (Sterling et al., 2003; Slade et al., 2014; Gupta et al., 2007; Ferrari, 2010).

Also identified in the high-CSI group were extreme scores of trait sensory hypo-sensitivity: the Low Registration and Sensation Seeking sensory profiles. Intuitively, higher levels of CS pain would be expected to be related to trait sensory hyper-sensitivity profiles, suggestive of a low neurological threshold for sensory stimulation. However, the prevalence of the Low Registration sensory hypo-sensitivity profile is suggestive of a high neurological threshold to some sensory stimuli (sensory hypo-sensitivity) and a passive adaptive response to sensory under-stimulation, more or much more than most (Brown et al., 2001). Similarly, others

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(Sensation Seeking) had a high neurological threshold for sensory stimulation, but they, however, tended to actively adapt to under-stimulation less or much less than others. Clinically this may mean that individuals with NSCLBP and CS with a high neurological threshold for sensory stimulation need to receive greater levels of sensory input to function healthily, which may in turn influence treatment programmes for these individuals.

Sensory hyper-sensitivity is a characteristic of CS pain and therefore the finding of trait sensory hypo-sensitivity in the current study may appear paradoxical. Other studies have also discussed sensory hypo-sensitivity (mis-localisation and reduced sensory discrimination) in populations who are likely to have a non-nociceptive, non-neuropathic pain mechanism (inferring predominantly CS pain) (Wand et al., 2010; Wand et al., 2013). The prevalence of sensory hypo-sensitivity to various sensory stimuli has been estimated at 25 - 50% of individuals with (unspecified) chronic musculoskeletal pain (Mailis-Gagnon & Nicholson, 2010; 2011). Sensory hypo-sensitivity has been found in relation to non-dermatomal somatosensory deficits which are defined as "unexplainable hypoaesthesiae (e.g. to cutaneous or other sensory modalities) ipsilateral to the site of pain (or worse pain), which do not conform to the distribution of peripheral nerves or dermatomes" (Mailis-Gagnon & Nicholson, 2011; p. 1787). This suggests an overlap between NDSDs and the definition of CS pain. Sixty-eight percent of the current study participants with NSCLBP and CS had extreme scores in the Low Registration sensory profile, more than that found in other studies (Mailis-Gagnon & Nicholson, 2010). This increase may be attributable to the sample in this study, which was specific to CS pain presentations and within the specific population of NSCLBP.

The results of the current study suggest there is a sub-group of people with CS pain who have extremes of high neurological thresholds and passive adaptive responses to under-stimulation. This important new finding may form part of the development of CS pain and warrants further investigation. Furthermore, this may have implications when using quantitative sensory testing to identify CS in people with NSCLBP because if some senses are hypo-sensitive because of a trait sensory profile of Low Registration, low levels of sensory sensitivity as a measure of the extent of CS could be misleading.

Personality Types

The way participants respond to pain may be influenced by their personality type (Myers, 2010). The largest proportion of participants in the current study were defensive high anxious individuals (45%). This was similar to a population with chronic fatigue syndrome (46%; Creswell & Chalder, 2001), a chronic condition characterised by central sensitisation (Nijs et al., 2012). Moreover, there is a higher prevalence of defensive high anxious individuals in a population with NSCLBP and CS compared with that found in a healthy population (Creswell & Chalder, 2001). Nineteen (12%) participants in the current study were in the extreme sub-group for defensive high anxious personality type, similar to work by (Lewis et al., 2012) who identified 13% extreme defensive high anxious individuals in a group of target shooters and hockey players with low back pain. In a chronic low back pain group (CS pain was not specified; Franklin et al., 2016), a prevalence of 26% extreme defensive high anxious individuals was found which is higher than the current study. However, the clinical-population-based cut-off score, using tertiary splits at 33% and 66%, was STAI ≥ 42. This was lower than the current study normative-based cut off score, using >+- 1SD, of STAI ≥ 49, which may explain the difference in prevalence found. Thirty-eight

percent of the extreme personality sub-group were defensive high anxious which is consistent with the prevalence of extreme defensive high anxious individuals in another chronic low back population (Lewis et al., 2012).

All extreme defensive high anxious individuals scored high on the CSI (CSI ≥ 40). This may reflect the proneness of extreme defensive high anxious individuals to attend to pain related symptoms (Franklin et al., 2016) and show persistence in their seeking of multiple medical interventions (Franklin et al., 2014) significantly more than the other three personality types. High anxious and defensive high anxious individuals are high in trait anxiety and therefore more prone to respond to stressors with physiological arousal than their low anxious counterparts (Eysenck, 1997). This was reflected in the significantly higher trait anxiety scores in the high-CSI group in the current study.

It is known that defensive high anxious and high anxious individuals attend to and interpret stimuli as threatening (Franklin et al., 2014; Myers, 2010). People with high anxious and defensive high anxious personality types have also been found to report their somatic and cognitive sensations of state anxiety as being debilitative to performance outcomes (Franklin, 2015), which suggests these groups could experience more debilitation and disability from their somatic and cognitive symptoms of anxiety associated with CS.

Low anxious (4%) and repressors (25%) made up the smallest group of participants in the current study. Repressors tend to self-treat and not attend physiotherapy and pain clinics as much as defensive high anxious individuals (Franklin et al., 2014). Contrary to expectation, the low- and high-CSI groups showed no significant difference in the proportion of defensive

high anxious and high anxious individuals, until the extreme personality types were extracted. Even then, only the proportion of extreme defensive high anxious and not the extreme high anxious individuals was greater in the high CSI group.

Linking Personality types to Sensory Profiles

Defensive high anxious individuals may also have high trait sensory sensitivity with extreme scores in the Sensory Sensitive profile. Defensive high anxious individuals show attentional bias towards threatening information (Eysenck, 1997; Franklin et al., 2014), which is similar to having a heightened sensitivity to sensory stimuli in the trait sensory hyper-sensitivity profiles. Repressors show an avoidant bias to threatening stimulation (Franklin et al., 2016) and individuals with the Sensation Avoiding sensory profile tend to actively avoid sensory over-stimulation, which suggests repressors and sensation avoiders may share similar profiles. The proportions of repressors and Sensation Avoidant profiles in the high and low CSI groups did not reflect this. Furthermore, repressors tend not to notice threatening stimuli (Derakshan et al., 2007) and people with a Low Registration sensory profile tend to miss sensory information (Brown & Dunn, 2002) suggesting that repressors may also have a Low Registration sensory profile. There was a similar prevalence of high extreme Low Registration profiles (63%) and extreme repressors (62%) in the high CSI group. The low CSI group showed 47% extreme Low Registration and 38% extreme repressors. Further investigation into relationships between these profiles is warranted here.

The clinical implications for these profiles are that when individuals present with NSCLBP and CS, identification of their sensory profiles and personality types may guide management accordingly. Explanation of CS pain including the disproportional relationships between the

extent of symptoms and the extent of tissue damage may reduce threat perception in the defensive high anxious and anxious individuals. Identification of active or passive behavioural patterns in response to sensory stimulation, using the sensory profiles, may help the individual to modify their behaviours.

Implications for the use of the CSI to identify CS symptoms in people with NSCLBP

CSI scores of less than 40 are classified as sub-clinical or mild (Neblett et al., 2017). It is possible that some people who score lower on the CSI do so because of their personality type in which they tend to avoid symptoms and not recognise them as threatening (repressors). Conversely, others will attend to their symptoms and report higher levels of pain (defensive high anxious and high anxious). This suggests that the CSI should not be used without objective clinical evaluation to diagnose CS pain, because of the variability in self-report responses across personality types.

The current study findings of a sub-group of low- CSI people with NSCLBP and clinically identified, predominant CS pain supports the clinical guidelines recommended by (Nijs et al., 2015), in which clinical criteria can be used to identify CS without there needing to be a score of CSI ≥ 40. It is proposed that a low CSI score should not discount those individuals as experiencing CS pain when 1) there is no evidence for predominant nociceptive or neuropathic pain mechanisms and 2) they have a repressor personality type and/or an extreme Low Registration sensory profile score.

Strengths and Limitations

Strengths of this study include the methodology, which followed the current clinical recommendations for identifying patients with NSCLBP and predominantly CS pain, thereby limiting heterogeneity within the sample. Bias was limited by ensuring participants were recruited by multiple participating clinicians, rather than just one principle investigator, and across three countries and two continents. The latter also optimizes external validity of the study findings. The study recruited more female than male participants, reflecting epidemiological studies showing chronic low back pain is more prevalent among women (Bernstein et al., 2017).

Potential weaknesses included a lack of information available from participating clinicians as to the number of participants refused to participate. Limitations were caused by the likely response bias related to questionnaires by different personality types and a lack of blinding of the researcher to some participants.

Conclusion

This study is the first to show that 1) trait sensory profiles and personality types are factors related to the extent of CS pain in people with NSCLBP and 2) low CSI scores are found in people with NSCLBP who are clinically diagnosed with predominantly CS pain. It is possible that the defensive high anxious personality type and high scores in the Sensory Sensitive trait sensory profile may play an aetiological role in the development of high levels of CS symptoms and this requires further investigation. Furthermore, low self-report levels of CS symptoms in people with NSCLBP may be attributable to under-reporting by individuals with a repressor personality type and/or sensory hypo-sensitivity associated with a Low

Registration trait sensory profile. Further investigations are required into which particular senses (of those investigated in the AASP) may be hypo-sensitive which may in turn guide individual treatment strategies. Investigations into the repressor personality type, regarding self-report measures, in CS pain populations are also warranted in order to avoid false negative results in pain research where questionnaires are utilised as methods of data collection.

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4.4 Discussion

At the time of developing the study design there was no questionnaire available to measure sensory processing and sensory sensitivity in NSCLBP nor in any CS pain population. This was a novel approach to CS pain in people with NSCLBP. The main sensory sensitivity measurement strategy used in pain research at the time of study planning was quantitative sensory testing (QST). QST measures sensory thresholds by recording sensory sensitivity to stimuli applied to the skin (Shy et al., 2003). There are limitations to the use of QST for the purpose of measuring aspects of trait sensory processing in the current study:

1) CS pain is likely to involve sensory sensitivity across multiple senses in addition to skin tactile, pressure and thermal senses, such as smell, taste, visual, auditory senses (Nijs et al., 2014).

2) QST is not specifically designed for testing hyposensitivity of some senses and it was not known at the study outset whether or not people with NSCLBP may have hypo-sensitivity of some senses as part of the manifestation of CS pain mechanisms, such as found by Wand and colleagues (Wand et al., 2010; Wand et al., 2011).

3) QST measures sensitivity at the time of testing, whereas the aim of the current study was to investigate trait characteristics assumed to have been present prior to the time of testing, pre-morbidly.

4) QST requires time and trained staff to administer the tests. In an international, multi-centre project the logistics of collecting data by QST were restrictive.

Instead, the administration of self-report questionnaires was chosen as the method of data collection from multiple international sites.

Study limitations applicable to articles 4 and 5 include the way in which the participants were recruited based on clinical guidelines only. Although the clinical assessment guidelines and selection criteria were stipulated in writing by the primary investigator (JC), there was no standardization of the operating procedures nor ongoing regular training provided for the participating clinicians. Explanation was given verbally in person or over the phone for most participating clinicians by JC, and a power point presentation was designed and sent by JC to one of the participating hospitals, by request of the participating clinicians there. Regular emails and phone calls were made by JC to all the participating clinicians over the course of the data collection to check for any problems, queries and to monitor the process. Due to the geographical spread of participating clinics it was not possible for JC to visit them regularly for ongoing training and monitoring. It may be argued that the quality of data may have been affected by this lack of quality control.

Another limitation to the studies in articles 4 and 5 is the lack of demographic information collected on the potential participants who were screened initially, considered unsuitable and subsequently excluded. Moreover, no demographic information was collected regarding the potential participants who were approached but who refused to participate. Therefore, it remains unclear as to how the participants who were excluded and who refused may have differed from the sample population, and how representative the study sample was of the general population with NSCLBP and CS who attend out-patient physiotherapy and pain clinics.

4.4.1 Measuring Aspects of Sensory Processing

At the time of the study planning there were a number of tools used to measure aspects of sensory processing. The Sensory Over-Responsivity (SOR) Questionnaire (S. Reynolds & Lane, 2009) is used in paediatrics to measure sensory sensitivity in children with autism spectrum disorder and had not been validated beyond a pilot study at the time of planning the current study. The Sensory Processing Measure-School (Miller-Kuhaneck et al., 2007) was also for use in paediatric populations only. None of these were appropriate for measuring adult populations and were discounted as possibilities for the current study. The Sensory Responsiveness Questionnaire (Bar-Shalita et al., 2009), however, has been validated in adults, using a small sample size of 24, to assess sensory sensitivity. No quadrants are determined to include behavioural responses to high *and* low sensory stimulation, presenting a limitation to its use for the purposes of the current study. The Adolescent / Adult Sensory Profile (AASP) questionnaire has been used extensively in adult populations with various sensory processing disorders (Brown et al., 2001). The AASP identifies trait sensory sensitivity profiles. The sensory hyper-sensitivity profiles in the ASSP have been found to correlate with the pain catastrophizing scale (Engel-Yeger & Dunn, 2011b) in typical adults and also with the state – trait anxiety inventory (Engel-Yeger & Dunn, 2011c) in healthy adults.

Logistically the AASP is more difficult to access compared with the SRQ due to costs of licencing for usage. However, owing to the better fit for the research questions and overall appropriateness of the AASP over the SRQ, Manchester Metropolitan University funded the

purchase of the AASP questionnaires with the associated license for use, from Pearson Assessments.

4.4.2 Calculating the sample size

The required sample size (for articles 4 and 5 above) was calculated based on multiple factors, and further details are given here. A previous study showed a prevalence of up to 26% of extreme personality types in a similar population of people with chronic low back pain (Franklin et al., 2016). For a regression analysis, with a power of 80% and alpha (α) set at 0.05, a value of $R^2 \geq 0.23$ can be detected with n = 50 participants (Thabane, 2004). The smallest number of participants anticipated to represent one variable was the extreme sub-group of personality types which would be used in a block entry regression analysis. If 26% of the current study group forms the minimum number (n = 50) required for the above anticipated regression analysis, then 100% would be n = 192. Alternatively, a minimum of 15 to 20 participants per variable is recommended for regression analyses (Thabane, 2004) and 10 to 15 participants per variable for correlation analyses (Field, 2009); there are 9 variables (i.e. 4 sensory profiles, 4 personality types and the CSI scores), therefore n = 180 accordingly. For multiple correlation (Thabane, 2004) suggests a rule of thumb of n > 50 + m8, where m is the number of variables, for a moderate effect size (minimum n = 122). Using these 3 suggested sample sizes, a mean sample size was derived: n = 165.   A post-hoc power analysis confirmed that the sample size in the current study was sufficient for meaningful results (13 per variable).

4.4.3 Analyses relating to trait anxiety and personality types

It was apparent from some of the literature in which personality types (Weinberger et al., 1979) have been investigated that there are a variety of ways to handle the personality type data. Personality types can be identified using score splits around the mean score of the trait anxiety measure and the defensiveness measure (Lewis et al., 2012), or by selecting out the extreme scores on the trait anxiety and defensiveness measures using tertiary (Franklin et al., 2014) or quartile (Derakshan & Eysenck, 2005) splits. Furthermore, the splits are based on either the study population scores (Franklin et al., 2016) or on normative data from healthy populations (Lewis et al., 2012). The rationale for extreme splits strategies used to identify personality types is to ensure enough heterogeneity between personality sub-groups (Myers, 2000).

It was decided that the trait anxiety and personality types would be identified using normative cut-off scores on the STAI and the MCSDS from healthy population studies because the AASP identifies each sensory profile using the same method, enabling a closer comparison between trait anxiety and sensory profiles. Secondly, normative cut-off scores were chosen because of the assumption that the scores on the trait anxiety measures and personality type measures are reflective of long-term stable characteristics, and as such, the range of scores would have been comparable to normative values pre-morbidly.

The AASP manual supplied data for the cut-off scores ranging along a normal distribution bell curve between -2SD to +2SD (SD = Standard deviation) whereby the five-point Likert scale answer "much less than most" = -2SD, and "less than most" = -1SD and "more than most" = +1SD and "much more than most" = +2SD, (Brown & Dunn, 2002). Therefore, to

make meaningful comparisons between the sensory profiles and personality types in people with NSCLBP and CS pain, the extreme personality types were identified using the same strategy around the mean and standard deviations found in healthy populations, similar to Lewis (2012).

The study was not limited to extreme personality types because the study sample of people with NSCLBP, specifically selected for their clinically identified predominance of CS pain, was a clinical sample typical of those seen in physiotherapy and pain clinics in 3 countries. Therefore, every individual would be identified under one of the four personality types, non-extreme or extreme, to reflect the spread of personality types in a clinic situation. Moreover, it was anticipated that loss of participants, by adding extreme personality types to the already strict inclusion criteria, may have reduced the study sample size considerably. Extreme personality types had not been included in the pilot study due to low participant numbers in the study protocol.

4.4.4 Analysis of associations using scale and categorical data

Trait anxiety was hypothesised as possibly sharing physiological mechanisms of sensitivity with sensory hyper-sensitivity profiles (Sensory Sensitive and Sensation avoiding) and CS. It was anticipated that trait anxiety and sensory sensitivity would be on a scale, or spectrum, of trait sensitivity in people with NSCLBP and CS, similar to that suggested by Clauw, (2009), in people with CS in a fibromyalgia population. The nature of the personality types is identified through two combined scales (STAI and MSCDS) and therefore personality types are classified as categorical data. Therefore, trait anxiety was separated from defensiveness

for part of the correlation and regression analyses to investigate relationships between the sensory profile, trait anxiety and CSI scales.

Regression analyses using personality type categorical data was performed in addition so as to identify the potential predictive power of each personality type (non-extremes and extremes) on the extent of CS symptoms.

4.4.5 Other Anxiety measures considered

Other anxiety measures considered for the current study were The Hospital Anxiety and Depression Scale (HADS) and the Beck Anxiety Inventory, reviewed by Julian, (2011). The HADS is a bi-dimensional scale developed to identify cases of depression and anxiety disorders among physically ill patients; the Anxiety section of the HADS (HADS-A) was developed to identify brief measures of generalized state anxiety and fear; the Beck Anxiety Inventory (BAI) briefly measures somatic symptoms of anxiety to help clinicians and researchers distinguish between state anxiety and depression (Julian, 2011). Neither the HADS-A nor the BAI are designed to measure trait anxiety and were therefore dismissed as possible measurement tools for the current study.

4.6 Conclusion

The core quantitative studies (articles 3 to 5) have identified that people with NSCLBP and CS have trait characteristics of sensory hyper-sensitivity, some sensory hypo-sensitivity, high trait anxiety and high trait anxiety-related personality types. Articles 4 and 5 also confirm relationships with sensory sensitivity, trait anxiety and CS symptoms. What is not clear, however, is whether these trait characteristics were present pre-morbidly; nor is it clear how these sensitivity-related traits may have evolved in the context of the lived lives of the participants with NSCLBP and CS.

The next chapter presents the concurrent supplementary qualitative study component of the current thesis, which will explore the contexts in which the CS pain developed. The findings of the qualitative study will show the context in which CS pain developed and any qualitative evidence of character traits of sensory processing differences and anxiety being present pre-morbidly. The findings will then be integrated with the results of the core quantitative study results and discussed in chapter 6.

Chapter 5

Exploring pre-morbid experiences and personal characteristics of a group of centrally sensitised people with non-specific chronic low back pain. A qualitative study.

The concurrent nested qualitative study.

5.1 Introduction

During the data collection period of the core quantitative study process, the concurrent nested qualitative study was initiated for the supplementary component. The reasons for designing a supplementary qualitative component within a mixed methods study, including the underpinning philosophical viewpoints behind the primary theoretical drive, have been discussed in chapter 3. The last chapter (chapter 4) presented and discussed the core quantitative study components of the current mixed methods study. This chapter will present and discuss the supplementary qualitative study, the findings of which will be integrated with the results of the core quantitative studies (chapter 4) in chapter 6. Below is the 'road map' to orientate the reader as to the position of the qualitative supplementary component of the thesis (figure 12).
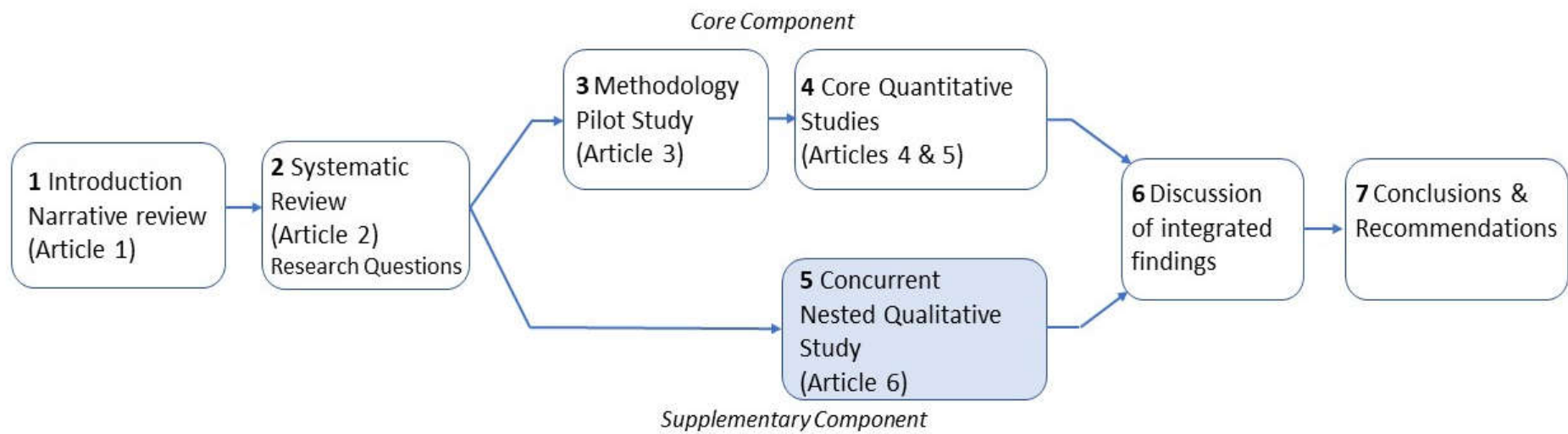
Figure 12: Roadmap through the current thesis: Concurrent nested qualitative study (supplementary component).

The primary investigator (JC) carried out the following roles in undertaking the qualitative study: purposive sampling process, sending information about the interview process out to each selected participant, undertaking the interviews (including the pilot interview) and co-analysing the data with a second researcher (GY).

A pilot interview was carried out with one participant to inform and refine the interview schedule and enable the primary researcher to become more familiar with the NVivo software used for the data management. A participant information sheet was sent out to each prospective interview participant detailing the interview process (appendix 5a). A consent form was signed prior to the interview (appendix 5b). An example of field notes following two participant interviews are included in appendix 5c. Excerpts of the full transcripts from two participant interviews are given in the appendix 5d.

All interviews were transcribed verbatim. Thematic analysis was used to analyse the data (Braun and Clarke 2006). The transcripts were uploaded onto NVivo 10 and the process of data organisation began. Initially there were copious nodes (categories) and child nodes (codes) many of which needed to be grouped together as they appeared to be inter-related. Analysis of the data began broadly in anticipation of unexpected codes and categories, as well as the theoretical data analysis related to sensory profiles and anxiety-related personality types. An example of early activity in the NVivo data organisation process is illustrated in the appendix (5e). Further organising and re-organising of data continued as the analysis evolved.

As the analysis process evolved iteratively, data were organised into themes and sub-themes from the codes and categories identified through NVivo (Braun & Clarke, 2006). All the data extracts related to each theme were transferred out of NVivo into Microsoft Word documents, an example of which is illustrated in appendix (5f). Table 35 below shows an example of the organisation of codes into categories from excerpts of the data extracts.

Table 35: *Illustration of the process of grouping data extracts into codes and categories for the anxiety category.*

Examples of participant data extracts	Codes	Category
When I look back, our life did create anxieties.	Anxiety in Childhood	
The panic would just swamp me completely.	Anxiety in Adulthood	
I felt I've got to get out of here... I had to get out because I couldn't handle it.	Behavioural Response to Anxiety	Anxiety
So I've always obviously been a bit anxious. My mum is a 'panicker'	Family traits of Anxiety	

These examples illustrate the process by which the research was undertaken throughout the qualitative study. The qualitative study has been submitted for publication to The Brazilian Journal of Physiotherapy (appendix 5g) and is now presented below.

5.2 Article 6: Exploring pre-morbid experiences and personal characteristics of a group of centrally sensitised people with non-specific chronic low back pain. A qualitative study.

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Abstract

Background and Aims: Central sensitisation (CS) pain is a predominant mechanism in a proportion of people with non-specific chronic low back pain (NSCLBP) and is associated with poor outcomes. How some people recover from NSCLBP whereas others develop CS pain remains unclear. It is proposed that the pre-morbid experiences and contexts in which the pain developed may play a role. The aim of this study was to explore the pre-morbid experiences and personal characteristics of participants with CS pain from a NSCLBP population.

Method: This was a qualitative, exploratory study, using a concurrent nested design within a mixed methods study. Twelve participants were recruited purposively from 6 groups based on four sensory profiles and personality types. Data were collected through semi structured

interviews, managed using QSR NVivo 10 software and analysed using theoretical thematic analysis.

Findings: Four themes emerged, developmental learning experiences, personal characteristics, and sensitivity and trauma. Reported was a general lack of confidence, low esteem and need to please others, physical hyper-sensitivities (smell, light, sound) and emotional sensitivity (anxiety) as well as physical hypo-sensitivity. Participants had also suffered emotional and/or physical trauma.

Discussion and conclusion: Learning difficulties, personality type, sensory sensitivities and trauma can be associated with autonomic stress responses, which in turn can be linked to physiological changes seen in CS pain. The role of pre-existing sensory processing disorders, as a component of altered CNS function in relation to CS pain warrants further investigation.

Introduction

Central sensitization (CS), when it is the predominant pain presentation, is responsible for persistent pain and poor outcomes in many musculoskeletal pain populations, such as whiplash (Coppieters et al., 2015), non-specific chronic low back pain (NSCLBP) (Nijs et al., 2015), fibromyalgia (Meeus & Nijs, 2007), osteoarthritis (OA) of the knee (Girbes et al., 2013) and shoulder pain (Sanchis, 2015). Centrally sensitised individuals experience high levels of pain disproportional to the extent of concurrent tissue pathology, with no clear pattern of provocation nor easement, and that is not distributed in the regular dermatomal patterns (Nijs, et al., 2014; Nijs et al., 2010; Smart et al., 2012).

It is not clear why some individuals develop CS pain, yet others make a full recovery. Compared to non-CS pain populations, people with CS pain show associated changes in the central nervous system (CNS), such as sensory processing (Roussel, 2013) and emotional networks (Mansour et al., 2013). It is not clear whether these differences were present prior to CS pain, or as a result of the onset of pain. Furthermore, the personal and environmental contexts in which CS pain develops might determine whether a person recovers or transitions to chronic pain.

Qualitative research is rare in studies investigating CS pain specifically, and yet it can afford valuable insight into the patient experience and lived life context surrounding their pain. Understanding aspects of pre-morbid CNS-related functioning and the contexts in which pain develops might provide insight into how CS pain arises. It was anticipated that exploring the pre-morbid lives of individuals with CS pain might help to identify areas of

interest, which will subsequently inform investigations into the aetiological factors behind CS.

The aim of this study therefore was to explore the pre-morbid experiences and personal characteristics of participants with CS pain from a NSCLBP population.

Methods

Theoretical framework

The primary theoretical drive was based on that of the concurrent quantitative stud component of this mixed methods study (articles 3 to 5). The present study was underpinned by a post-positive philosophical position paying attention to: (1) the quality of the data, whereby questionnaires are one dimensional and do not give voice to the context and reasons behind answers; (2) the use of an integrated approach whereby subjective experiences account for some of the pain outcome being studied; and (3) the context of the targeted phenomenon, in this case, the development of CS pain (Adam, 2014). This study is reported according to the Standards for Reporting of Qualitative Research (SRQR; O'Brien et al., 2014).

Design

This is a qualitative, exploratory study, using a concurrent nested design within a larger mixed methods study.

Recruitment and Sampling

Participants were recruited from the quantitative sample by purposive sampling (Tashakkori & Teddlie, 2010). Following a pilot study (Clark et al.) in press), potential participants were stratified into N=6 groups based on their sensory profiles and personality type combinations. N=12 individuals were purposively selected (N=2 from each group). Individuals were provided with information about the study prior to giving written consent. Those who consented were given the option of being interviewed in their own home, at a physiotherapy clinic, or the University campus.

Interview schedule

Questions for the interview schedule were derived from the literature around sensory sensitivity and trait anxiety and from information which emerged from the pilot study, (Clark et al. *in press*). The interview schedule is summarised in table 36. Interviews were digitally recorded and transcribed verbatim. Transcripts were sent to each participant for verification. Participant anonymity was assured through allocation of a number (P1-9). Data were protected by password encryption and managed using NVivo 10 software (NVivo, 2012).

Table 36: The interview guide used for centrally sensitised people with non-specific chronic low back pain, to understand the context in which CS developed in relation to pre-morbid anxiety and sensory sensitivity characteristics.

Topics	Questions and Prompts
Opportunity to enlarge on their questionnaire responses.	Invite any comments regarding questionnaires
What are their current pain experiences?	1. coping strategies with pain, 2. what environmental factors might aggravate or ease their pain (particularly in relation to sensory processing and anxiety traits.) 3. How have they adapted their environment to manage their pain. From this make note of words they've used and return to them.

Were they hyper-sensitive to sensory stimuli pre-morbidly?	1. Sensory sensitivity (explore sensory thresholds: hyper- or hypo-sensitivity)
	
	2. Explore awareness and behavioural responses: "Tell me about…"
	
	    i. Do they feel sensory overwhelm? E.g. responses to light / busy malls / smells / travel sick etc.
	
	    ii. Do they feel under-stimulated, e.g. need to move / get out of house/ put loud music on etc.?
	
	    iii. What does this feel like? "can you give examples?"
	
	    iv. How do they respond? (does this match sensory profile?)

Explore possible reasons for pre-morbid sensory hyper-sensitivity	Schooling, sports, academic experiences, family and social environment, anxiety, traumas etc.
Were they prone to anxiety pre-morbidly?	How much are they aware of experiencing anxiety now and did they pre-mobidly? Note any references to high pulse rate / high breathing / 'air huger' / feeling "frazzled" 1. How aware are they when they become anxious and when did they start noticing anxiety? 2. When / what tends to trigger feelings of anxiety? "Can you give examples….." Does it seem to relate to worry, or sensory overload? 3. What do they do about it? (including not attending to it – Repressors; Does this match personality type?)

Ethics

Ethical approval was granted by Manchester Metropolitan University, United Kingdom (UK) (ref:1205) and permission was granted by the Northern Y Ethics committee, New Zealand (NZ).

Data analysis

Data were analysed using a 'theoretical' thematic analysis approach. Analysis was driven by the analytic focus of the primary theoretical driver in the concurrent quantitative study. 'Theoretical' thematic analysis provides a detailed analysis of certain aspects of interest predetermined by the researcher (Braun & Clarke, 2006). The aspects of interest were around pre-morbid trait characteristics related to sensory processing and personality.

Transcripts and field notes were used for analysis. Field notes assisted understanding contexts in which interview data were given. Transcription data were analysed using thematic analysis according to guidelines by (Braun & Clarke, 2006). Data were coded from participant data extracts and collated into categories. Categories were grouped into themes and sub-themes. Two researchers [JC and GY] analysed the data independently and were in substantial agreement over the final themes following the discussion of any semantic differences.

Participant demographics will be presented followed by data under the theme and sub-theme headings.

Participants

N=12 participants were initially identified from NZ and the UK. N=4 participants were lost to the study: N=2 participants could not be contacted (N=1 in UK, N=1 in NZ), N=1 UK participant declined due to unavailability at the time of the interviews, and N=1 because she felt she had recovered from her NSCLBP. N=1 further participant was recruited from New Zealand so a total of N=9 participants were interviewed, N=8 from NZ and N=1 from UK.

Participants were aged 28 to 64 years, N=6 female and N=3 male. Based on scores from the Adolescent, Adult Sensory Profile (Brown & Dunn, 2002), N=3 participants scored in the extreme ranges for the Low Registration sensory profile. All scored in the extreme ranges for the Sensory Sensitive Sensory and Sensation Avoiding profiles. Based on measures of trait anxiety and defensiveness (Weinberger et al., 1979), personality types included N=4 Defensive High Anxious, N=3 Repressor and N=2 High Anxious individuals. N=5 participants had widespread pain (WP) as well as non-specific chronic low back pain (NSCLBP), the others had regional NSCLBP (Table 37). Data saturation was reached from the 9 interviews

Table 37: Participant demographics: identification (ID) label, age, trait sensory profile and personality type characteristics, and the presence of widespread pain (WP).

ID Label	Age	Male / Female	Sensory Sensitive	Sensation Avoiding	Sensation Seeking	Low Registration	Defensive High Anxious	High Anxious	Repressor	WP
P1	50	F	++	+	-	++			*	*
P2	52	M	N	N	-	++			*	
P3	28	M	++	++	N	++		*		*
P4	56	F	++	++	N	+	*			
P5	41	F	++	++	N	-	*			*
P6	64	F	++	++	N	N	*			
P7	45	F	++	N	N	N			*	*
P8	57	F	+	N	N	N	*			*
P9	49	M	++	++	-	++		*		

Key: ++ Much more than normal; + more than normal; N normal; - Less than normal, -- much less than normal. 'P' indicates the words of the participant and 'I' those of the interviewer.

Four themes emerged: Developmental Learning Experiences, Personal Characteristics,

Sensitivity and Trauma (Table 38). Findings in relation to each theme were divided into sub-

themes and sub-headings. Due to the complexity and number of elements included, sub-

themes overlap. The data extracts related to each theme are listed in table 39.

Table 38: Themes grouped into sub-themes, categories and codes

Theme	Sub-theme	Category	Code
1 Developmental Learning Experiences	Developmental learning difficulties and weaknesses	Learning difficulties	Dyslexia
			Attention Deficit Hyperactive Disorder
			Dyspraxia
			Poor speech processing
			Poor auditory skills
		Behavioural difficulties	Fights with teachers
			Fights with siblings / friends
			"got to get out" behaviour
			Relationships at school
		Sport and motor control difficulties	"Could never swim"
			Uncoordinated
			"Hated sport"
	Developmental Learning Strengths	Learning style strengths	Visual skills
			Maths skills
			Memory skills
			All round academic skills
		Sport an motor skill strengths	"Good at Running"
			All round athlete
2 Personal Characteristics	Confidence	Self-efficacy	Pushing through
			Active response to difficulties
		Self-identity	Own meaning and interpretation of life
			Self-image
		Self esteem	Teacher's opinions
			Putting self down
			Not meeting own expectations

	Sense of Control	Diligence	Organised / perfectionist
			Needing to achieve to own expectations
			Competitive
			Push self beyond limits
		Response to adversity	Response to negative feedback from parents/teachers
			Response to abuse
			Passive response to difficulties
			Feeling isolated
			Feeling overwhelmed
		Controlled by others	"I don't understand"
			Feeling judged by others
			No-one listens
			People pleasing
			Forced upon by others
			Feeling out of control
3 Sensitivity	Emotional sensitivity	Anxiety	Anxiety in childhood
			Anxiety in adulthood
			Behavioural Response to Anxiety
			Family Traits of Anxiety
		Sensitive to the opinion of others	Sensitivity to injustice
			Teachers / parents' responses
			Sensitivity to unmet expectations
	Physical sensitivity	Sensory hyper-sensitivities	Sound and Light sensitivity
			Sensitive smell
		Behavioural response to sensory overload	Tactile sensitivity
			Food taste and texture sensitivities
		Sensory hypo-sensitivities	Reduced smell sense
			Reduced body feedback
3 Trauma	Physical Trauma	Physical Abuse	Adult physical abuse from spouse
			Childhood physical abuse from other children

			Childhood Physical abuse from adults
		Accident-related trauma	Accidental trauma to self
			Accidental trauma of loved ones
	Emotional Trauma	Emotional Abuse	Emotional abuse from parents
			Emotional abuse from teachers
			Emotional abuse from spouse/partner
			Teasing / bullying at school
			Bullying at work
			Emotional abuse from parents
		Loss	Death of parent in childhood
			Loss of identity
			Loss of possessions
			Loss of trust

Table 39: Direct quotations representing identified themes and subthemes from centrally sensitised people with non-specific chronic low back pain

Theme 1: Developmental Learning Experiences

Sub-theme: Developmental Learning Difficulties and Weaknesses

"Academically I failed 5th form. I worked out I don't quite learn that way … I learn more by being shown how to do it, and then doing it, rather than being lectured about it". (P5)

"I did struggle to learn just off the ... off the board, I needed someone to actually show me it. (P3)"

"P: I hated school. I didn't learn that way. I don't learn now that way.
I: So what was 'that way'?
P: Ok - see I'm a big picture person … You see I think I learn pictorially … books and magazines, but pictures … I pick them up, and then I translate them". (P4)

"Yeah, and homework was just such a battle. I struggled. I've always struggled with maths – that was my worst subject … I was in mathematics with applications which meant maths for dummies". (P5)

"I used to be distracted, like I couldn't sit in a class and there might be something going on out ... out the window like a caretaker or something, and I always ... I was always tempted to leave just like that, straight away". (P3)

"A lot of my behaviour was based on sheer frustration, but sometimes teachers thought it was just me misbehaving". (P3)

"I had really good balance but the most crappiest co-ordination you've ever seen. If I threw a stone it would come down and hit me on the head. I couldn't catch a ball and I couldn't kick a ball". (P2)

Sub-theme: Developmental Learning Strengths

"Yeah and I can pull things apart once and remember how they go together … Yeah I've got a very good memory for that". (P2)

"But at intermediate and at college I was usually put in the accelerant for things like maths. I was always sort of like really, really good at spelling, and English and grammar, they were my sort of strong suits at school". (P8)

"I wasn't fast – I just had the stamina to keep going … I couldn't swim very well. You're either a runner or a swimmer – you're not both - and I was a runner … I … did not want to go to school swimming sports, because … because everyone else could swim, and I couldn't swim in the pool". (P1)

Theme 2: Personal Characteristics:

Sub-theme: Confidence

> *"(The convent was) really where I wanted to go ... And if I'm really truthful today, that's where I'd like to be. That is me, that is who I am ... that is who I am. I'm a woman of prayer and a lover of God ... that is me". (P6)*

> *"I really struggle with low energy because I'm a person of high energy and motivation. So ... I really struggle with it". (P3)*

> *"I do believe that what you go through as a child it shapes your core beliefs. It shapes your core beliefs, and in my family you just get on with it, you don't complain". (P5)*

> *"I think.. a lot of how I grew up was feeling subdued, feeling like I had to be different. I had to be like them, and I wasn't". (P4)*

> *"And ... if I'm thinking I'm stupid, well they're going to think I'm stupid ... so there was two people at the table I didn't know, and because I didn't know them, I was tense and stressed for at least the first hour or so. Yeah because it was just out of my comfort zone cause I didn't know them. Yeah which is silly – it does seem silly". (P5)*

> *"I've learnt to relax in terms of you can only do what you can do, you can only influence what you put your hand to so don't stress out. And I've learnt to ... even though I may not be able to spell, but I can read it, learnt to write lists or write things down..." (P3)*

> *"I just had the stamina to keep going. Mm. Just keep going in life. I don't know, I just put up with it, I just put up with life really". (P1)*

Sub-theme: Sense of Control

> "It should be like this. … I think 'this' was like harmony, like everyone … everyone is in harmony, and there's understanding, and it's happy and it's joyful. Yeah it's harmonious. It's not disjointed and fragmented … it's not fragmented. I felt my life was very fragmented, and I felt very much alone". (P6)

> "In my mind if I didn't get something done, if there was a deadline or there was going to be some kind of negative problem from it, I would push myself, I would just carry on and do it even though I knew that I wasn't really being very kind to myself". (P7)

"I have to learn to say no, so I'm learning to say no to things … Never (said) no. … I think it was the fear. It was a fear of upsetting someone". (P7)

"Yeah, I just couldn't handle that. I used to have to go away and crawl under the house ... So you lived this life of, "wait a minute, if this is how it is then I'm the only one, I have to take control of me. I have to really make sure that I know what I'm doing and no-one, and I repeat no-one, is going to shake that." (P6)

Theme 3 Sensitivity:

Sub-theme: Emotional Sensitivity

"So I've always obviously been a bit anxious. My mum is a 'panicker' … Yeah, and she'd install her fear into me I guess without knowing it, and that would make me anxious, you know. Yeah. … It was like 'oh my goodness', and that would just instantly put anxiety into me". (P2)

"I absolutely panicked over exams, just panicked in exams and go completely blank just because of the stress of not doing well, more than anything. … My mum always used to say before exams, 'now we know you've worked really hard so don't worry,' and then if I didn't get anything there or what they thought I should get I was in terrible problems – trouble". (P7)

"It's so weird [chuckles]. It's all very, very odd, but yeah I … yeah I worry about what people think too much". (P5)

"… if I have made a mistake I beat myself up ... to quite some considerable amount…. And I've got a big thing about being normal and not showing anyone any type of weakness. And if people do find that weakness and sort of make a joke about it, it hits home pretty hard". (P3)

"I've always thought, and I don't know if it's exact anxiety as such, but I've always thought if I haven't got something to worry about I'll make something up … yeah my dad's a worrier, his mother was a worrier, you know, it's a bit of a family trait" (P8).

"I think again, seeing my kids is very interesting because I think there's definitely a natural genetic in it that they're sensitive to people. Particularly (son) and (daughter) are both similar to me in that they're very sensitive … well they're all sensitive to other people's feelings, but they are very sensitive to people and what they think and getting things wrong. Yeah so I think for me there's a combination of already being like that naturally…" (P7)

Sub-theme: Physical Sensitivities

"Yeah, well I know I've got sensitivity to light. I don't recall how long that's been going on, but ... needing sunglasses on even if it wasn't bright sunlight". (P8)

"I'm massively sensitive to sound. I get very irritated with sound, any kind of repetitive sound. And there's one particular kind of music which … is it house music where it's just like the same beat all the time, I literally feel like I want to hit my head against a wall. Yeah sound is one thing, but then the sound of water or something I really like, but there are certain sounds that can very quickly get me highly irritated". (P7)

"I know I've always been startled easily by loud noises, like somebody popping a balloon or oooh!" (P8)

"…but too strong - if it's a bad smell, like turps or kerosene - and I can smell burning a mile off - I became afraid of smell … The smell I was actually nauseous". (P1)

"Oh I bounced – oh yeah I bounced. Mum would say to me too much cheese would affect me, but yeah different foods … But I had to be a bit careful…". (P2)

"It's the texture and the thought of biting down. I mean I've tried a few new foods but I can't even tell you what they taste like because the anxiety level was so high and the thought of chewing down on them is just … (screws up face) … Like even now when I roast the chicken I use tongs to pull the meat off, … there's no way I'd touch them". (P5)

"Often in the evenings I will do my fitness, then come home and that's when I tend to just sort of almost like blob out, just watch something and just try and block all things out. And there's often ... if I get too over-stimulated I can't get to sleep at night". (P3)

"So yes, and I also get quite – not panicky exactly, but agitated if I've got too much going on in the week". (P8)

"It doesn't bother me – strong smells [chuckles]. I've worked with sewerage pumps [laughs] … I don't smell things that other people say they smell, frequently". (P2)

Theme 4 Trauma:

Sub-theme: Physical trauma
Some described physical abuse:

"…And he just grabbed me and smacked me, like kept on punching me and punching me and punching me and punching me and punching me. And he

grabbed a knife and held it to my throat, and that was it, my life was over. … He used to smash all my stuff - … He used to, you name the abuse, he just didn't care". (P1)

"I mean I used to get smacked, I suppose in those days you'd call it. Well the nuns used to strap me. Oh, they would strap me for being naughty, and I would just go, "I was just having fun". (P4)

Others described physical trauma related to an accident:

"It was massive disappointment because I loved it so much and it was really, really fulfilling in every way, sort of emotionally, physically, everything. So yeah it's sort of very hard to then think well what can I do, because you're so fulfilled with what you do…" (P7)

"And then (daughter) was in a car accident when she was ... she was 17. So that actually's when all of this started". (P8)

Sub-theme: Emotional trauma

"I had a husband before [husband 2] – [husband 1] … he also was abusive … He used to threaten to burn me in my bed, standing with petrol cans and a lighter, and go "shall I do it now, shall I burn you now?" (P1)

"I mean I wasn't (physically) abused as a child or anything like that, but I think there's different ways of damaging children… But I mean mum used to try to get me to eat things, and (step-father) used to really try to the point where the house would just be a tense, stressful, shouting, horrible place to be at the dinner table, every single night". (P5)

"'Cos then my cousin was killed when she was just 18, and her parents I ... you know, spent my holidays with so I was really close with her. And then (daughter) was in a car accident. So that is actually when all of this started … I still feel like the worst of everything started up at that accident, the last accident". (P8)

"Growing up with only one parent I think is going to be stressful for a start … So my first stress – obviously my mother (dying). And this is what I think all of this stems from is post-traumatic stress". (P8)

Theme 1, Developmental learning experiences, related to childhood and adolescent

experiences of school and the environment in which they grew up. Participants described

diagnosed difficulties in learning such as dyslexia, or related disorders such as dyspraxia and

ADHD. Other participants described differences in learning preferences but who had never received any formal diagnoses. Difficulties holding attention in class and a tendency towards boredom was reported by nearly half of the participants. A few participants described themselves as poorly coordinated in sports and play activities as a child; this was found in participants who had learning difficulties and a Low Registration sensory profile, characterised by reduced sensory feedback and slower movement (Brown et al., 2001).

Participants with learning difficulties also displayed learning strengths in other aspects of their development. Contrary to learning difficulties, two of the participants demonstrated all round learning strengths and intelligence, such as reading, writing and maths. Conversely to having all-round sports strengths, two participants (both with extreme scores in the Low Registration sensory profile) described themselves as having strength in only running sport but being uncoordinated in other motor skills.

Theme 2, Personal characteristics, determines how a person copes with challenges and unexpected events as well as aspects of resilience and confidence. Personal characteristics also determine behavioural responses and their tendency to interpret situations in a positive light or, alternatively, as situations which are threatening. The theme of personal characteristics encompasses two sub-themes, Confidence and Sense of Control.

Confidence covers aspects of attitudes and behaviours related to self-confidence, such as self-efficacy, self-esteem and self-identity. Having a strong sense of self-identity appeared to have a positive and a negative impact on individuals. Self-identities appeared to be enduring

and learned from childhood. A negative impact of holding to these strong identities meant that a few of the participants developed a tendency to push themselves past their limits of wellbeing. A mismatch between expectation and the real lived experiences often led to low self-esteem and a sense of being weaker than peers.

A Sense of control encompasses the categories of diligence and responses to adversity, both of which relate to behaviours of staying in control; and being controlled by others. Responses to adversity to regain a sense of control varied from active through to passive responses across the group and this appeared to relate closely to their individual trait sensory profiles and personality types.

Theme 3, Sensory sensitivity, relates to the reception and perception of sensory stimuli, with higher sensitivity implying a lower neurological threshold for stimulation. Sensory sensitivity was apparent in the lives of all participants and presented in various forms of emotional and physical sensitivities. A large component of emotional sensitivity was anxiety, in which individuals were prone to responding to potential or actual threats with anxiety. Other emotional sensitivities emerged which were sensitivity to the opinion of others and sensitivity to injustice or unmet expectations. Physical sensitivity included sensitivity to touch, sound, light, smell and body feedback, as well as sensitivity to certain foods and food textures. Participants varied in their responses to sensory discomfort depending on their individual sensory profile.

All participants reported various physical sensitivities. Most participants reported high sensitivity, not handling as much as they considered they should in terms of certain physical stimuli, possibly suggestive of sensory hyper-sensitivity. A small number also reported they were unable to feel or sense certain sensory stimuli as much as others or as much as they thought they should, possibly suggesting sensory hypo-sensitivity. There was clearly overlap between sensory discomfort and emotional response, such as feelings of anxiety, linking together physical and emotional sensitivity.

Theme 4, Trauma, relates to both emotional and physical trauma. Emotional trauma was experienced in the forms of abuse, being controlled by others and in personal loss and overlaps with physical trauma. Physical trauma was experienced by many participants in the form of physical abuse and accident related trauma. Emotional trauma was reported by many of the participants, some as a result of abuse from others and some as a result of circumstances outside of their control, such as loss, or being controlled by others.

Discussion

The aim of this study was to explore the pre-morbid experiences and personal characteristics of participants with CS pain from a NSCLBP population and this is the first time this has been done. The emergence of the theme of developmental learning experiences was unexpected, in so much as a large proportion of the study group appeared to have diagnosed or undiagnosed learning difficulties. Learning difficulties, such as dyslexia, have only been recognised relatively recently in terms of formal diagnoses in New Zealand (Gregory, 2007).

Learning difficulties are associated with sensory processing differences (Davies et al., 2009; Dunn et al., 2002). The way the CNS processes sensory information affects learning function (Engel-Yeger et al., 2011). Learning difficulties are associated with impaired sensory gating which includes sensory hypo-sensitivity and hyper-sensitivity (Davies et al., 2009; Engel-Yeger et al., 2011). The latter is characteristic of CS pain (Latremoliere & Woolf; Nijs et al., 2014; Smart, et al., 2012) and reported by participants in the current study. The sensory processing differences seen in people with learning difficulties are likely to alter sensory-motor function whereby gross motor skills decrease with increasing learning disability (Westendorp et al., 2011), noted in the sports performance reported by some of the participants in the current study.

Our data supports links between sports skills and developmental learning strengths. The most versatile sports skills belonging to the women with the most normal sensory profile scores. Both women (P7 and P8) also alluded to long term tendencies towards anxiety through emotional sensitivity. They might have experienced ongoing stress responses due to anxieties rather than sensory processing difficulties.

Personal characteristics involving people pleasing and being goal focussed appeared to motivate people to continue pushing themselves beyond their capacity creating stresses. Participants with repressor personality types appeared to under-play negative affect and report seemingly stressful situations with a "positive spin." Repressors are known to respond to stressors with autonomic arousal but remain positive in their reporting of

information about themselves (Derakshan et al., 2007). Participants with high anxious or defensive high anxious personality types reported many events as stressful, such as being bullied for their learning difficulties, difficulty in sports or academics at school, and are therefore more likely to have regularly been prone to physiological arousal through autonomic stress responses.

Sensory hyper- and hypo-sensitivity emerged as having been present from a young age in many participants. This supports the results of other work (Clark et al., *in submission*), in which extreme scores in sensory hyper- and hypo-sensitivity profiles were found in people with CS and NSCLBP. Pre-morbid hyper-sensitivity found in the current study also supports of the results of a systematic review (Clark et al., 2017) in which pre-morbid or baseline hyper-sensitivity (using quantitative sensory testing or genetic markers) was a factor in the development of CS pain.

Sensory hyper- and hypo-sensitivities have been found by others to be associated with autonomic stress responses in young people (Gomez et al., 2017). Similarly, trauma is known to create a stress response in the traumatised individual, involving autonomic arousal and behavioural responses (Schouten et al., 2013). Trauma and childhood adversities are also prevalent in the lives of people with various CS pain disorders such as fibromyalgia and somatoform disorders (Walker et al., 1997; Imbierowicz and Egle Ulrich, 2012) although the mechanisms leading to CS are unclear.

Trait anxiety-based personality types are said to be developed from a young age and are linked to the development of   defensive coping strategies employed during difficult times in

youth (Weinberger, 1998). Individuals do not "grow out of" learning difficulties or associated sensory processing disorders, they persist into adulthood (Paul et al., 1990). Persistent sensory processing disorders can include auditory and visual perception, speaking, maths, reading, spelling and coordination difficulties (Paul et al., 1990). All of these were apparent in the lives of most of the participants in this study. Some of these disorders of the CNS may overlap with those seen in people with CS pain (e.g. visual processing disturbance in (De Kooning et al., 2017; Don et al., 2017).

A common link between sensory sensitivity and trauma is in the stress response, which may heighten sensitivity to sensory stimuli through the upregulation of glial cells and neuro-inflammation in the CNS (Nijs et al., 2017). Furthermore, post-morbidly, CS pain may heighten emotional sensitivity in people with high trait anxiety, by increasing state anxiety. Physical sensitivity to various sensory stimuli was reported by all the participants and a few were even hypo-sensitive. Extremes of sensory sensitivity are associated with sensory processing disorders (Davies et al., 2009; Holstein et al., 2013) and anxiety (Ansari and Derakshan, 2011) and relationships between these and CS pain require further investigation.

Strengths and limitations

The interviewer was an experienced physiotherapist with a clinical knowledge of people with CS pain. This, as well as information from the pilot study, helped inform the interview schedules and direct the theoretical thematic analysis (Braun & Clarke, 2006). No participants reported being uncomfortable during the interviews and no participant having

difficulty expressing their opinion/experience. The quality of the data was ensured through verification by each participant and rigor was improved through having a second data analyst. This study did satisfy our requirements for theoretical representativeness i.e. both male and female participants and representative of all personality type.

Memory recall of past events among the interviewees may have been influenced by personality type (Myers, 2010). All participants had sought treatment and therefore may not reflect people in the community who self-treat or do not seek physiotherapy.

Conclusion

This study explored pre-morbid experiences in people with CS pain in order to develop a better understanding of sensory profiles and personality types in this population. Four main themes were identified, developmental learning experiences, personal characteristics, and physical and emotional sensitivity and trauma. There was a general lack of confidence, low esteem and need to please others, although most had coping strategies. All participants recounted multiple physical hyper-sensitivities such as smell, light, sound and/or emotional sensitivity and a few reported physical hypo-sensitivity. Many had suffered emotional and/or physical traumas pre-morbidly. All themes may be related to stress responses in the CNS, and in turn may be linked to some of the physiological changes seen in CS pain. Further investigation into the role of pre-existing sensory processing disorders, as a component of impaired or altered CNS function, in relation to CS pain is warranted.

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5.3 Discussion

To date this remains the only study to explore pre-pain lived experiences in people with NSCLBP and CS. However, a recently published thesis (Peplinskie, 2016) showed some similar findings in a group of women with fibromyalgia, a condition characterised by CS pain (Clauw, 2009). When asked to talk about momentous events in their past and events which may have initiated their pain, Peplinskie found that there was a tendency to recall previously endured hardships (pre-pain), down-play the severity of traumatic life events and hold the responsibility of being a care giver. Although the study participants were people with fibromyalgia and not NSCLBP the characteristics of people with fibromyalgia are similar to those in the current study with NSCLBP in the following ways:

1. Individuals with NSCLBP and CS in the current study were willing to disclose traumatic events;

2. The participants with a repressor personality type appeared to down-play the severity of seemingly traumatic events;

3. Some participants were care givers, although this was not specifically explored in the current study. However, if being a care giver can be interpreted as being a situation involving being 'controlled by other' circumstances emerged and / or feelings of loss of control, then it may be that there is some overlap between the current study theme of 'confidence and control' and the theme of 'acting as care giver' in (Peplinskie, 2016). Peplinski characterised the theme of 'acting as care giver' as involving the "giving scarce heed to one's own needs while elevating the desires of others" (Peplinskie, 2016; p.109). This is similar to the sub-theme of people pleasing in the current qualitative study.

If this qualitative study were to be repeated as a stand-alone study, a different analysis procedure may yield more information, such as an inductive thematic analysis from data collected through an unstructured interview. Inductive thematic analysis is the process whereby the data is coded without trying to fit it into the preconceived ideas or a predetermined coding framework (Braun & Clarke, 2006). In other words, analysing the data without the pre-conceived theory of sensory processing alterations and anxiety characteristics may provide the opportunity to yield different information about the contexts in which CS pain developed in people with NSCLBP and CS. However, the over-arching research question relating to the qualitative study was specific to a pre-conceived theory and driven by a quantitative theoretical perspective (Morse, 2010).

Many of the participants had experienced trauma and adverse childhood experiences. It is already recognised that adverse experiences in childhood have a deleterious affect on health and quality of life (Corso et al., 2008) and this may be related to the development of CS pain. The first study in adverse childhood experiences (ACE) was published in 1998 (Felitti et al, 1998) which began 20 more years of research into ACE. The research (ACE, 2018) showed that childhood trauma was very common and that it was linked directly to adult onset of chronic disease, depression, suicide, being violent and being a victim of violence; accounts like these were apparent in the qualitative data in article 6.

Further questions which emerged from the current qualitative study for investigation are discussed in the next chapter (chapter 6).

5.3.1 Limitations

On reflection it may have been of benefit to have reported more demographic data regarding the interview participants to further enrich the context for the reader. For example, how long they had been experiencing their pain, how many treatment providers had they seen for their pain, if they were they still working or unable to work due to their pain.

5.4 Conclusion

This chapter has presented the process and findings in the concurrent nested qualitative study, including the presentation of the research report. The themes of sensitivity, developmental learning experiences, personal characteristics and confidence and control emerged. The next chapter will discuss the integration of the findings from the current qualitative study with the results from the core quantitative component shown in chapter 4.

Chapter 6

Discussion of the integrated results and findings from the mixed methods study and future directions.

6.1 Introduction

This chapter will discuss the integrated results and findings of the mixed methods study, the three articles from which were presented in chapters 4 and 5. It will begin with a reiteration of the research questions followed by a discussion on stressors. Subsequently, how the themes found in the supplementary qualitative study might inter-relate with the results relating to extreme trait sensory sensitivity profiles, including hypo-sensitivity, trait anxiety, personality types and central sensitisation symptoms in people with non-specific chronic low back pain (NSCLBP) and central sensitisation (CS) will be discussed. The roadmap below (figure 13) may help orientate the reader, indicating the position of this discussion chapter in the thesis. A hypothesis of the proposed pathway to CS in people with NSCLBP will be illustrated to conclude the discussion (figure 14; see section 6.6).
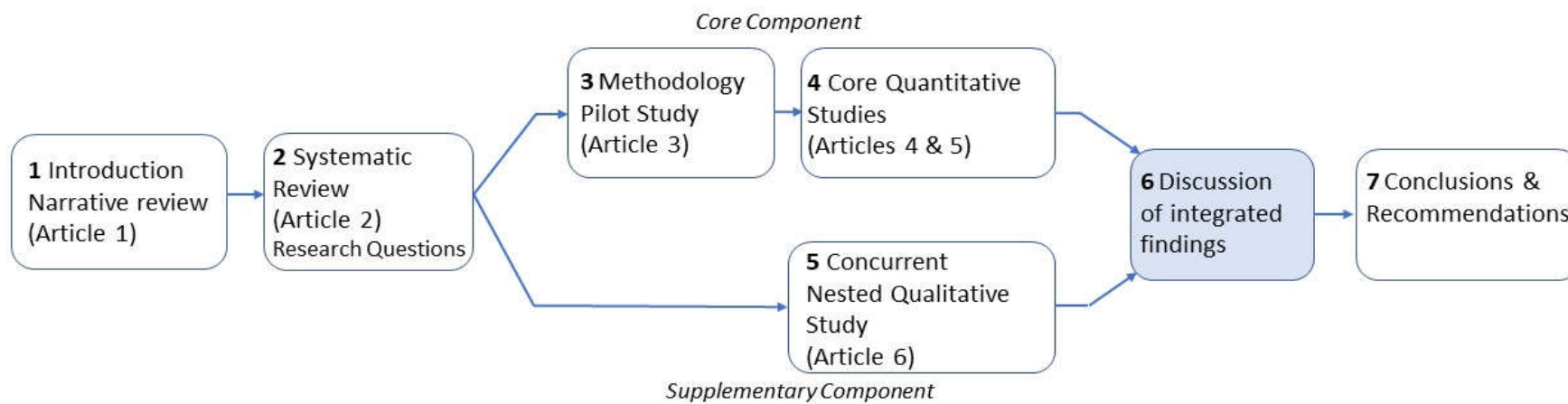
Figure 13: Roadmap through the thesis: Discussion of integrated findings and conclusions.

6.2 Thesis Objectives and research questions reiterated

The over-arching objective of this thesis was to investigate sensitivity-related trait characteristics of centrally sensitised people from a non-specific chronic low back pain (NSCLBP) population and to explore how these characteristics might be related to CS pain. The primary focus of this thesis was CS in patients with NSCLBP and the pre-morbid factors, which in turn may have contributed to its aetiology. The main phenomenon of interest was the autonomic physiological arousal which occurs in the event of over-stimulation by stressors and which leads to heightened sensitivity (Eysenck, 1997). It was hypothesised that physiological arousal would be more likely to occur in individuals with NSCLBP who have pre-morbid high sensitivity and trait anxiety and that the outcome of CS pain would be partly dependent on the behavioural responses of the aroused individual with NSCLBP (article 1). The study therefore set out to ask the following research questions in two components:

Core component:

- What aspects of (pre-morbid) sensitivity of character, specifically sensory sensitivity profiles, trait anxiety and personality types, can be observed in people with CS pain, in a NSCLBP population?

- What are the relationships between these characteristics and the extent of CS symptoms?

For these aspects a core quantitative design was implemented.

Supplementary component:

- How do pre-morbid contexts in which CS pain developed relate to trait sensitivity and anxiety-related characteristics in a sub-group of the core component participants?

- Can the existence of the observed characteristics found in the core component be confirmed as likely to have existed pre-morbidly?

For these aspects a nested qualitative design was concurrently implemented.

The outcomes were two-fold for people with predominant CS pain in a NSCLBP population: 1) premorbid trait characteristics and contexts were identified. This provided further research implications for predicting CS pain in a longitudinal study; and 2) sensitivity-related characteristics were identified as predictive of the extent of CS symptoms, providing implications for the development of   potential treatment strategies.

The results of the core component showed that people with predominant CS pain in a NSCLBP population:

1. Clinically classify as having predominant CS pain yet a sub-group report lower levels of symptoms of CS (Central Sensitisation Inventory (CSI) scores < 40);

2. Show characteristics of extreme trait: a) sensory hyper-sensitivity profiles (Sensory Sensitive and Sensation Avoiding), more so in the high CSI sub-group; and b) sensory hypo-sensitivity (Low Registration) in both the low and high CSI sub-groups;

3. Show characteristics of high trait anxiety-related personality types (defensive high anxious, high anxious and repressor): a) a high prevalence of defensive high anxious and high anxious individuals across the study population of people with NSCLBP and CS; b) significantly more repressors in the low CSI sub-group; and c) significantly greater levels of trait anxiety in the high defensive anxious and high anxious individuals in the high CSI sub-group than in the low CSI group.

4. Are predicted to experience greater levels of CS symptoms when they have:

a. Extreme Sensory Sensitive and/or Low Registration profile scores; and / or

b. High trait anxiety, and / or

c. An extreme defensive high anxious personality type.

The contexts of the sensory processing differences and anxiety-related factors emerged from the qualitative data in the supplementary component. The findings in the supplementary component for people with predominant CS pain in a NSCLBP population identified four themes around pre-morbid traits and experiences:

1. physical and emotional sensitivities,

2. physical and emotional traumas,

3. developmental learning experiences including sensory processing disorders, and

4. a low sense of confidence and control.

The themes found in the supplementary component are inter-related and may be closely linked with the trait sensory profile, trait anxiety and personality characteristic results found in the core component. Each factor is discussed individually in each research study (articles 4 to 6). This chapter will now discuss the integrated study findings from the quantitative (core) and qualitative (supplementary) components, their possible inter-relationships and how the findings relate to the wider literature. It will begin by laying the foundation to argue that autonomic physiological arousal and heightened sensitivity occurs more in prone individuals in response to stressors.

6.3 Stressors

Two aspects are to be considered with relevance to the heightened sensitivity seen in CS: stressors and stress responses. Stressors are stimuli which disrupt the homeostatic equilibrium of the individual and which are perceived by the organism as novel, unpredictable or uncontrollable (Ehlert et al., 2001; Koolhaas et al., 2011). Such stimuli may be related to over- or under-stimulation of the senses (Aron & Aron, 1997; Brown et al., 2001; Heller, 2003), psychological stressors (Eysenck, 1997; Spielberger, 1983; Speilberger & Vagg, 1984), experimentally induced emotional or physical stressors (e.g. Haggman et al., 2010) or stimuli from ingested substances such as caffeine or certain foods, which emerged in the interview data in the supplementary qualitative study (article 6). A stress response is a reaction of the organism aimed at regaining control and homeostasis involving two processes – physiological arousal and a behavioural response (Koolhaas et al., 2011). The physiological arousal is activated through the hypothalamic pituitary adrenocortical (HPA) axis and the sympathetic adreno-medullary system (SAS), and is an important pre-requisite in the preparation and support of a behavioural response to the stressors (Koolhaas et al., 2011).

The physiological arousal can be measured in physical terms, such as heart rate, skin conductance and resistance, salivary cortisol. These measurements are often taken during experiments in which individuals is subjected to sensory stimuli designed to induce state anxiety (Eysenck, 1997; Koolhaas et al., 2011). Physiological arousal may occur in the absence of perceived threat when homeostasis may be threatened. Examples of this can be found in the somatic symptoms of physiological arousal (such as tachycardia and tremor) seen in Grave's disease, thought to be a result of thyrotoxicosis (Trzepacz et al., 1989) and in

cases of intake of dietary stimulants such as those described by interview participants in the supplementary qualitative study (article 6). It is therefore proposed that the physiological arousal may occur even in the absence of conscious threat perception and that sensory over-or under-stimulation may be an unconscious source of arousal. Once the physiological arousal is perceived by the individual then it is subject to cognitive evaluation (Koolhaas et al., 2011). Evaluation is partly dependent on interpretation of the source of the arousal and in people with high anxiety, the source can be misinterpreted in relation to pain (Rosa-Esteve & Camacho, 2008). It is hypothesised that when symptoms of physiological arousal are perceived, and these have been generated through stimulation from non-noxious stimuli (such as caffeine or food sensitivities or sensory discomfort from sound or light, as seen in the interview data in article 6) and 1) they are not attributed to these sources and 2) are interpreted as threatening in relation to their pain condition, the sensations may then be experienced as pain.

Interpretation of the sensations of physiological arousal and perceived sensory discomfort is likely to depend on the nature of individual personality types and the active or passive response tendencies. Personality types will be discussed in section 6.6.1 below. First, sensory sensitivity will be discussed in light of the results of the current thesis and the wider literature.

6.4 Sensitivity and developmental learning experiences

Results of the core quantitative studies (articles 4 and 5) showed a high prevalence of extreme scores on the sensory hyper-sensitivity profiles (Sensory Sensitive and Sensation

Avoiding). Furthermore, the extent of CS symptoms could be predicted by scores on the Sensory Sensitive profile, the two scales being positively correlated. Physical and emotional sensitivities were prevalent among the interview participants in the supplementary qualitative study (article 6). Physical sensitivities included touch, sound, light, smell and food sensitivities, including food textures and these were reported as being adverse. Emotional sensitivities included sensitivity towards the moods or opinions of others about the sensitive individual, which were associated with anxiety in some participants. Sensory hyper-sensitivity is a salient feature of CS pain (Latremoliere & Woolf, 2009; Nijs et al., 2010; Woolf, 2011) and is accepted as being a predominant feature of NSCLBP (Arendt-Nielsen et al., 2018; Arendt-Nielsen et al., 2015). One of the main points of this thesis is that sensory hyper-sensitivity may not just be a post-morbid response to pain, but that trait characteristics of sensitivity may have existed pre-morbidly. Pre-morbid trait sensitivity is proposed as being a potential risk factor in the development of CS pain.

The likelihood that the trait sensitivity characteristics existed pre-morbidly is strengthened by other literature in which healthy populations have been identified as having traits of high sensory processing sensitivity (Acevedo et al., 2018). Sensory processing sensitivity is defined as the extent to which an individual may receive, process and respond to external stimuli or factors (Acevedo et al., 2018; Aron & Aron, 1997).

6.4.1 The context of high sensory sensitivity

Difficulties in developmental learning experiences were reported in the majority (7 of the 9) of the interview participants so it is likely that those participants had some pre-morbid sensory processing disorders. Furthermore, the sensory processing disorders may have been

associated with pre-morbid autism spectrum disorders, attention deficit hyperactive

disorder (ADHD) or learning difficulties such as dyslexia, which emerged in some of the

interview data. In the wider literature, other non-pain populations have also been found to

have high sensory sensitivity, such as: 1) People with sensory processing disorders without

comorbidities, identified through analysis of white matter microstructure (Chang et al.,

2016; Owen et al., 2013); and 2) sensory processing disorders with comorbid related

diagnoses including adults and children with autism spectrum disorders (Chang et al., 2016;

Crane et al., 2009; Tavassoli et al., 2014), ADHD, (Holstein et al., 2013; Shimizu et al., 2014)

and learning difficulties such as dyslexia (Ewing & Parvez, 2012). Sensory processing

disorders can affect individual abilities to process sensory feedback accurately and this in

turn can have an effect on cognitive and learning functions (Leisman et al., 2014).

Experiences of learning difficulties, formally diagnosed or implied, were prevalent among

the interviewees in the supplementary qualitative study (article 6). Confirmation of the role

of such sensory processing disorders in the development of CS pain requires further

investigation.

6.4.2 Sensory sensitivity and stress responses to various sensory stimuli

Sensory processing disorders tend to have sensory hyper-sensitivity in common according to

their overlapping sensitivity-related brain circuitry activity, where white matter was

analysed using functional MRI, in response to stressful emotional, social or salient

stimulation (Acevedo et al., 2018). Sensory hyper- (and hypo-) sensitivity has been shown to

be associated with varying degrees of autonomic arousal responses in children with sensory

processing disorders, measured using various physical autonomic measures, although some

results were conflicting due to methodological weaknesses according to a review (Gomez, 2017). The review did not extend to adult populations.

It has been found that 20-31% of the healthy adult population are highly sensitive in nature, to environmental stimuli, through a combination of genetic and environmental factors (Aron & Aron, 1997; Lionetti et al., 2018). Pluess hypothesised that a highly sensitive person may or may not become sensitised to environmental stimuli depending on the presence of a supportive developmental environment (Pluess, 2015). A lack of supportive developmental environments was apparent among most of the participant interviewees in the qualitative study (article 6) in which emerged a high prevalence of relationship anxieties, bullying and abuse. These circumstances are proposed to lead to stress responses in individuals high in sensitivity to environmental stimuli (Pluess, 2015).

In summary, high trait sensory sensitivity is prevalent in people with CS and NSCLBP, predictive of the extent of CS symptoms, is likely to have been a trait characteristic prior to the onset of CS pain and is associated with trait anxiety and sensory processing disorders. High trait sensory sensitivity may lead to a greater susceptibility to stressors in people with NSCLBP.

6.4.3 Sensory Hypo-sensitivity

A most interesting aspect of sensory sensitivity which emerged from the quantitative data in article 4 was the high prevalence of extreme sensory hypo-sensitivity scores on the Low Registration sensory profile. Trait sensory hypo-sensitivity in people with CS pain is

unexpected considering that one of the salient features of CS is somatosensory hypersensitivity. Furthermore, there was a significant prevalence of extremes in low and high scores of Low Registration in the low CSI sub-group. Low Registration is characterised by the missing of sensory information due to a high neurological threshold and a passive adaptive response. An extreme score in the low range is suggestive of being less passive in their behavioural response so that they miss less information than most, conversely a high score is interpreted as meaning they miss stimuli more than most (Brown & Dunn, 2002). If sensory stimuli are missed, or not perceived, by the individual it would seem acceptable to infer that they might report a lesser extent of CS symptoms and be less sensitised. Alternatively, it could be hypothesised that when the central nervous system (CNS) requires sensory feedback and does not receive it, it may be more difficult to make meaning of the environment and this could lead to a stress response of physiological arousal. The Low Registration sensory profile has been positively correlated with anxiety in healthy adults (Engel-Yeger & Dunn, 2011c) suggesting a relationship between lack of sensory input and sensory discomfort, and physiological arousal associated with anxiety.

Local or regional tactile hypo-sensitivity has been identified in chronic low back pain in the form of sensory mis-localisation and reduced sensory discrimination ability using two-point discrimination (Wand et al., 2010; Wand et al., 2013). Furthermore, widespread sensory hypo-sensitivity has been found in fibromyalgia (Mailis-Gagnon & Nicholson, 2010), a condition characterised by CS pain with predominantly CNS changes (Sluka & Clauw, 2016). A prevalence of sensory hypo-sensitivity to various sensory modalities has been estimated in as many as 25-50% of chronic pain populations (Mailis-Gagnon & Nicholson, 2010). This is similar to the 29% prevalence of people in healthy populations found to have low

environmental sensitivity (Lionetti et al., 2018). Environmental sensitivity is a self-reported

measure of individual differences in responsiveness to environmental stimuli through the

senses (Lionetti et al., 2018). The hypo-sensitivity described in fibromyalgia is termed as

non-dermatomal somatosensory deficits (NDSDs), defined as, "unexplainable

hypoaesthesiae (e.g. to cutaneuous or other sensory modalities) ipsilateral to the site of

pain (or worse pain), which do not conform to the distribution of peripheral nerves or

dermatomes." (Mailis- Gagnon and Nicholson, 2011; p. 1787). The definition of NDSDs

overlaps with the definition of CS, in that the CS pain distribution is not anatomically

plausible (Nijs et al., 2010; 2014; 2015).

6.4.4 Which senses become hyper-sensitive?

Each participant has a score for each of the four sensory profiles on the Adolescent Adult

Sensory Profile (AASP). The results showed that many had extreme scores for both the

sensory hyper-sensitivity and the Low Registration profiles. The sensory profile raw scores

did not allow for discrimination between senses as to which are particularly hyper- and

hypo-sensitive. Clinical observations suggest that auditory, visual and light touch senses may

become hyper-sensitive, while bodily senses and proprioception become hypo-sensitive.

This may be speculatively interpreted as meaning that the former senses are heightened 'at

the expense' of body feedback, affecting sensory-motor function and motor control. These

patterns were apparent in the interview data in article 6 and warrant further investigation.

Further analysis of hypo-sensitivity across each of the senses is necessary if treatment

protocols are to be developed for increasing 'missing' sensory input.

6.4.5 Sensory Hypo-sensitivity and a stress response

The Low Registration sensory profile scores held some predictive capacity for the extent of CS symptoms in people with NSCLBP. The mechanism behind sensory hypo-sensitivity and CS symptoms is unknown. A passive behavioural response suggests there could be a continuation in a state of sensory under-stimulation which, speculatively, may lead to a stress response or autonomic arousal if under-stimulation is interpreted as threatening by the CNS (if sub-conscious 'interpretation' by the CNS is a plausible phenomenon) or the individual.

A research implication might be that using quantitative sensory testing to test for CS pain may not reveal sensory hyper-sensitivity if there is an extreme Low Registration sensory profile affecting the sense being tested, even when the individual is classified as having predominant CS.

In summary, trait sensory hypo-sensitivity is prevalent in people with NSCLBP and CS pain, is predictive of the extent of CS symptoms and is likely to have been a trait characteristic prior to the onset of low back pain. The mechanism behind the relationship between sensory hypo-sensitivity and CS in people with NSCLBP is unclear.

6.4.6 Poor motor control and coordination

Sensory under-stimulation may lead to reduced sensory-motor feedback and therefore poor motor control and coordination. A number of interview participants reported poor coordination and sports abilities. Two participants with extreme Low Registration sensory profiles (and concurrent dyslexia which is associated with sensory processing disorders

(Ewing & Parvez, 2012) reported better than average endurance running abilities but poor coordination at other sports. Running may be a way to increase general bodily sensory input but which does not require as much sensorimotor coordination as other sports do, such as swimming.

A hypothetical aspect of poor coordination which is linked with the study findings in article 6 is the possibility of retained primitive reflexes in the people with sensory processing disorders. Retained primitive reflexes are a feature in young people with sensory processing disorders associated with autism spectrum disorders (Chinello et al., 2016), ADHD (Konicarova et al., 2013) and some learning difficulties such as dyslexia (McPhillips & Sheehy, 2004). In healthy school children aged 4 – 6, retained primitive reflexes were negatively correlated with lower motor efficiency (Gieysztor et al., 2018). This suggests that retained primitive reflexes may interfere with sensory motor function even in healthy individuals, which may be a pre-morbid characteristic in some, but this was not tested in the current thesis. A small study found remnants of primitive reflexes in a chronic low back pain population which affected motor control in an abdominal hollowing (motor control exercise) maneuver (Parfrey, 2014). It is possible that the reported poor sports and motor control skills among the interview participants in the current thesis (article 6) may be partly related to retained primitive reflexes, but evidence supporting this idea is currently unavailable and this warrants further investigation.

Figure 14 below, shows the proposed pathway to CS in people with NSCLBP beginning with heightened sensitivity leading to a physiological arousal, and the potential stressors of

sensitivity, sensory processing differences associated with developmental learning experiences and the sensory profiles.
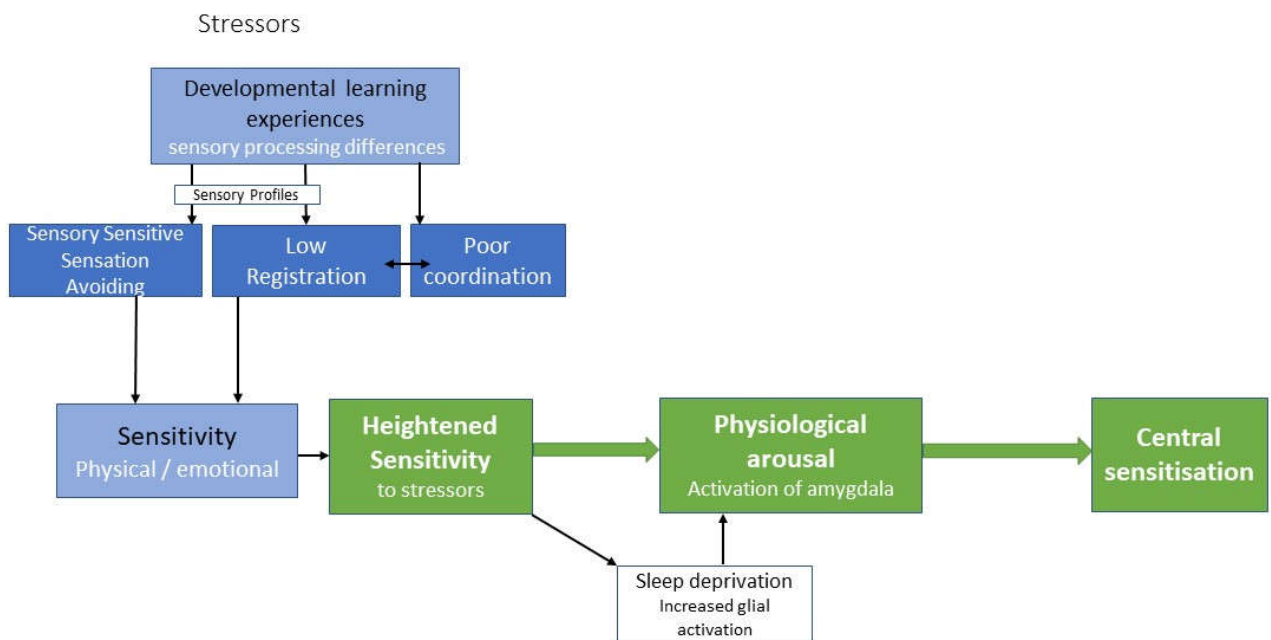
Figure 14: The proposed pathway to CS in people with NSCLBP beginning with aspects of sensitivity leading to a physiological arousal, and the potential stressors of physical and emotional sensitivities, and sensory processing differences associated with developmental learning experiences and the sensory profiles.

6.5 Emotional sensitivity, high trait anxiety and trauma

Emotional sensitivity emerged as a recurring theme in the interview data of the supplementary qualitative study (article 6). Emotional sensitivity was apparent in all the interview participants in the form of sensitivity to the moods and opinions of others about them, to perceived injustices, concerns about under-achieving and worries about uncertainties, with the apparent outcome of state anxiety. Trait anxiety is a stable

characteristic in which an individual is more prone to state anxiety in response to

psychological stressors (Spielberger, 1983). In populations without NSCLBP, anxiety has been

found to be related to high sensory sensitivity by other authors, such as anxiety being

significantly greater in people with trait sensory hyper-sensitivity (measured on a sensory

defensiveness questionnaire) than those with normal sensory sensitivity (Kinnealey & Fuiek,

1999). However, the study numbers were small and there was no distinction made between

trait or state anxiety. High trait anxiety is a characteristic found in the current study

population of people with NSCLBP and CS pain and was identified as a predictive factor in

the extent of CS symptoms. The sensory Sensitive and Sensation Avoiding profiles predict

(state and) trait anxiety in healthy populations (Engel-Yeger & Dunn, 2011c) and it may be

hypothesised from this that the trait sensory profiles may predict trait anxiety which in turn,

or concurrently, predicts CS symptoms in CS pain populations.

Threat perception is heightened after trauma and abuse, most obviously in cases of post-

traumatic stress disorder (PTSD) (Moeller-Bertram, 2012). Although PTSD was not

investigated in the current thesis, trauma and abuse were prevalent themes in the interview

data (article 6). These may have contributed to the development of CS in patients with

NSCLBP through heightened threat perception and physiological arousal. Childhood

adversity has been shown to be linked to heightened stress responses such that a major

trauma later in life will trigger generalised anxiety and symptoms of post-traumatic stress

(Meyers et al., 2015). Some of the interviewed participants in the supplementary study

(article 6) reported pain onset at the time of an emotional trauma, having reported previous

traumatic events which had not been initiators of pain. Childhood adversity has been shown

to be a factor related to signs of CS as assessed using quantitative sensory testing (You &

Meagher, 2016) whereby healthy adults who had reported multiple (mean= 5) physical,

emotional or psychological adverse events before the age of 18 showed heightened

sensitivity in QST and slower decay of the effect of QST compared with the non-adverse

events group. However, there was blunting of the sympathetic responses to the stimuli, not

heightened physiological arousal and this may be due to the laboratory setting with minimal

threat associated with the context, or that they were healthy adults and not in pain.

6.5.1 Sleep deprivation

Poor sleep was reported among a few of the interview participants (article 6) with NSCLBP

and this was reported to be in association with sensory over-stimulation or hyper-arousal. A

low sensory neurological threshold is thought to lead to sensory over-responsivity and

physiological arousal (Acevedo et al., 2018; Aron et al., 2012; Dunn, 1997) which is a stress

response. Hyper-arousal of the sympathetic "flight or fight" response system may make

falling asleep more difficult. Based on animal studies, major acute stress responses, chronic

stressors and diminished sleep are thought to lead to an activation of glial cells in the CNS

and neuroinflammation which in turn may lead to CS pain (Nijs et al., 2017).

Figure 15 shows the proposed pathway to CS in people with NSCLBP with the addition of the

potential stressors related to trauma, such as childhood adversity and its relationship with

emotional sensitivity trait anxiety and sleep deprivation.

Figure 15: the proposed pathway to CS in people with NSCLBP with the addition of the potential stressors related to trauma, such as childhood adversity and its relationship with emotional sensitivity, trait anxiety and sleep deprivation.

6.5.2 Sensation seeking less than most

The Sensation Seeking sensory profile was the least prevalent profile in the current thesis and none of the participants with predominant CS pain and NSCLBP showed high scores for trait Sensation Seeking. Instead 41% of the quantitative data set (articles 4 and 5) showed a Sensation Seeking score of less and much less than most. Sensory Sensitive, Sensation Avoiding and Low Registration profiles have all been found to be associated with negative affect, whereas Sensation Seeking is associated with positive affect (Engel-Yeger & Dunn, 2011a) in healthy adults. Sensation Seeking was the only sensory profile in the current study population of people with CS and NSCLBP to be negatively correlated with CS symptoms. Healthy adults with extreme sensation seeking profiles tend to enjoy and seek after sensory

input (Engel-Yeger & Dunn, 2011a), and may therefore be less likely to be distressed by bodily sensations of physiological arousal. If these sensory profiles are reflective of pre-morbid traits, then it would seem plausible that the character traits of people with CS and NSCLBP tend to be low in the Sensation Seeking profile because they are not characteristically drawn towards increased sensory input.

6.6. Behavioural responses

The way in which individuals respond to the physiological arousal in response to stressors may depend on their personal characteristics of confidence and sense of control and whether they tend to respond with active or passive adaptive behaviours. Furthermore, individual personality types play an important role in the behavioural responses to stressors.

The results of the current thesis (articles 4 and 5) showed that both the sensory profiles with a passive adaptive response were predictive of increased CS symptoms (Sensory Sensitive and Low Registration). Although there was a high prevalence of Sensation Avoiding extreme scores in the high-CSI group, this sensory profile did not hold any predictive capacity for CS symptoms. It may therefore be the case that the active adaptive response of the individual to the sensory discomfort of over-stimulation provides compensation by removal of or from the stimuli when possible. Active adaptive responses may link with the themes of confidence and sense of control through self-efficacy. When applied to pain, the sensory avoidant individual may apply self-efficacy to regain control of the sensations or pain, such as seek treatment or administer self-help, thereby reducing the risk of CS pain. Conversely, a passive adaptive response to sensory (or nociceptive) stimulation or to the symptoms of a

physiological arousal response may lead to increased sensitisation if these are perceived as threatening. The high prevalence of passive responders in the current study (articles 4 and 5), detected by the high extreme Sensory Sensitive and Low Registration profile scores, predictive of higher CS symptoms, shows that people with CS tend to demonstrate passive responses and fail to activate compensation or remediating behaviours.

Figure 16 builds on the proposed pathway to CS in people with NSCLBP with the addition of the potential responses related to personal characteristics of confidence and control and passive or active adaptive responses.

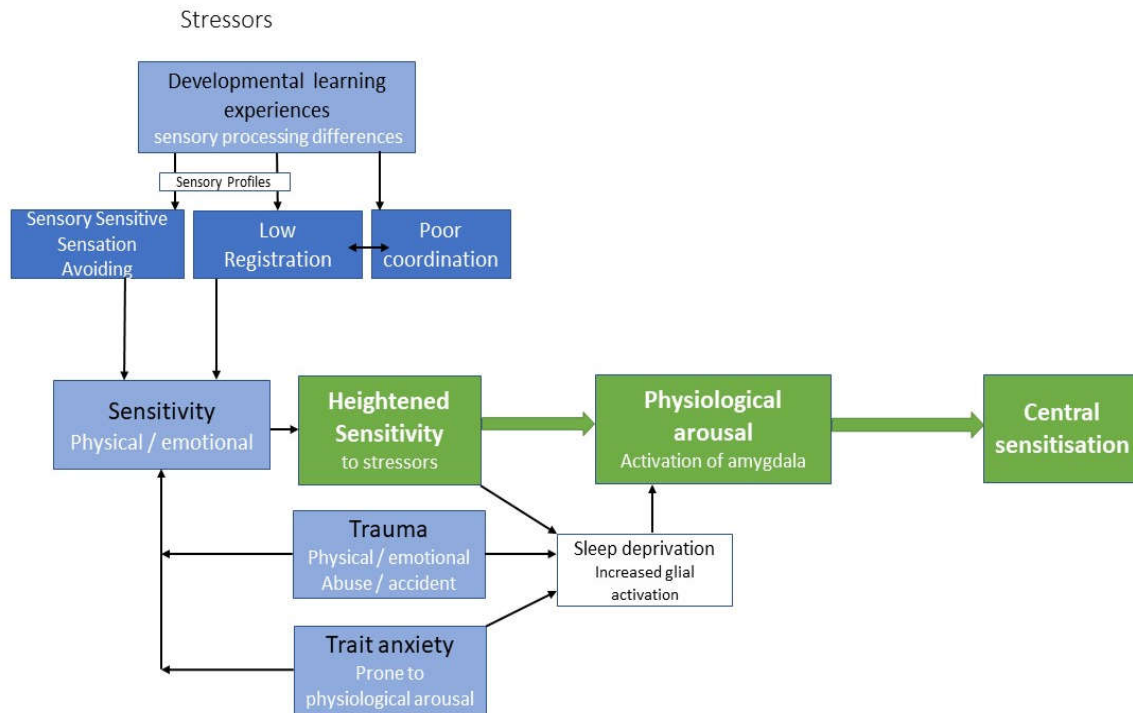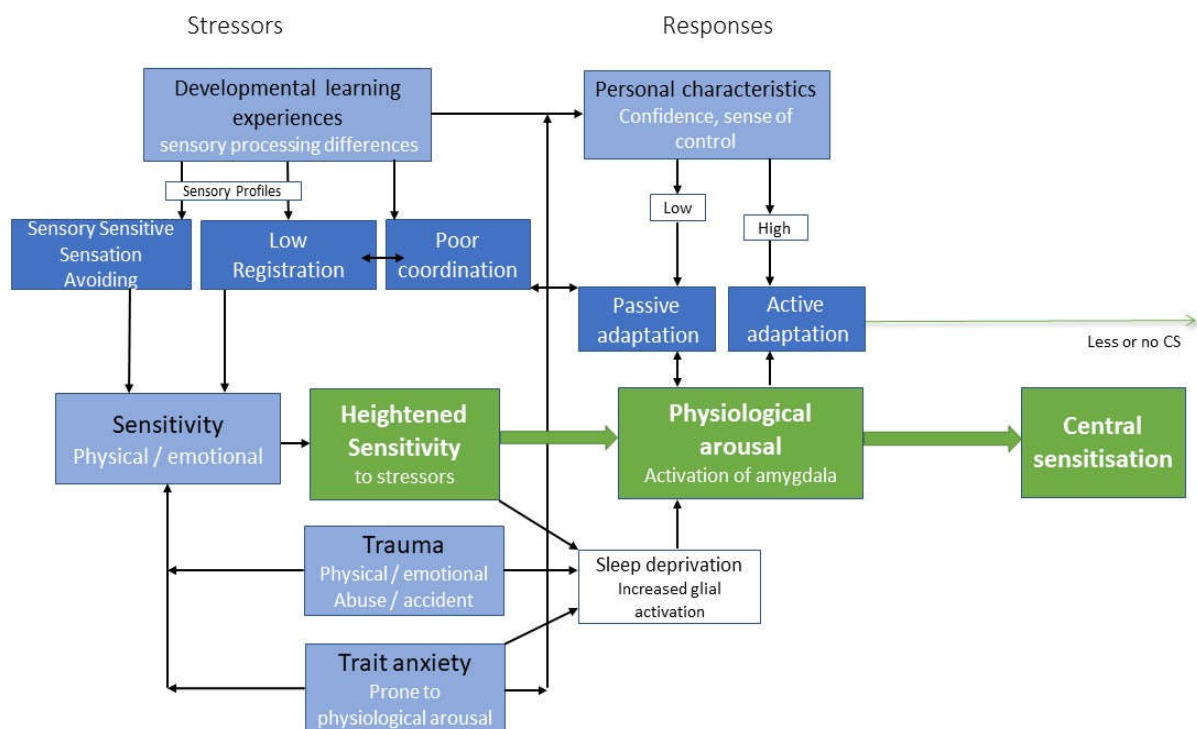*Figure 16: the proposed pathway to CS in people with NSCLBP with the addition of the potential responses related to personal characteristics of confidence and control and passive or active adaptive responses.*

6.6.1 Trait anxiety and personality types – responses to physiological arousal

The results in article 4 showed a high prevalence of high trait anxiety-based personality types (defensive high anxious, high anxious) and repressors, who are prone to physiological arousal compared with the low trait anxiety personality type (low anxious) (Eysenck, 1997). Therefore, it can be inferred that personality type impacts the outcome of CS pain. Eysenck (1997) proposed that individuals with different personality types possess cognitive biases in the way they attend to sensations and stimuli and interpret them (Eysenck, 1997). Individuals with high trait anxiety tend to direct attention towards a stimulus and are highly distractible by task irrelevant stimuli (general hyper-vigilance) or by specific stimuli (specific hyper-vigilance). These responses to stimuli are unlike those of their low anxiety counterparts who direct attention away and do not display hyper-vigilance (Eysenck & Byrne, 1992). These cognitive biases may heighten physiological arousal, which may be further heightened when there is a passive adaptive behavioural response related to their sensory profiles.

As discussed in the articles included in this thesis (articles 4 and 5) extreme defensive high anxious individuals tend to respond with heightened vigilance towards the perceived stimuli, interpretation of the sensations as threatening (Eysenck, 1997; Franklin et al., 2016; Franklin et al., 2014) and persistence in their seeking of multiple medical interventions for their chronic low back pain (Franklin et al., 2014). This may explain why the factor of extreme defensive high anxious personality type contributes, in part, to the prediction of symptoms of CS. Furthermore, people with high anxious and defensive high anxious personality types

have also been found to report their somatic and cognitive sensations of state anxiety as being debilitative to performance outcomes (Franklin et al, 2015), which suggests these groups could experience more debilitation and disability from their somatic and cognitive symptoms of physiological arousal.

Conversely, repressors tend to avoid attending to sensations of physiological arousal and interpret away from threat, self-treat and not attend physiotherapy and pain clinics as much as defensive high anxious individuals (Franklin et al., 2014). This may explain the low numbers of repressors across the current study population of people with NSCLBP and CS, and the higher proportion of repressors in the low CSI sub-group.

Interpretation of physiological arousal and resultant behavioural responses has been studied elsewhere in the related area of anxiety sensitivity. Anxiety sensitivity is the fear of anxiety-related symptoms (physiological arousal) and was first described by Reiss (Reiss et al., 1986). People who are high in trait anxiety are more prone to physiological arousal in the face of stressors (stimuli perceived as threatening, uncontrollable or novel) and the perception of physiological arousal is high in people with anxiety sensitivity (Reiss et al., 1986). Reiss (1986) suggested that people high in anxiety sensitivity would be hyper-vigilant to internal physical sensations or cues, by self-monitoring. Based on a study in which heightened vigilance (shorter detection latency) towards experimentally induced electrical stimuli was found in people high in anxiety sensitivity it was confirmed that anxiety sensitivity is characterised by heightened attention towards physiological sensations (Rosa-Esteve & Camacho, 2008). Anxiety sensitivity is considered to be a lower order construct under trait anxiety (Rosa-Esteve & Camacho, 2008) and has been found to correlate with trait anxiety in

healthy young adults using self-report measures (Smári et al., 2003). This may explain the prevalence of high trait anxiety and of personality types who are more prone to physiological arousal in the current thesis.

Interpretation and vigilance for threat is likely to be related to situations in life contexts in which a sense of safety and control are lost or diminished. The interview participants, in the current supplementary qualitative study, with defensive high anxious, high anxious personality types, demonstrated many situations in which they felt out of control, particularly situations involving physical and emotional abuse and bullying from school peers, teachers and adult-hood work peers and these were linked with vigilance for threat. Other situations in which control was lost included unexpected changes in circumstances such as a loss of career dreams, childhood loss of parent and change of job under adverse circumstances and emigration into a different culture. Furthermore, one participant reported heightened sensitivity to sound but only to sounds that were out of her control and evaluated as unpleasant. Auditory sensory threshold alone did not mean inevitable sound hyper-sensitivity, but instead her story was suggestive of sensitisation to specific sounds.

6.6.2 Sensitivity, sensitisation and CS pain.

What is apparent from studying these aspects of sensitivity, anxiety and personality types is that there is a difference between sensitivity and sensitisation. Sensitivity is described in terms of neurological thresholds (Brown et al., 2001) and is said to be partly related to genetic background (Aron & Aron, 1997; Diatchenko et al., 2005; Eysenck, 1997). General sensory processing sensitivity is said to also be enhanced by early life circumstances and the

presence or not of a supportive environment (Jones, 2015; Pluess, 2015; You & Meagher, 2016).

Sensitisation (heightened sensitivity towards a specific stimulus) appears to be associated with vigilance towards, interpretation of and behavioural responses to particular stimuli which are associated with a threatening source, even if the source is misinterpreted. For example, physiological arousal may increase sensitivity to various normally innocuous stimuli which may be attributed to threatening sources such as damaged tissues in the spine, particularly by defensive high anxious and high anxious individuals. Although state anxiety was not measured in the current study (because the focus was on premorbid traits), state anxiety may play a role in the maintenance of stimulus and pain perception. It is proposed that when stimuli and bodily sensations are intensified through attentional and interpretational bias for threat then the individual may become sensitised towards those sensations. Furthermore, it is proposed that the higher the extreme sensory profiles and trait anxiety and the more extreme the defensive high anxious personality type, the greater the variety of bodily sensations to which the individual becomes sensitised. It is already widely known that normally non-noxious stimuli are perceived as painful in CS pain (e.g. Latremolier and Woolf, 2011) with this thesis demonstrating some of the potential mechanisms behind the development of CS pain. This forms the structure of the proposed model of the pathway to CS pain (figure 17). The results of this thesis give support to the hypothesis proposed in chapter 1 that people with NSCLBP and CS have pre-morbid trait sensitivity-related characteristics which may have contributed towards the development of their CS pain. Figure 17 illustrates the complete proposed pathway to CS in people with NSCLBP, with the addition of the potential responses related to personality types.
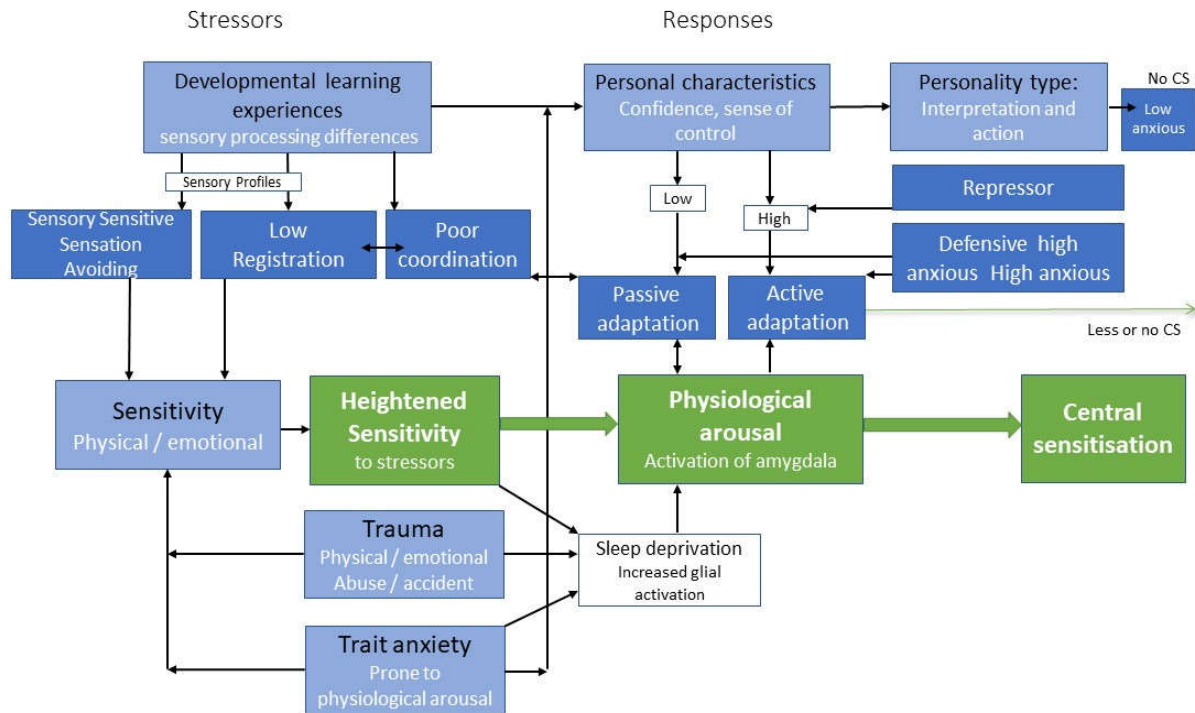
Figure 17: illustration of the complete proposed pathway to central sensitisation (CS) in people with NSCLBP in people with NSCLBP from stressors to physiological arousal to the responses which determine the outcome of CS or no CS.

6.3 Additional comments – measuring CS.

It should be made clear that all the thesis study participants with NSCLBP were selected based on their predominant CS pain mechanism, even though the CSI scores did not reflect this. Nearly a quarter (22%) of the group with a clinically classified predominant CS pain presentation, according to the current clinical guidelines (Nijs et al., 2015; Nijs, Torres-Cueco, et al., 2014), self-reported low CS symptoms (CSI < 40). This outcome may have been related to their Low Registration sensory hypo-sensitivity profile, or to their repressor personality type. None-the-less, this outcome suggests that the CSI may have limitations in its ability to identify clinically relevant CS in people with NSCLBP using the cut off scores supplied by Neblett and colleagues (Neblett et al., 2013; Neblett et al., 2016). It is suggested that

different personality types and sensory profile characteristics should be accounted for in further studies where clinically significant cut-off scores on the CSI are being determined.

Furthermore, measuring CS using quantitative sensory testing (QST) may also be confounded by personality type and sensory profiles because of their cognitive biases and different sensory thresholds respectively. Whether Weinberger's four personality types (Weinberger, 1979) would respond differently to QST is unknown. However, on the basis that some people with NSCLBP and clinically identified, predominant CS (articles 3 to 5) have a high threshold for sensory stimulation, QST may not be an appropriate way to identify CS in these people. Further research is recommended into the responses of people with an extreme Low Registration sensory profile to QST to possibly improve the reliability of QST for identifying CS.

6.4 Overall Strengths and limitations

This section will discuss the strengths and weaknesses not already discussed fully in articles 3 to 6. A key strength in this thesis is the CS-specific selection criteria for predominant CS pain within the NSCLBP population. There is likely to be a spectrum of individuals with varying degrees of nociceptive pain as well as the CS pain (Sluka & Clauw, 2016). NSCLBP is likely to have peripheral nociceptive stimulus inputs particularly where there is likely to be spinal degenerative disease (Arendt-Nielsen et al., 2018). In order to minimise the inclusion of people with predominant nociceptive pain mechanisms, the selection process for participant recruitment included a criterion which meant that if non-steroidal anti-

inflammatory medication had been found to be effective the participant would be excluded. Furthermore, the age limit was under 65 to reduce the likelihood of severe degenerative disease so that the focus could be on mainly central mechanisms of CS.

A further strength of the current thesis is in the design itself, whereby the use of mixed methods enabled a much fuller picture to be seen surrounding the development of CS pain in people with NSCLBP compared with using questionnaires alone (Tashakkori & Teddlie, 2010). Another design strength was that recruitment bias was minimised by having multiple health care providers across three countries and two continents. This recruitment strategy may in turn have enhanced the generalisability of the results.

A limitation in this thesis, specific to its ability to predict factors which contribute to CS pain in people with NSCLBP, is the cross-sectional study design element. To fully test and confirm the predictive strength of pre-morbid trait characteristics, a longitudinal design could be implemented which would measure baseline sensory profiles, trait anxiety, personality types and provide interview data collected through narrative methods about previous life experiences before the onset of CS pain. Interview recall bias, as evidenced through different personality types (Eysenck, 1997), implies that the information given through interviews may not have accurately represented previous life events. Seen from a 'theoretical thematic analysis' perspective this could present as a minor limitation insomuch as 'facts' may be altered by recall bias. However, it could equally be argued that individual perspectives and responses to life events was part of the interview exploration and was linked with the response factors measured through the personality types and sensory profiles. With the lack of longitudinal design and recall bias from the interviews, pre-morbid

'causative' factors in the development of CS symptoms in people with NSCLBP remain unclear. There is, however, enough supporting evidence, direct and indirect, in the wider literature to give the results of this study some weight in terms of the pre-morbid trait characteristics and their potential role in the prediction of CS in people with NSCLBP. A platform is set for a longitudinal study and further investigations into important emergent information.

On reflection, a further limitation was a lack of additional demographic information which may have served to enhance interpretation of some of the data. For example, a count of how many previous health providers may have been sought previously may have been used to show differences in response behaviours between defensive high anxious and repressor individuals. It may have also been useful to distinguish between participants with regional NSCLBP and those with non-specific chronic low back and widespread pain. Widespread pain is a feature of fibromyalgia, a condition characterised by CS (Clauw, 2009). Part B of the CSI contains an item which asks whether the participant has been diagnosed by a doctor with fibromyalgia, requiring a yes / no response. This information was not used in the current thesis. Future analysis of the data collected in this thesis could include an investigation into differences in trait characteristics between those with NSCLBP with and without widespread pain.

There is a possible limitation related to the use and interpretation of the State Trait Anxiety Inventory (STAI) scores in the current study. The trait section of the STAI was originally designed to identify a proneness of an individual to state anxiety in the face of perceived psychological threats, particularly where personal adequacy was threatened, or a sense of

failure experienced, whereby high trait anxious individuals would respond with state anxiety much more than low trait anxious individuals (Spielberger et al, 1983). Physical threats or pain related threats, such as the threat of an electric shock or imminent surgery, did not appear to show the same response differences between high and low trait anxious individuals (Spielberger et al, 1983). If personal adequacy is threatened or a sense of failure is experienced by the presence of non-specific low back pain and CS then high trait anxious individuals may respond to these symptoms with higher levels of state anxiety and corresponding physiological arousal. Spielberger's work (Spielberger, 1983) would suggest that high trait anxious individuals may not respond to pain, which may be a 'physical threat', with physiological arousal, unless the pain becomes a psychological threat. It may be argued that sensory discomfort from excessive sensory stimulation may present as a psychological threat to personal adequacy if the individual fails to respond adaptively to regulate the sensory 'overload'. This may be relevant to the development of sensitisation to the threat and may play a role in the development of CS.

To take this argument further, some more recent work by Walsh et al., (2015) found that individuals with high trait anxiety personality types were sensitive to situations involving social evaluation but not those characterized by threats to their health or physical well-being. However, the threats were presented to the participants in written form, and then participants were asked how they would feel if they were to encounter each situation. No 'real' threats were posed, and no physical symptoms were provoked. To confirm whether high trait anxiety personality types respond to physical symptoms associated with their back pain would require further investigations.

Finally, limitations may have been imposed by the use of the Adolescent / Adult Sensory Profile, used for measuring sensory sensitivity profiles in people with NSCLBP and predominant CS pain. This limitation is based on there being very limited evidence (Graper et al, *unpublished*) to show that this measurement tool is appropriate for use in CS or NSCLBP populations.

6.5 Conclusion

The over-arching objective achieved in this thesis was to investigate sensitivity-related trait characteristics of centrally sensitised people from a NSCLBP population and to explore how these characteristics might have contributed to the development of CS pain. This is the first study to link aspects of trait sensory processing differences and trait anxiety with the development of CS pain in people with NSCLBP. It is proposed that physiological arousal occurs in response to excessive over- or under-stimulation. It is proposed that excessive over-or under-stimulation pose as a threat to homeostasis, whether this threat is conscious or not. Once the physiological arousal is perceived by the individual, the source of the arousal is cognitively evaluated in preparation for a response. The cognitive evaluation is determined by a sense of confidence and control over the source, by attentional biases towards or away from the symptoms and interpretation bias for or against threat. Cognitive biases towards symptoms and for threat lead to heightened sensitivity towards any specific bodily sensations which may be interpreted as pain, or increased pain. This is the proposed pathway to the development of CS in people with NSCLBP.

The next and final chapter will provide conclusions and recommendations which have been developed in response to the research studies (articles 1 to 6) presented throughout this thesis.

Chapter 7

Conclusions and Recommendations

7.1 Introduction

The following chapter will conclude this thesis by identifying the clinical and research implications for people with non-specific chronic low back pain (NSCLBP) and central sensitisation (CS). Then future research recommendations will be summarised.

Figure 18 shows the road map to assist the reader in orientating through the thesis, arriving at the final chapter.
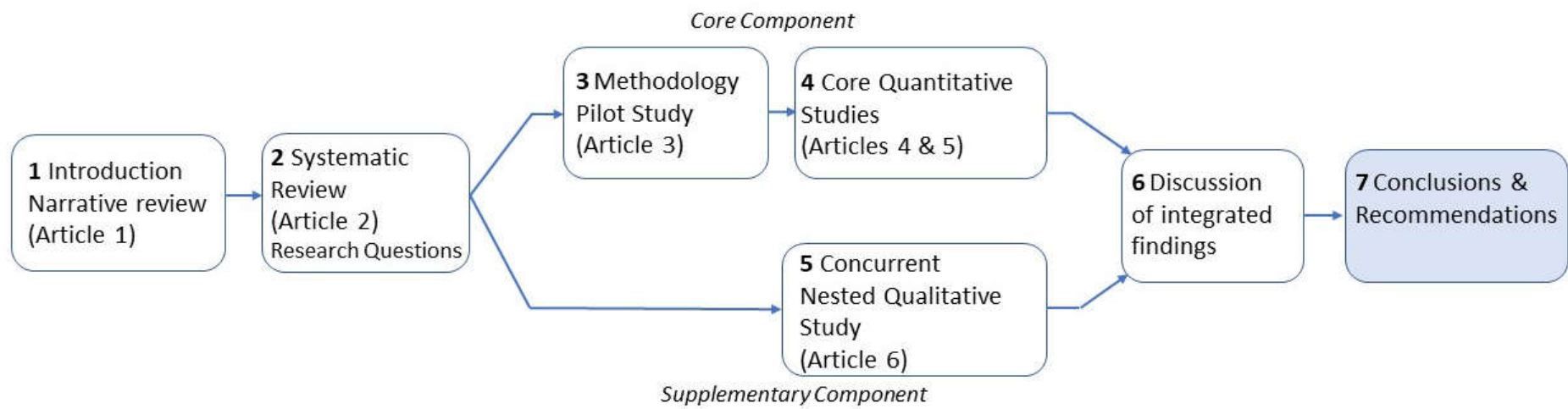
Figure 18: Road map through the thesis – conclusions and recommendations.

7.2 Clinical and research implications

The current thesis provides some novel clinical implications for pain clinicians and researchers, for application to people with NSLBP who present with a clinically classified predominant CS pain mechanism (Nijs et al., 2015). The following assessment recommendations may enhance clinicians' understanding of the individual with NSCLBP and CS. A more detailed understanding of individual characteristics may in turn lead to enhanced rapport and communication between the clinician and the individual. This has been shown to be important in (patient-centred) physiotherapy where one of the themes identified was that of getting to know the individual, as well as the confidence of the physiotherapist (Wijma et al., 2017). The following assessments of people with NSCLBP and CS are recommended:

7.2.1. Clinical assessment of sensory processing characteristics

People with CS pain and NSCLBP can be assessed for differences in sensory processing compared with most people. A detailed subjective assessment may include questions related to their 'natural' or pre-morbid sensory processing sensitivity, developmental learning experiences, ongoing stress and sleep quality and childhood trauma (there is a response item on the Central Sensitisation Inventory which identifies the frequency of childhood trauma). A self-report measure, the Adolescent / Adult Sensory Profile (AASP), could be used to provide a score for sensory hyper- and hypo-sensitivity and to indicate

whether the individual has extremes of sensory hyper- or hypo-sensitivity and passive or active adaptive response behaviours. Particular attention should be given to extreme sensory profiles of Sensory Sensitive and Low Registration as these profiles are characterised by a passive adaptive response and are predictive of a greater extent of CS symptoms in people with NSCLBP.

7.2.2 Clinical assessment of personality type and response behaviours

Assessment of personality type in centrally sensitised people with NSCLBP can be done using the State-Trait Anxiety Inventory (STAI; trait section) and the Marlowe Crowne Social Desirability Scale (MCSDS) and the active or passive response behaviours can be identified through the AASP, as was used in the current thesis. The cut off scores of 39 for the STAI and 5 for the MCSDS can be used to identify Weinberger's four personality types in people with NSCLBP and CS which includes the non-extreme and extreme personality types. Extreme personality types can be identified using cut off scores of ≤ 29 and ≥ 49 on the STAI and ≥ 8 and ≤ 4 on the MCSDS in people with NSCLBP and CS.

Particular attention should be paid to the extreme defensive high anxious individuals because this has been found in the current thesis to be predictive of increases in the extent of CS symptoms in people with NSCLBP and CS. Subjective assessment may also alert the assessor to an extreme defensive high anxious personality type if there are reports of a history of multiple health care providers and attention to multiple symptoms (Franklin et al., 2014).

Identification of these trait characteristics may enhance the pain neuroscience education

treatment process currently recommended for people with CS pain (Louw et al., 2016;

Moseley & Butler, 2015) by tailoring the education information to suit the individual

characteristics. Management may require education about sensory requirements and

responses to stressors and this warrants further investigation.

7.3 Summary of further research recommendations

The results of the current thesis pave the way for further investigations into the development of CS pain in people with NSCLBP and the development of potential treatment strategies. Below follows a summary of further research recommendations which have been highlighted throughout the thesis. It is recommended to:

- Investigate trait sensory profiles and trait anxiety characteristics, and personality types as predictive factors for the development of CS pain from a pre-CS pain status, using measurements starting from a pre-morbid or acute-pain-stage baseline.

- Investigate the relationships between each sensory profile and each personality type, such as whether repressors show a predominant Low Registration (because of missing sensory information) and / or sensation avoiding sensory profile (because of the avoidant behaviours associated with the repressor personality type), or between defensiveness (as an action) and active adaptive response sensory profiles (e.g. Sensation Avoiding).

- Investigate whether people with the repressor personality type are prone to under-report CS symptoms on the Central Sensitisation Inventory (CSI).

- To re-consider the ability of the CSI to identify people with central sensitivity syndromes using the current cut-off score of 40, depending on different sensory profiles and personality types. This recommendation is based on the lack of ability of the CSI to identify CS (assuming CS is identified when CSI ≥ 40) in people with NSCLBP

when they had extreme Low Registration profile and a repressor personality type, even though they had been clinically classified with CS pain using clinical guidelines (Smart et al, 2012).

- To consider the research implication that using quantitative sensory testing to test for CS pain may not reveal sensory hyper-sensitivity if there is an extreme Low Registration sensory profile affecting the sense being tested, even when the individual is classified as having predominant CS.

- Further analyse the sensory profile data used in the current thesis to ascertain which senses tend to become heightened and which tend to become dulled in relation to the altered sensory processing in CS pain in people with NSCLBP. The interview data and clinical experience would suggest that visual, auditory and light touch might become heightened and pressure sense and bodily proprioception might become diminished in people with NSCLBP and CS.

- Investigate the role of pre-existing sensory processing disorders, as a component of impaired or altered CNS function, as a possible risk factor in the development of CS pain. Extremes of sensory sensitivity, found in the results of this thesis, are associated with sensory processing disorders (Davies, 2009, Holstein et al., 2013) and anxiety (Ansari & Derakshan, 2011b) but the relationships between these and altered CNS functions seen in CS remain unclear.

- Investigate possible aspects of management of people with NSCLBP and CS using an intervention involving education about sensory requirements and responses to stressors, according to their trait sensory processing and anxiety-related characteristics, to add to existing pain neuroscience education programmes.

- Investigate the presence of retained primitive reflexes associated with sensory processing and learning differences, as a possible factor behind poor coordination in people with NSCLBP and CS (article 6).

- Test the hypothesis, if possible, that physiological arousal may occur even in the absence of conscious threat perception and that sensory over-or under-stimulation may be an unconscious source of physiological arousal.

7.4 Final Conclusion

This thesis may impact researchers and clinicians who are interested in understanding why it might be that some people recover from low back pain, yet others develop CS pain transitioning to NSCLBP. It is suggested that the extreme trait sensory profiles and high trait anxiety characteristics found in the current study population of people with NSCLBP and CS may be generalised to other clinical NSCLBP populations with CS. A pathway from trait characteristics related to heightened sensitivity to stressors, to increased physiological arousal and resultant responses, to the outcome of CS pain has been proposed. Areas for

continued research into the ability of these factors to predict CS pain from a pre-CS baseline have been suggested. Additional related areas for further investigation which developed through reasoning and discussion of the results have been highlighted. Information which emerged from the interview data, which related well to the wider literature, but which cannot be generalised, requiring further investigation have also been highlighted.

Final word from the author

The ultimate objective of identifying people at risk of developing CS pain prior to its onset may reduce the burden of CS pain on individuals, their families, carers and health care providers. There is more work to be done on achieving this objective and it is likely to be an endeavour I share with many fellow pain researchers internationally. It is my hope that this thesis and the enclosed published articles may contribute some valuable new knowledge to help pave the way towards achieving this important and worthwhile objective.

Jacqui R Clark

Appendices

Appendix 1: Evidence of journal submission of article 1:

Jun 04, 2018

Dear Mrs. Clark,

Your submission entitled "How might trait sensory processing, anxiety and personality type characteristics contribute to the development of central sensitisation pain? A review." has been assigned the following manuscript number: CJP-D-18-00254.

****
****
***Please note that copyright information is now provided completely on-line, in the form of a questionnaire. All of your co-authors will have been sent links to complete their own copyright information, based on the email addresses you provided. Please be in touch with your co-authors and encourage them to complete the form, as no accepted manuscript will be able to be sent into production without a completed questionnaire for each named author. ***

****
****

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author.

https://cjp.editorialmanager.com/

Your username is: jacqui.r.clark
https://cjp.editorialmanager.com/l.asp?i=152277&l=P47HXXJY

Thank you for submitting your work to The Clinical Journal of Pain.

Kind Regards,

James Adair, -
Managing Editor
The Clinical Journal of Pain

Appendix 3a: Ethical approval.

MANCHESTER METROPOLITAN UNIVERSITY
FACULTY OF HEALTH, PSYCHOLOGY AND SOCIAL CARE

M E M O R A N D U M

To   Jacqui Clark

From   Prof. Carol Taylor Haigh

Date   20/02/201

Subject: Ethics Application

Title   What pre-existing trait anxiety and sensory processing characteristics do non-specific chronic low back pain (NSCLBP) with central sensitisation have?

Thank you for your application for ethical approval.

The Faculty Academic Ethics Committee review process has recommended approval of your ethics application. This approval is granted for 42 months for full-time students or staff and 60 months for part-time students. Extensions to the approval period can be requested.

If your research changes you might need to seek ethical approval for the amendments. Please request an amendment form.

We wish you every success with your project.

Prof Carol Haigh and Prof Jois Stansfield Chair and
Deputy Chair
Faculty Academic Ethics Committee

Appendix 3b: Health care providers information letter.

Health Care Provider Information Sheet

Research Project Title: **What pre-existing anxiety and sensory processing characteristics do patients with chronic low back pain have?**

Date

Dear …,

This is a call for research participants with chronic pain (central sensitisation) to answer questionnaires.

Thank you for expressing an interest in assisting in our international research programme in central sensitisation in non-specific chronic low back pain (NSCLBP) being undertaken in association with Manchester Metropolitan University, UK and in collaboration with the University of Brussels, Belgium.

The Problem

NSCLBP is defined as **ongoing back pain (+/- buttock / leg pains) with no specific pathological cause** (such as malignancy/ infection/ inflammatory disease like ankylosing spondilitis. NICE guidelines, 2009). One of the main pain mechanisms in NSCLBP is considered to be central sensitisation, a non-mechanical, pain hypersensitivity due to increased responsiveness of central neurons. There is very limited understanding as to why some people recover from a back injury but others develop NSCLBP and central sensitisation.

It is proposed that people who develop NSCLBP may have pre-exisiting characteristics related to the way individuals process pain and other senses and this is the focus of our investigation.

Your Help

Your help is extremely valuable in reaching enough participants around New Zealand to give our results some meaning in identifying those at risk of developing chronic back pain. In turn this knowlege will direct appropriate clinical management for back pain sufferers and reduce the burden of cost on health providers. **I would be grateful if you would select from your clinical case-load individuals between ages 18-64 (inclusive) with central sensitisation & NSCLBP and, with their consent, give them four questionnaires**, which I enclose.

What are the questionnaires about?

The four questionnaires ask about the following sections of interest: 1) their pain and pain sensitivity (Central Sensitisation Inventory); 2) their natural psychological character (State-Trait Anxiety Inventory), 3) their natural sociability as a character trait (Marlowe Crowne Social Desirability Questionnaire) and 4) the way they process their senses (Adult Sensory Profile). It is anticipated that people who develop chronic pain with central sensitisation may process senses differently and may have associated

psychological characteristics. These differences may be identifiable before they become chronic pain sufferers as risk factors.

<u>What to do</u>

Select participants competent in the English language to volunteer who:

- are aged 18-64 inclusive.
- have been experiencing significant back pain most days for more than 6 months.
- do not have a clear diagnosis as to where the pain is currently coming from (such as malignancy/ infection/ inflammatory disease like ankylosing spondilitis etc.) and where NSAID (anti-inflammatory) medication has been used these have not been found to be helpful for the pain.
- experience pain that is disproportionate to the current extent of the injury or pathology.
- experience pain in variable areas around the back +/- other body parts and that is not always in the same place, with a pain distribution that is not neuro-anatomically logical.
- experience pain that can worsen for no apparent reason and flare up with little provocation.

<u>Exclude</u> participants if any of the following apply to them:

- Pain that is predominantly neuropathic pain (see point 1. below)
- Pain that is predominantly nociceptive pain (i.e. clear aggravating / easing factors and responds well to NSAIDs if used)
- Pregnancy and/or having given birth in the past 12 months
- Spinal surgery within the last 12 months
- Any rheumatic disease
- Any neurological disease
- Any cardiac, respiratory, metabolic or endocrine disorder

1) If you suspect they have primarily neuropathic pain (i.e. due to nerve pathology) exclude these people using the S-LANSS Pain Score, a short 7 point questionnaire, provided. A score of more than 12 on the S-LANSS Pain Score excludes the person from participating in this study.
2) Give the individual the Participant Information Sheet provided and ensure they understand it.
3) If they agree to participate, administer the four questionnaires allowing them time to complete them all (approximately 15 minutes).
4) Collect the four questionnaires **making sure they have answered *every* question.**
5) I will collect them when arranged.

This study has been given approval by the Manchester Metropolitan University Ethics Committee, UK.

<u>What next?</u>

If you wish to discuss it further or to ask any questions, please contact me on 07 548 2382 or +6421 023 67104, or at jacqui@thephysioshed.com. If you are happy to proceed now, please give your participant the questionnaires enclosed to complete. Thank you for your help, your time is much appreciated.

Yours sincerely,

Jacqui Clark MSc, MCSP, MPNZ

Physiotherapist, Post Graduate Lecturer & PhD Researcher
Guest Senior Lecturer Manchester Metropolitan University UK
The Physio Shed
8 Beach Grove
Omokoroa 3114
Tauranga
New Zealand   **+64 (0) 7 548 2382; +64 (0) 21 023 67 104**

Appendix 3c: Participant information sheet.

Participant Information Sheet

Research Project Title: **What pre-existing anxiety and sensory processing characteristics do patients with chronic low back pain have?**

Date

Dear ….,

I would like to invite you to volunteer to participate in an international research study in chronic low back pain. *Before you decide* we would like you to understand why the research is being done and what it would involve for you. I would be happy to go through the information sheet with you and answer any questions you have.

About The Study

This study in chronic low back pain is being undertaken in association with Manchester Metropolitan University, UK and in collaboration with the Vrije Universiteit of Brussels, Belgium. There is currently limited understanding as to why some people recover from a back injury but others develop chronic back pain. It is believed to be related to the way the individual's brain processes pain and other senses and this is the focus of our investigation.

Your input as a person experiencing chronic low back pain is highly valuable to us. You can provide unique information specific to chronic back pain sufferers that we cannot obtain anywhere else. If we can identify characteristics of individuals who are likely to be at risk of developing chronic pain following a back injury through this study, we can then target appropriate and individualised treatments. We would be very grateful for your participation.

If you feel the following points apply to you, please take time to consider the information in this letter and think about whether you would like to volunteer. You:

- are aged between 18-64 inclusive.
- have been experiencing significant back pain most days for more than 6 months.
- do not have a clear diagnosis as to where the pain is currently coming from (such as malignancy/ infection/ inflammatory disease like ankylosing spondilitis etc.) and where anti-inflammatory medication has been used these have not been found to be helpful for the pain.

- experience pain in variable areas around the back +/- other body parts, that is not always in the same place and that can worsen for no apparent reason and flare up with little provocation.

I have contacted you personally because you are known to me as a person with chronic low back pain. Your decision to participate or not will in no way affect any treatment you may receive in future. You are free to withdraw at any time, without giving a reason. This would not affect the standard of health care you usually receive.

Your Protection

Study participation will involve answering four questionnaires about your pain experience and aspects of your personal character and brain function. These will be given to you by your health provider / posted to you. It is estimated the questionnaires will take approximately 15 minutes to complete.

You will be asked to return the fully completed questionnaires to your health provider / me by post. You are welcome to request the results and outcome of our research project after it is completed for your interest.

A small number of questionnaire respondents will be invited at a later date, by correspondence, for a follow-up interview process. More details of the interview procedure will be explained in the correspondence and you will be under no obligation to accept the invitation should you be selected.

Your Protection

This research project has been approved by the Manchester Metropolitan University Ethics Committee, UK. We will follow ethical and legal practice and all information about you will be handled in confidence. Once the research has been completed and the questionnaires are no longer required in the research process the questionnaires will be destroyed. If you do consent to participate in the study this will mean you also consent to me contacting you once by telephone if necessary, to help you complete any unanswered questions remaining on any of the questionnaires.

If you have any questions or concerns about your rights as a participant in this research study you can contact the Director of Studies, Dr. Peter Goodwin at Manchester Metropolitan University, Faculty of Health, Psychology & Social Care, Birley Fields Campus, 53, Bonsall St., Manchester M15 6GX . E-mail:p.goodwin@mmu.ac.uk, Telephone: +44 (0)161 247 2941.

If you would like to participate in this study we will give you four questionnaires, which usually take approximately 15 minutes to complete. If you would first like to discuss it further or ask questions about this study please contact me on 07 548 2382 or 021 023 67104, or at jacqui@thephysioshed.com within the next 3 days.

Yours sincerely,

Jacqui Clark MSc, MCSP, MPNZ

Physiotherapist, Lecturer and PhD Researcher
Guest Senior Lecturer Manchester Metropolitan University UK.
The Physio Shed, 8 Beach Grove, Omokoroa 3114, Bay of Plenty. www.thephysioshed.com

Appendix 3d: Participant questionnaire consent form.

Patient Identification Number for this trial:

CONSENT FORM - Questionnaires

Research Title: **What pre-existing anxiety and sensory processing disorder characteristics do patients with chronic low back pain have?**

Name of Primary Researcher: **Jacqui Clark, PhD student, Manchester Metropolitan University**

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated **[DATE]** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I agree that my participation is voluntary and that I am free to withdraw until 5 days after completion and handing in of the questionnaires without giving any reason, without my medical care or legal rights being affected.

3. I agree to consent to my GP being informed of my participation in this study.

4. I agree to take part in the above study.

Name of Participant	Date	Signature

Name of Person taking consent.	Date	Signature

Research Title: **What pre-existing anxiety and sensory processing disorder characteristics do patients with chronic low back pain have?**

Date...

Thank you for participating in the above research study in chronic low back pain. To

help us understand more about people with chronic low back pain please complete

the following four questionnaires.

- Your current medications: name and dose (if known)_____

  _____
  NB: This 'current medications' item was not included in the pilot study

- Please answer all the questions. (You may ignore the scoring sheets on pg.5-7 of the Sensory Profile.)

- If you make a mistake clearly delete the error and mark your preferred answer instead.

- Please avoid marking on the line between two answer boxes as this makes it difficult for us to know which answer you prefer.

- If you leave out or forget to answer one or more questions I would like to give you a quick call on the telephone and talk it through with you to help you complete the unanswered questions.
  To do this it would help me if you would leave your contact name and number below without obligation.
  Name (e.g. Mrs. Smith / John.)_____
  Contact phone number:_____
  Convenient time of day to call: _____
      or choose: Any / mornings/ afternoons / evenings **(circle as appropriate.)**

- Once all your questions are complete this front page with your contact details will be completely separated from the questionnaires and your questionnaires will become anonymous.

- **If you think you may be interested in participating in a follow-up interview to talk with me confidentially about your experiences with chronic low back pain, please leave your postal or email address below so I can contact you again:**

_____

Thank you.

Appendix 3f: Ethics approval from Dublin, Ireland.

St. Vincent's Healthcare
GROUP LIMITED

UCD
DUBLIN

Ethics and Medical Research Committee
ELM PARK, DUBLIN 4
Tel. (01) 2214117 Fax (01) 2214428
email: joan.mcdonnell@ncd.ie or jacinta.mcmanus@ucd.ie

2nd February, 2015.

Dr. Keith Smart,
Clinical Specialist Physiotherapist,
St. Vincent's University Hospital,
Elm Park,
Dublin 4.

**Re: - What trait anxiety and sensory processing profile characteristics do patients
with non-specific chronic low back pain with central pain mechanisms have?
Standard Application Form. PIL/Consent vs 2 Letter to Consultant. Study
Proposal. Questionnaires.**

Dear Dr. Smart,

We have received the clarifications and revised documents from Ms Clark that were
requested at the Ethics and Medical Research Committee meeting held on Wednesday
7th January 2015 at which the above study was reviewed

Following review of the clarifications and revised documents, this study is now granted
full ethical approval.

Yours sincerely,

Dr. E. McKone,
Chairman,
Ethics & Medical Research Committee

cc   Mrs Jacqui Clark, The Physio Shed, New Zealand.

Appendix 3g: Ethics approval from IRAS, England

Hi Jacqui

On that basis I am happy for you to get started. Good luck with recruitment.

Best wishes

Natalie

Natalie Garratt
Research & Development Lead
Salford Royal NHS Foundation Trust
Tel: 0161 206 5203
natalie.garratt@manchester.ac.uk

From: Jacqui Clark [mailto:jacqui@clarkiesmail.com]
Sent: 26 June 2015 02:53
To: Natalie Garratt
Cc: ruth.Williams@srft.nhs.uk
Subject: FW: Research Study at SRFT - 2015/099misc

Hi Natalie,
Please see my reply below to Maureen. Her automatic reply email says to contact you in her absence – I'm just hoping we now have permission to begin data collection.

Thanks, and kind regards,
Jacqui

From: Jacqui Clark [mailto:jacqui@clarkiesmail.com]
Sent: Friday, 26 June 2015 1:21 p.m.
To: 'Maureen Daniels'
Cc: 'ruth.Williams@srft.nhs.uk'; 'Peter Goodwin'; 'Gillian Yeowell'
Subject: RE: Research Study at SRFT - 2015/099misc

Hi Maureen,

Sorry for the delay. My supervisors and I have decided that I should have face to face contact with the participants for interviews in their own homes only. I hope we can now get started, with your permission.

Thanks for your help,

Kind regards,
Jacqui

From: Maureen Daniels [mailto:Maureen.Daniels@manchester.ac.uk]
Sent: Friday, 12 June 2015 1:44 a.m.
To: jacqui@clarkiesmail.com
Cc: ruth.Williams@srft.nhs.uk
Subject: Research Study at SRFT - 2015/099misc

Dear Jacqui
Study: Sensory processing and anxiety characteristics in NSCLBP patients
Further to your email to Natalie Garratt submitting your documents for review, I have now issued
the R&D reference number of 2015/099misc and this should be quoted in all correspondence.
Can you confirm if you will have any face to face contact with the participants and where the
interviews will take place?

Best wishes
Maureen

Maureen Daniels
Associate Research & Development Manager
Research and Development
Salford Royal NHS Foundation Trust
Summerfield House, 544 Eccles New Road
Salford M5 5AP
Tel: 0161 206 7051
Maureen.daniels@manchester.ac.uk

This email has been checked for viruses by Avast antivirus software.
www.avast.com

Appendix 3h: Ethics permission from New Zealand

From: hdecs@moh.govt.nz
Subject: Re: FAO Kelly - Minimal Risk Observational Study
Date: 5 November 2014 at 12:12:15 PM NZDT
To: <jacqui@thephysioshed.com>

Hi Jacqui,

Thanks for your email. An observational study requires HDEC review only if the study involves more than minimal risk. An observational study always involves more than minimal risk if it involves one or more of the following:

- One or more participants who will not have given informed consent to participate, or
- One or more participants who are vulnerable, or
- Standard treatment being withheld from one or more participants, or
- The storage, preservation or use of human without consent, or
- The disclosure of health information without authorisation.

From the information you have given, your project would meet the definition of a minimal risk observational study and HDEC review is therefore not required.

Please let me know if you have any queries in relation to this.

Kind regards

Kelly

Kelly Traynor
Advisor
Ethics Committees
Business Services
Office of the CMO
Clinical Leadership
Protection & Regulation
Ministry of Health
DDI: 04 819 6832
Fax: 04 496 2343

http://www.health.govt.nz
mailto:Kelly_Traynor@moh.govt.nz

From: "The Physio Shed" <jacqui@thephysioshed.com>
To: <hdecs@moh.govt.nz>,
Date: 05/11/2014 10:25 a.m.
Subject: FAO Kelly - Minimal Risk Observational Study

Hi Kelly,

Thanks for your advice over the phone. Please can you confirm whether I need ethical approval for my study. The details are as follows:

I will be recruiting 40-50 patients from my own clinic and from other colleagues' clinics in New Zealand who have chronic back pain. They will be asked if they would be willing to answer 4 questionnaires about their symptoms and their character traits (anxiety and sensory processing). A select few of them (approx 6-8) will be asked at a later date if they would be willing to participate in 1-2 in depth interviews about their pre-morbid experiences related to back pain. Subjects of a sensitive nature are not anticipated to come up.

I attach the health providers' information letter. I already have ethical approval from my UK university.

I look forward to hearing from you.

Thank you and kind regards,

Jacqui

Jacqui Clark MSc, MPNZ, MCSP
Physiotherapist, Post Graduate Lecturer & PhD Researcher
Guest Senior Lecturer Manchester Metropolitan University UK
Member of the Pain in Motion International Research Collaboration

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8 Beach Grove
Omokoroa 3114
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www.thephysioshed.com
http://www.paininmotion.be/EN/index-E.html

[attachment "Information sheet EMAIL for health providers (4).docx" deleted by Kelly Traynor/MOH]
****

Appendix 3i: Central Sensitisation Inventory

CENTRAL SENSITIZATION INVENTORY

(Meyer et al, 2012; Neblett et al 2013)

A	Please circle the best response to the right of each statement	Never	Rarely	Sometimes	Often	Always
1	I feel un-refreshed when I wake up in the morning					
2	My muscles feel stiff and achy					
3	I have anxiety attacks					
4	I grind or clench my teeth					
5	I have problems with diarrhoea and/or constipation					
6	I need help in performing my daily activities					
7	I am sensitive to bright lights					
8	I get tired very easily when I am physically active					
9	I feel pain all over my body					
10	I have headaches					
11	I feel discomfort in my bladder and/or burning when I urinate					
12	I do not sleep well					
13	I have difficulty concentrating					
14	I have skin problems such as dryness, itchiness, or rashes					
15	Stress makes my physical symptoms get worse					
16	I feel sad or depressed					
17	I have low energy					
18	I have muscle tension in my neck and shoulders					
19	I have pain in my jaw					
20	Certain smells, such as perfumes, make me feel dizzy and nauseated					
21	I have to urinate frequently					
22	My legs feel uncomfortable and restless when I am trying to go to sleep at night					
23	I have difficulty remembering things					
24	I suffered trauma as a child					
25	I have pain in my pelvic area					
	TOTAL					
B	**Have you been diagnosed by a doctor with any of the following disorders?** Please check the box to the right for each diagnosis and write the year of the diagnosis	NO	Yes	Year diagnosed		
1	Restless leg syndrome					
2	Chronic fatigue syndrome					
3	Fibromyalgia					
4	Temporomandibular joint disorder (TMJ)					
5	Migraine or tension headaches					
6	Irritable bowel syndrome					
7	Multiple chemical sensitivities					
8	Neck injury (including whiplash)					
9	Anxiety or panic attacks					
10	Depression					
	Total					

SELF-EVALUATION QUESTIONNAIRE

Developed by Charles Spielberger
In collaboration with
R.L. Gorsuch, R. Lushene, P.R. Vagg, and G.A. Jacobs

Manchester Metropolitan University

About you: **Age** _____   Gender: **Male / Female** (circle as appropriate)

Directions: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate *how you generally feel*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel pleasant	①	②	③	④
2. I feel nervous and restless	①	②	③	④
3. I feel satisfied with myself	①	②	③	④
4. I wish I could be as happy as others seem to be	①	②	③	④
5. I feel like a failure	①	②	③	④
6. I feel rested	①	②	③	④
7. I am "calm, cool and collected"	①	②	③	④
8. I feel that difficulties are piling up so that I cannot overcome them	①	②	③	④
9. I worry too much over something that really doesn't matter	①	②	③	④
10. I am happy	①	②	③	④
11. I have disturbing thoughts	①	②	③	④
12. I lack self-confidence	①	②	③	④
13. I feel secure	①	②	③	④
14. I make decisions easily	①	②	③	④
15. I feel inadequate	①	②	③	④
16. I am content	①	②	③	④
17. Some unimportant thought runs through my mind and bothers me	①	②	③	④
18. I take disappointments so keenly that I can't put them out of my mind	①	②	③	④
19. I am a steady person	①	②	③	④
20. I get in a state of tension or turmoil as I think over my recent concerns and interests	①	②	③	④

Appendix 3k: Marlowe Crowne Social Desirability Scale

Manchester Metropolitan University

About you: Gender **M / F** (circle as appropriate) **Age_____**

Marlowe-Crowne 2(10) Social Desirability Scale

Listed below are a number of statements concerning personal attitudes and traits. Read each item and decide whether the statement is a true or false statement about you personally. Circle the word True or False accordingly. Thank you for your time.

1. I never hesitate to go out of my way to help someone in trouble. **True / False**

2. I have never intensely disliked anyone. **True / False**

3. There have been times when I was quite jealous of the good fortune of others. **True / False**

4. I would never think of letting someone else be punished for my wrong doings. **True / False**

5. I sometimes feel resentful when I don't get my way. **True / False**

6. There have been times when I felt like rebelling against people in authority even though I knew they were right. **True / False**

7. I am always courteous, even to people who are disagreeable. **True / False**

8. When I don't know something I don't at all mind admitting it. **True / False**

9. I can remember "playing sick" to get out of something. **True / False**

10. I am sometimes irritated by people who ask favours of me. **True / False**

ADOLESCENT/ADULT
SENSORY PROFILE™

Catana Brown, Ph.D., OTR, FAOTA
Winnie Dunn, Ph.D., OTR, FAOTA

Self Questionnaire

Name: _____ Age: _____ Date: _____

Birthdate: _____ Gender: ☐ Male ☐ Female

Are there aspects of daily life that are not satisfying to you? If yes, please explain. _____

_____

_____

_____

INSTRUCTIONS

Please check the box that **best** describes the frequency with which you perform the following behaviors. If you are unable to comment because you have not experienced a particular situation, please draw an X through that item's number. Write any comments at the end of each section.

Please answer all of the statements. Use the following key to mark your responses:

ALMOST NEVER	When presented with the opportunity, you **almost never** respond in this manner (about 5% or less of the time).
SELDOM	When presented with the opportunity, you **seldom** respond in this manner (about 25% of the time).
OCCASIONALLY	When presented with the opportunity, you **occasionally** respond in this manner (about 50% of the time).
FREQUENTLY	When presented with the opportunity, you **frequently** respond in this manner (about 75% of the time).
ALMOST ALWAYS	When presented with the opportunity, you **almost always** respond in this manner (about 95% or more of the time).

Item		A. Taste/Smell Processing	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
I	1	I leave or move to another section when I smell a strong odor in a store (for example, bath products, candles, perfumes).					
∫	2	I add spice to my food.					
—	3	I don't smell things that other people say they smell.					
∫	4	I enjoy being close to people who wear perfume or cologne.					
I	5	I only eat familiar foods.					
—	6	Many foods taste bland to me (in other words, food tastes plain or does not have a lot of flavor).					
⊚	7	I don't like strong tasting mints or candies (for example, hot/cinnamon or sour candy).					
∫	8	I go over to smell fresh flowers when I see them.					

Comments

Item		B. Movement Processing	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
⊚	9	I'm afraid of heights.					
∫	10	I enjoy how it feels to move about (for example, dancing, running).					
I	11	I avoid elevators and/or escalators because I dislike the movement.					
—	12	I trip or bump into things.					
⊚	13	I dislike the movement of riding in a car.					
∫	14	I choose to engage in physical activities.					
—	15	I am unsure of footing when walking on stairs (for example, I trip, lose balance, and/or need to hold the rail).					
⊚	16	I become dizzy easily (for example, after bending over, getting up too fast).					

Comments

2

Item		C. Visual Processing	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
∫	17	I like to go to places that have bright lights and that are colorful.					
|	18	I keep the shades down during the day when I am at home.					
∫	19	I like to wear colorful clothing.					
⊚	20	I become frustrated when trying to find something in a crowded drawer or messy room.					
—	21	I miss the street, building, or room signs when trying to go somewhere new.					
⊚	22	I am bothered by unsteady or fast moving visual images in movies or TV.					
—	23	I don't notice when people come into the room.					
|	24	I choose to shop in smaller stores because I'm overwhelmed in large stores.					
⊚	25	I become bothered when I see lots of movement around me (for example, at a busy mall, parade, carnival).					
|	26	I limit distractions when I am working (for example, I close the door, or turn off the TV).					

Comments

Item		D. Touch Processing	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
⊚	27	I dislike having my back rubbed.					
∫	28	I like how it feels to get my hair cut.					
|	29	I avoid or wear gloves during activities that will make my hands messy.					
∫	30	I touch others when I'm talking (for example, I put my hand on their shoulder or shake their hands).					
⊚	31	I am bothered by the feeling in my mouth when I wake up in the morning.					
∫	32	I like to go barefoot.					
⊚	33	I'm uncomfortable wearing certain fabrics (for example, wool, silk, corduroy, tags in clothing).					
⊚	34	I don't like particular food textures (for example, peaches with skin, applesauce, cottage cheese, chunky peanut butter).					
|	35	I move away when others get too close to me.					
—	36	I don't seem to notice when my face or hands are dirty.					
—	37	I get scrapes or bruises but don't remember how I got them.					
|	38	I avoid standing in lines or standing close to other people because I don't like to get too close to others.					
—	39	I don't seem to notice when someone touches my arm or back.					

Comments

3

Item		E. Activity Level	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
∫	40	I work on two or more tasks at the same time.					
—	41	It takes me more time than other people to wake up in the morning.					
∫	42	I do things on the spur of the moment (in other words, I do things without making a plan ahead of time).					
|	43	I find time to get away from my busy life and spend time by myself.					
—	44	I seem slower than others when trying to follow an activity or task.					
—	45	I don't get jokes as quickly as others.					
|	46	I stay away from crowds.					
∫	47	I find activities to perform in front of others (for example, music, sports, acting, public speaking, and answering questions in class).					
⊚	48	I find it hard to concentrate for the whole time when sitting in a long class or a meeting.					
|	49	I avoid situations where unexpected things might happen (for example, going to unfamiliar places or being around people I don't know).					

Comments

Item		F. Auditory Processing	ALMOST NEVER	SELDOM	OCCASIONALLY	FREQUENTLY	ALMOST ALWAYS
∫	50	I hum, whistle, sing, or make other noises.					
⊚	51	I startle easily at unexpected or loud noises (for example, vacuum cleaner, dog barking, telephone ringing).					
—	52	I have trouble following what people are saying when they talk fast or about unfamiliar topics.					
|	53	I leave the room when others are watching TV, or I ask them to turn it down.					
⊚	54	I am distracted if there is a lot of noise around.					
—	55	I don't notice when my name is called.					
|	56	I use strategies to drown out sound (for example, close the door, cover my ears, wear ear plugs).					
|	57	I stay away from noisy settings.					
∫	58	I like to attend events with a lot of music.					
—	59	I have to ask people to repeat things.					
⊚	60	I find it difficult to work with background noise (for example, fan, radio).					

Comments

Summary Score Sheet

Quadrant Grid

Instructions: Transfer from the *Self Questionnaire* the item raw score that corresponds with each item listed (refer to the *User's Manual* for directions on how to obtain item raw scores). Add the Raw Score column to get the Quadrant Raw Score Total for each quadrant.

— QUADRANT 1		∿ QUADRANT 2		⊚ QUADRANT 3		∣ QUADRANT 4	
Low Registration		**Sensation Seeking**		**Sensory Sensitivity**		**Sensation Avoiding**	
Item	Raw Score	Item	Raw Score	Item	Raw Score	Item	Raw Score
3		2		7		1	
6		4		9		5	
12		8		13		11	
15		10		16		18	
21		14		20		24	
23		17		22		26	
36		19		25		29	
37		28		27		35	
39		30		31		38	
41		32		33		43	
44		40		34		46	
45		42		48		49	
52		47		51		53	
55		50		54		56	
59		58		60		57	
Quadrant Raw Score Total		Quadrant Raw Score Total		Quadrant Raw Score Total		Quadrant Raw Score Total	

SCORE KEY	
1	Almost Never
2	Seldom
3	Occasionally
4	Frequently
5	Almost Always

ICON KEY	
—	Low Registration
∿	Sensation Seeking
⊚	Sensory Sensitivity
∣	Sensation Avoiding

5

Quadrant Summary

Quadrant Summary Chart for Ages 11–17

Quadrant	Quadrant Raw Score Total	Much Less Than Most People --	Less Than Most People -	Similar To Most People =	More Than Most People +	Much More Than Most People ++
1. Low Registration	/75	15 ---------- 18	19 ---------- 26	27 ---------- 40	41 ---------- 51	52 ---------- 75
2. Sensation Seeking	/75	15 ---------- 27	28 ---------- 41	42 ---------- 58	59 ---------- 65	66 ---------- 75
3. Sensory Sensitivity	/75	15 ---------- 19	20 ---------- 25	26 ---------- 40	41 ---------- 48	49 ---------- 75
4. Sensation Avoiding	/75	15 ---------- 18	19 ---------- 25	26 ---------- 40	41 ---------- 48	49 ---------- 75

*Classifications are based on the performance of individuals without disabilities ($n = 193$).

Quadrant Summary Chart for Ages 18–64

Quadrant	Quadrant Raw Score Total	Much Less Than Most People --	Less Than Most People -	Similar To Most People =	More Than Most People +	Much More Than Most People ++
1. Low Registration	/75	15 ---------- 18	19 ---------- 23	24 ---------- 35	36 ---------- 44	45 ---------- 75
2. Sensation Seeking	/75	15 ---------- 35	36 ---------- 42	43 ---------- 56	57 ---------- 62	63 ---------- 75
3. Sensory Sensitivity	/75	15 ---------- 18	19 ---------- 25	26 ---------- 41	42 ---------- 48	49 ---------- 75
4. Sensation Avoiding	/75	15 ---------- 19	20 ---------- 26	27 ---------- 41	42 ---------- 49	50 ---------- 75

*Classifications are based on the performance of individuals without disabilities ($n = 496$).

Quadrant Summary Chart for Ages 65 and older

Quadrant	Quadrant Raw Score Total	Much Less Than Most People --	Less Than Most People -	Similar To Most People =	More Than Most People +	Much More Than Most People ++
1. Low Registration	/75	15 ---------- 19	20 ---------- 26	27 ---------- 40	41 ---------- 51	52 ---------- 75
2. Sensation Seeking	/75	15 ---------- 28	29 ---------- 39	40 ---------- 52	53 ---------- 63	64 ---------- 75
3. Sensory Sensitivity	/75	15 ---------- 18	19 ---------- 25	26 ---------- 41	42 ---------- 48	49 ---------- 75
4. Sensation Avoiding	/75	15 ---------- 18	19 ---------- 25	26 ---------- 42	43 ---------- 49	50 ---------- 75

*Classifications are based on the performance of individuals without disabilities ($n = 261$).

Quadrant Profile

Instructions: Transfer the information from the classification columns of the Quadrant Summary Chart (the areas marked with an X) to the Quadrant Profile. Circle the classification symbol in each quadrant below that corresponds with the classification information for that quadrant. Finally, check the appropriate age box.

The following symbols are used to represent the classifications on the Quadrant Profile:

– –	Much Less Than Most People
–	Less Than Most People
=	Similar to Most People
+	More Than Most People
+ +	Much More Than Most People

Low Registration	Sensation Seeking
+ + + = – – –	+ + + = – – –
Sensory Sensitivity – – – = + + +	**Sensation Avoiding** – – – = + + +

See chapter 5 for more information regarding interpretations and intervention.

Check the correct age:

- ☐ 11–17 years
- ☐ 18–64 years
- ☐ 65 years and older

7

Appendix 3m: Leeds Assessment for Neuropathic Signs and Symptoms (S-LANSS)

THE S-LANSS PAIN SCORE - for screening neuropathic pain.

These questions help us to know more about the kind of pain you are experiencing. Please read each question and indicate your answer by circling a) or b) for each question. If you make a mistake clearly delete the error and circle your preferred answer. Thank you for your time.

1. **In the area where you have pain, do you also have 'pins and needles', tingling or prickling sensations.**

   a)   NO – I don't get these sensations   (0)
   b)   YES – I get these sensations often   (5)

2. **Does the painful area change colour (perhaps look mottled or more red) when the pain is particularly bad?**

   a)   NO – The pain does not affect the colour of my skin   (0)
   b)   YES – I have noticed that the pain does make my skin look different from normal   (5)

3. **Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this?**

   a)   NO – The pain does not make my skin abnormally sensitive to touch   (0)
   b)   YES – My skin in that area is particularly sensitive to touch   (3)

4. **Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like 'electric shocks', jumping and bursting might describe this.**

   a)   NO – My pain doesn't really feel like this   (0)
   b)   YES – I get these sensations often   (2)

5. **In the area where you have pain, does your skin feel unusually hot like a burning pain?**

   a)   NO – I don't have burning pain   (0)
   b)   YES – I get burning pain often   (1)

6. **Gently <u>rub</u> the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?**

   a)   The painful area feels no different from the non-painful area   (0)
   b)   I feel discomfort, like pins and needles, tingling or burning in the painful   (5)
        area that is different from the non-painful area

7. **Gently <u>press</u> on the painful area with your finger tip and then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?**

   a)   The painful area does not feel different from the non-painful area   (0)
   b)   I feel numbness or tenderness in the painful area that is different from the   (3)
        non-painful area.

Attention Healthcare Provider: a score of 12 or more suggests pain of predominantly neuropathic origin and, for the purposes of this research study, means no further questionnaires are required.

Appendix 3n: Acceptance email from the Journal of Bodywork and Movement Therapies

Dear Dr. Clark,

We are pleased to inform you that your accepted manuscript (unformatted and unedited PDF) is now available online at:

https://doi.org/10.1016/j.jbmt.2017.11.007

You might like to bookmark this permanent URL to your article. Please note access to the full text of this article will depend on your personal or institutional entitlements.
This version of your article has already been made available at this early stage to provide the fastest access to your article. It is not intended to be the final version of your article. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note changes to the article should not be requested at this stage.

Your article can already be cited using the year of online availability and the DOI as follows:
Author(s), Article Title, Journal (Year), DOI.

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To track the status of your article throughout the publication process, please use our article tracking service:

https://authors.elsevier.com/tracking/article/details.do?aid=1634&jid=YJBMT&surname=Clark

Kind regards,
Elsevier Author Support

Appendix 4a: STROBE statement

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders

		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 4b: Evidence of submission of article 4

Dear Mrs. Clark,

Your submission entitled "The Extent of Central Sensitisation Symptoms can be Predicted by Trait Sensory Profiles, Trait Anxiety and Extreme Personality Type in People with Non-specific Chronic Low Back Pain." has been received by The Journal of Pain.

You may check on the progress of your paper by logging on to the Elsevier Editorial System as an author. The URL is https://ees.elsevier.com/jpain/.

Your username is: jclark@thephysioshed.com If you need to retrieve password details, please go to: http://ees.elsevier.com/jpain/automail_query.asp

Your manuscript will be given a reference number once an editor has been assigned.

PLEASE NOTE: If you haven't yet, please send the required Mandatory Submission Form, signed by all authors. You may download this at http://cdn.elsevier.com/promis_misc/jpaincopyright.pdf, send the signed document, as an attachment, to jpain@jpain.us.

Thank you for submitting your work to this journal.

Kind regards,

Elsevier Editorial System
The Journal of Pain

APPLY for APS membership, or renew your membership:
http://persweb.connect2amc.com/aps/MEMBERSHIP/tabid/113/Default.aspx

Appendix 4c: Evidence of submission of article 5.

Jun 27, 2018

Dear Mrs. Clark,

Your submission entitled "Prevalence of Extreme Trait Sensory Profiles and Personality types in Non-specific Chronic Low Back Pain with Predominant Central Sensitisation: Secondary analysis of an international observational study" has been received by the journal editorial office.

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author.

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Appendix 5a: Participant Information Sheet for Interviews

Participant Information Sheet

Research Title: **What pre-existing anxiety and sensory processing disorder characteristics do patients with chronic low back pain have?**

Date

Dear

Thank you for participating in the first part of our international research programme in chronic low back pain earlier this year/ last year. The time you took to complete the questionnaires has been much appreciated.

As a follow-up to the questionnaires I would like to invite you to talk to me by interview to help me gain some deeper insights. *Before you decide* we would like you to understand why the research is being done and what it would involve for you. I will be happy to go through the information sheet with you and answer any questions you have, with no obligation.

About the Study

This study in chronic low back pain is being undertaken in association with Manchester Metropolitan University, UK and in collaboration with the University of Brussels, Belgium. At present there is limited understanding as to why some people recover from a back injury but others develop chronic back pain. It is believed to be related to the way the individual's brain processes pain and other senses and how life's experiences may have an influence on recovery systems within the body. These concepts will form the basis of the interview framework from which we can explore meaning in your life history relevant to your chronic back pain.

Why you have been chosen

We have contacted you personally because you are known to myself or one of my colleagues as a person with chronic low back pain / because you have been recommended by another participant in the study who is aware of your chronic low back pain.

Your input as a person experiencing chronic low back pain is highly valuable to us. You can provide unique information specific to chronic back pain sufferers that we cannot obtain anywhere else. If we can identify characteristics of individuals who are likely to be at risk of developing chronic pain following a back injury through this study, we can then target appropriate and individualised treatments and

prevent many patients from developing chronic back pain. We would be very grateful for your participation.

Your decision to participate or not will in no way affect any treatment you may receive in future. You are free to change your mind about participating before the interview, without giving a reason. This would not affect the standard of health care you usually receive.

<u>What your participation will involve</u>

After discussing this information with me and if you agree to volunteer as an interviewee, you be required to sign the research consent form. We will arrange a convenient time for you to meet with me for an interview either at my office/the office of your health care provider or in your home, wherever you feel more comfortable. I will invite you to recount aspects of your life story, as it relates to who you are now with your back pain.

Before the interview it may be helpful for you to consider life stages such as your childhood, teen years, earlier adult years and later adult years and perhaps to consider giving me an account of your life in terms of topics such as health, development, schooling, sports and recreation, achievements and difficulties, occupations and hobbies, learning experiences, including those of your close relatives (for possible familial similarities) and any other areas you feel are of interest and relevance to you. I will guide you with some broad areas of focus to discuss.

It is anticipated that as interesting and relevant information emerges from your interview I may ask you to participate in one or two follow-up interviews to explore themes further, at a time that is convenient to you.

The interview(s) will be recorded on an audio recording device and will take place over approximately one hour. I will give you a copy of the interview transcript(s) for you to review. You will be given a period of 5 days to amend parts of the transcript(s) or withdraw certain information if you so wish. You will have the right to withdraw your interview data entirely from the study if you wish during that time.

<u>Your protection</u>

We will follow ethical and legal practice and all information about you will be handled in confidence. Your interview will remain anonymous. At no time will your real name be used in the transcripts nor in any of the reporting of the research. Every attempt will be made to conceal your identity such as changing the names of people and places that could identify you in some way to others.

This research project has been approved by the Manchester Metropolitan University Ethics Committee, UK.

If you have any questions or concerns about your rights as a participant in this research study you can contact the Director of Studies, Dr. Peter Goodwin at Manchester Metropolitan University, Faculty

of Health, Psychology & Social Care, Elizabeth Gaskell Campus, Hathersage Rd., Manchester M13 0JA . E-mail:p.goodwin@mmu.ac.uk, Telephone: +44 (0)161 247 2941

If you would like to express your interest in participating as an intervewee, discuss it further or to ask questions about this study please contact me on **07 548 2382** or **021 023 67104,** or at **jacqui@thephysioshed.com** within the next 3 days. Thank you.

Yours sincerely,

Jacqui Clark MSc, MCSP, MPNZ

Physiotherapist, Lecturer and Researcher

Appendix 5b: Consent Form for Interviews

![Manchester Metropolitan University logo]

Patient Identification Number for this trial:

CONSENT FORM - Interviews

Research Title: **What pre-existing anxiety and sensory processing disorder characteristics do patients with chronic low back pain have?**

Name of Researcher: **Jacqui Clark**

Please initial all boxes

5. I confirm that I have read and understand the information sheet dated **[DATE]** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.   ☐

6. I agree that my participation is voluntary and that I am free to withdraw until 5 days after receipt of the transcript without giving any reason, without my medical care or legal rights being affected.   ☐

7. I agree to consent to all the interview procedures set out in the information sheet for the above study.   ☐

8. I agree to allow the use of anonymised quotations from my interview transcript in the reporting of the research.   ☐

9. I agree to take part in the above study.   ☐

Name of Participant	Date	Signature

Name of Person taking consent	Date	Signature

Appendix 5c: Field Notes excerpt

Field notes: Participant P4

Keen that interview be done at her home so that I would understand her more fully.

Home very creative, uncluttered and tidy.

Keen that I should understand who she is. Wasn't sure she would be able to talk much but talked freely for 1 hour 20 mins.

She mentioned as she was making a pot of tea that when she used to go to cafés with a friend, she would think she was having a good day and coping well, but then would have a cake and suddenly feel overwhelmed by the noise in the café and become vigilant about what was going on around her for threat like she was anxious. But she didn't feel she had gone in to the café at all anxious or worried. It happens every time she eats a sugary food.

On leaving she mentioned her neighbour at war with her every day with "picky faults to find." (? Safe home environment.) Supportive husband.

Field notes and impressions: Participant P5.

Works at home. Sits in LazyBoy comfy chair. Sat on leg tucked under her and said she forgot it was there so that when she got up it was numb. (?? Bodily hyposensitivity.)

Rocked in the chair the whole time through the interview. - ? stimulating vestibular system? Distracting from pain?

Very smiley. Good social skills. Not demonstrating pain - ?defensiveness?

Came from background of not feeling wanted, no-one cared about her pain or her struggles, dismissed them when she mentioned any of them to family (particularly mother). Still not understood be her family now. Kept calling herself "weird."

Questionnaires – now says that in retrospect she did not answer questionnaires truthfully / honestly because she was in self-denial.

This is very much like a repressor. Re-did the anxiety questionnaire (STAI) but she scored higher by 1 point in 4 questions and lower by 1 in 4 questions so came to same result of 44 – moderate anxiety. Yet she is seeing psychologist for predominant anxiety issues.

Food is a major problem – she has never eaten well.

Appendix 5d: Excerpts of the participant raw transcripts

.

Participant P4

… So my muscles don't feel stiff and achy. I don't have anxiety attacks. That was put in at 'sometimes'. Well it was probably more than I even thought then. It was probably often, but I don't have those anymore. I can go to coffee and I can sit there and not feel that panic and that anxiety rising in me. I used to sit there and I would think I've got to get out, how do I get out, where do I go – regardless that there's a door there. The panic would just swamp me completely.

I: In the coffee shop?

P: Yeah. And now I don't have those. I was grinding and clenching my teeth. Even the dentist said what are you doing? I didn't know - it was in the night. And I mean I had problems with diarrhoea – I had that. I put 'rarely' but obviously I know now that it was actually high. So you diagnosed me as highly centrally sensitised. I was probably more than that.

I: Right.

P: Because I look at these and I think no you had diarrhoea, not so much so like you get when you've got a bug, but it was definitely not what it should have been.

I: Oh how interesting.

P: Yeah.

I: So looking back with retrospect you can see …

P: Yeah I can see I actually answered it positively and I was probably worse.

I: Interesting.

P: So I'm sensitive to bright lights. I didn't realise how much I was until now that I understand it. I get tired easily. I feel pain not so much all over my body. I wasn't sleeping. I had difficulty concentrating. Well I put 'often' and I did. I couldn't even follow the recipe for baking a cake without help, and yet I'd been really good at it. And I think that's the thing. It was what I'd come from. I was a clever, able person. I could do stuff – it would take seven women to keep up with me on a sewing machine in terms of output. My capacity was huge. What I think I've come to realise is that that capacity was what broke me. It became too highly tuned, too much going on in terms of the senses in my brain. I don't know whether that makes sense to you.

I: Yes.

P: But I can see it now.

I: Like an overload.

P: It became an overload and it broke. Now whether that happened through a pain or emotional stress I don't really know, but I know that it must have happened.

I: Do you remember what came first?

P: The pain or the …

I: Or some emotional stress or being overloaded?

P: I don't know. I think they were so closely aligned cause with seven children there was a lot of emotional stress going on in their lives and therefore in mine. So I can feel the pain coming now – right now – in this area – my left hand side. And the reason for that is that I know now why that is. See I could never say to you why that is, but all of a sudden I know that it's because we're talking about emotional stress. Now we all have it. I mean I've got six girls and we've gone through divorce, we've gone through all the stuff that the world does – alcoholism – all the things in the world that they get dragged into that they choose to do, and you wish you could shake them and say don't do that. I had such a vision for my girls - most of my family were girls – and I had such a vision. They were so beautiful and I wanted them to be beautiful. I mean we all want our girls to be beautiful don't we?

I: Yeah.

P: Well I wish they were all dead ugly now.

I: [Chuckles].

P: I do. I wish they had big bulbous noses.

I: Why is that?

P: Well because the boys wouldn't have caused all the trouble they caused. I'm not blaming the boys, but it doesn't help.

I: No.

P: It doesn't help. So we went through - and me particularly - my husband basically just put his shoes on and went to work because he wasn't emotional like I was. He wasn't affected like I was. But I fought it, I fought it for years and that probably had an emotional impact on me.

I: Yeah.

P: So when people say to me now, you need a counsellor, you've had a complete physical and mental breakdown, I think yeah but where am I going to find a counsellor who's going to understand this stuff. And to me the only one that could do that was God and so I poured out my heart before him.

I: Mm yeah.

P: And I believe I'm hugely better in that area because those things are still happening. Those girls are still living the life of Riley. But now I can put it there and say, Lord, I can't do anything about it, this is going to take a miracle. And I say to the Lord, I want that miracle in their lives, and I'm waiting for it.

I: Yeah.

P: I always say - I have one of my daughters - number three - I call them by numbers – number three, and she's like a kamikaze pilot, and she's been like that since she was probably little. She has done the stupidest of things and she's still living. And I say to people – I used to think to myself when Axx gets saved, when she trusts Christ as her Saviour, I'm going to hire a plane and I'm going to put a flyer on the back of it, and it's going to say 'Axx's saved', and I'm going to fly it round so everyone can see.

…

P: I'd barely been in her class three months, and I've been in both places.

I: So why did she say that do you know?

P: Well I look back, and I reflect, and I think yeah … because you basically – think of the book 'Explain Pain', and it talks about pacing and graded exposure. I'm a boom and bust. I recognised me straight away. That's the beauty of the book. You could read it, and you could think that's me, that's my pain. That's where my pain is coming from. And in that graded exposure it talks about the different types of personalities that we are, I suppose, and I was boom and bust. And this teacher must have seen in me Mxx will either go for the top and get there or she'll fall to the bottom. And that was me.

I: Yeah. What were your school experiences like?

P: [Laughs] very bad. I was the naughtiest girl at school.

I: Were you? You wouldn't know it Mxx.

P: I was shocking. I went to a nuns' school cause I was Catholic then, and in third form this little nasty maths nun said to me 'I hate you Mxx *Surname*'.

I: Really?

P: Yeah she did. And do you know what I said to her? I was heading off, I might say on my bike. I was ready to go home. It was the middle of the day and I always did that. And she said 'I hate you Mxx *Surname*', and I said to her 'and I hate you too'. And you know what she said to me another day? I was in sixth form by this time. Do you know at sixth form – I was 2nd year fifth, I passed one subject in School C with 51. I was in the high learner class, accelerate classes in those days. They used to do it by IQ. And they would not put me into the general classes because I was too bright. I didn't know that at the time. And I was 2nd year fifth which was degrading. I got into sixth form by the skin of my teeth. I had not done a scrap of work since I was about Form One and I got into sixth form by the skin of my teeth. I think I managed to get 2½ subjects in School C after two years. Got into sixth form and I thought I am not going to be 2nd year sixth. So I started working, and I went from the

bottom of the class – this is sixth form – I'm talking about the whole sixth form level so I think there were a couple of hundred sixth formers - and I went to the top in English, Science, Maths, not Geography – I hated Geography, and the other one. I went from the bottom to the top, and in English as well, and they couldn't believe it. That was in the first set of exams. In the second set of exams it was summer. I mean I was brown by October the 23rd.

…

P: I didn't learn that way. I don't learn now that way.

I: So what was 'that way'?

P: Oh I had a fantastic French teacher. She was amazing. She was red-headed, she was huge, she was wonderful. We had a blackboard – a massive thing - see I'm a big picture person. And she had this chalk, and she used to come in and she would do the French lesson on the blackboard right in front of us in big letters, and I thought wow. She was amazing. I don't remember much French at all, but I remember her. You see I think I learn pictorially, and I don't know, I don't understand that completely. But I'm a very disciplined person, I'm a very in order person, I can't work with mess, and everything has to be lined up like ducks and then I'll shoot the lot. Do you know what I mean?

I: Yeah.

P: I have to know that it's going to work and so I don't use – how can I put it – it's in here *(pointing to head).* People used to say to me don't you run out of ideas? I said what? They're all up here. They're gleaned from books and magazines, but pictures. When I get a magazine I don't read the story, I look at the pictures, and I pick them up, and then I translate them. And sometimes I'll be doing something and I'll think wow, or I'll flick through some of my old pictures that I've cut out and thought one day I'd like to mimic that, whatever it is. And all of a sudden I'll remember and I'll go back and I'll find the same thing that I've actually created. But the picture was in there you see, so I don't know. But I had a very unhappy learning experience through my years because I wanted to be at the top, and, how can I put it … nuns are very nun-like. They liked the boxes ticked, and they like everything in line, but they don't understand the creativity side because they have developed through discipline and austereness so the pictorial side isn't sort of huge to them. And so I don't know, they just had a way of learning that wasn't me, and I didn't know that. And my mum was a principal of a school.

Participant P5

…I don't think anything's gotten worse, I think I'm just more open to noticing things now, and recognising the chain of events that happened from something like that.

I: Yeah.

P: And when I see something with Scooby Doo well I know I start to get stressed, and I know if I start to get stressed out by him, then I flick a switch. It snowballs. There's a couple like I work on two things at the same time, I try not to do that now cause it just gets me … I struggle.

I: Right, yeah.

P: I struggled.

I: What happens when you do try and multi task?

P: I almost become overwhelmed which is frustrating because when I look back ten years ago, I prided myself on how efficient I was, how I could handle all these balls in the air and manage everything at work, and having ten different things on the go at work at once and still cross the finish line and all the rest of that. And I just can't do that now. I just don't seem to have the physical capacity to handle lots of things but also the mental.

I: Mm.

P: I woke up tired and sore this morning, and so even in my anxiety course I've just been to, I mean I struggled to keep listening, and to actually take in what she was saying. Even if I was listening, sometimes it was just words. I couldn't actually get meaning from it.

I: Right.

P: And she asked us to do something, and in 10 seconds I forgot what we were meant to be doing [laughs].

I: So the struggle is with the thinking brain?

P: Mm because I was so tired, and I was sore and uncomfortable in the chair I was in. Even though they bring in a special comfy chair for me, it was just all too much, and I struggled. And if I have something I want to say I struggle to say it properly so that it actually sounds whoohoo in the head sometimes.

I: Right. What like finding the right words or … ?

P: I do do that. I struggle on words sometimes or I stutter on them. But sometimes I know what I want to say in my head but it comes out not quite the meaning I wanted it to mean [chuckles], if you know what I mean?

I: Yeah.

P: Yeah mm. I understand my body letting me down, I don't like it, I hate it, but I understand it. But when my brain lets me down I think that makes me feel the least of a person than when my body lets me down. I don't feel as smart as I used to.

I: Yeah.

P: I know people say they drive places and they can't remember how they got there. Well I'm like that most of the time. In fact I've actually driven past our street with my daughter right next to me. She goes "**mum!**", you know? And I've taken her to a friend's house, and I dropped her off there once before, I knew where it was. It's one street along there and I drove past this house twice. She's like "**mum!**" [chuckles]. That's hard.

I: So when did this start to happen? Do you remember when these things began?

P: Probably in the last 2½ to 3 years, and it's just steadily gotten a little bit worse. The way I look at things is I was functioning, and then when I had my operation and then I lost my job, and after I walked out of the job, that physical and emotional stress, I can see where things really started to go down.

I: Right, okay.

P: Like really, really go downhill - like I can pinpoint it to that month even.

I: So you had surgery and lost your job. Was that because of the surgery?

P: Two weeks' after my surgery, it wasn't even just that I lost my job, he was my friend.

I: Oh.

P: And the way he did it, it was not deserved, he's even apologised to me since. He said you didn't deserve it and I wish I hadn't of done it. But he got a bee in his bonnet, and I came the first day back from my surgery he had made a meeting with me and his friend who was an HR hatchet lady. And he just sat there – (husband) came in with me - and he didn't say a word. Oh he said, and how are you feeling? And that was it. And then yeah she fired me and well cancelled my contract. And (husband) stood up and said oh I'm cancelling the contract, and we went back to the office, picked up our stuff, and came home.

I: Right, so you both worked in the same company?

P: Yeah.

I: Oh my goodness.

P: Mm, so it was pretty traumatic, and yeah, I can see from there my pain started to get worse. Because it was almost like I had the surgery to get the breast reduced, and everyone knew I was doing it to fix my back, and I was just kind of keeping quiet because it hadn't fixed anything. And like the physio had said to me oh it'll take a while for your muscles to adjust to 'rah rah rah', and it was just here's me thinking [chuckles] it's not getting any better.

I: No.

P: It's just not getting any better - it's getting worse.

I: So you'd had your back pain for quite a while before the surgery?

P: For years.

I: OK

P: (husband) and I have known each other for 12 or 13 years. I had it before I met him.

I: Right.

P: He'll remember having to rub my shoulders for me. I get pain in my shoulders - my back was sore. I had a lot of times where I just twisted my neck funny and my shoulder went out, and that was in my 20's.

I: Mm.

P: But I always had such massive breasts [chuckles] as a teenager.

I: Right.

P: Because they came so early I hunched.

I: Yes.

P: And yeah it would have been early 20s – mid-20's – when I started to have just niggly problems where things just happened, or it was always niggly or sore or aching. And then in the 30's it just got to a point where I was starting to rely on pills, I couldn't sleep at night, that sort of thing.

I: Yeah.

P: Mm.

I: And meanwhile you were working and you were saying before it wasn't till the surgery you noticed the cognitive changes?

P: Mm, mm, all that stress and stuff.

I: Mm.

P: But I mean leading up to that surgery I was taking slow release Tramadol, fast release Tramadol, plus I was getting Panadeine from the chemist, and just so I could go to work, and I'd be at work and I'd be so sore. And I was actually being treated … they thought I had tennis elbow and RSI in my wrist because I was just struggling with the mouse at work, and I'd just be coming at home at night and just crying. I remember *(husband)* standing right there - what else can we do?

I: Mm.

P: What else can we do. Yeah and it was just every night just pain. I'd go to bed and I'd wake up stiff and sore.

I: Oh every day?

P: Yeah. We changed [chuckles] our mattress and our bed every year [chuckles].

I: Okay.

P: You know, it would start off it would be alright and I'd wake up okay and then no good.

I: Yeah.

P: Yeah.

I: So how did you manage your pain - did you acknowledge it? From what you said earlier you weren't a great acknowledger [chuckles].

P: Well it got to the point like I was just crying at night, and I'd be so unsettled on this couch. I'd be lying down and I'd have to swap sides, and then I'd sit and I was just so uncomfortable all the time. By that stage I was acknowledging it, but kind of trying to ignore it in a way, but it was almost to the point where I couldn't ignore it.

…

What was that different to when you'd been back here?

P: I don't know. I mean there's probably something deep-rooted in my psyche, it's probably psychological, but there was just freedom in it.

I: Mm.

P: That nobody knew me. I mean my family [chuckles] – according to my psychologist, a lot of my emotional issues are tied to my childhood.

I: Oh okay.

P: [Laughs] yeah. I always thought it was such a cliché when you see on TV where the psychologist sits down and goes "tell me about your childhood" … but [laughs] … it was like for crying out loud, you can't blame everything on childhood, but I do now believe that what you go through as a child it shapes your core beliefs. It shapes your core beliefs, and in my family you just get on with it, you don't complain.

I: Interesting., okay.

P: And I mean they didn't know. They knew I had back pain I guess but they didn't really talk about it or anything like that. And when I came round and said I had the fibro diagnosis we didn't talk about it then or whatever, and it's caused … I don't know how my talking about it may have made it different, I don't know. But then my cousin having something in Cambridge - well it was my cousin's cousin - he's trying to make a world record and a lot of my family are going over. That drive for me will be hard, and then getting to his gym, well there's not going to be a nice comfy chair for me to rest in, and then there's the whole social anxiety thing which I suffer from, going into a whole room full of people I don't know. There's that, and then the drive home, and realistically it's just too much for me.

I: Mm.

P: For something that's important, and I support him, but it's not worth it.

I: Mm hmm. What will you do?

P: And yeah so Mum's talking about how she's going and are you going? And I went no. And she was like why not? And I said well the drive may be a bit too much for me Mum. Oh [sighs], don't be ridiculous, it's only an hour [laughs]. So then that lack of understanding

completely … I guess now that I do know there's actually something wrong with me and it's not all in my head, I probably am more inclined to be honest in the decisions I make and what I'm feeling. I even had a friend say to me … she said since you've been diagnosed you're so much worse. And I said no, I'm just more honest about it.

I: Yeah, yeah. That's an interesting change isn't it?

P: Mm. You can't plan things cause you end up cancelling so much, and at least now I've got a reason for cancelling. I can be honest and say I'll be absolutely exhausted, and I'm sorry I can't do it, whereas before I just used to make up all sorts of lame excuses and I probably look like a really crappy friend. Yeah so being diagnosed in one way has been really good, not that I have an excuse, but I have a legitimate reason that people can understand.

Appendix 5e: NVivo excerpts

A) – illustration of early development of categories (called 'nodes' in NVivo) using NVivo 10 software. The green coding on the left indicates the emergence of the most prominent categories.

B) – illustration of early development of codes (called 'child-nodes' in NVivo) using NVivo 10 software, from the category "controlled by others"

Appendix 5f: Illustration of all the quotes extracted from the data organised through NVivo related to the theme of "sensitivity"

- the sub-themes of emotional sensitivity and physical sensitivity.

Emotional Sensitivity

(P2): So I've always obviously been a bit anxious. My mum is a 'panicker' which I went to a really good counsellor and she pointed out some really obvious facts… Yeah and that didn't help – just me being me - and my mum would panic like mothers do, but no, my mum's pretty good at it. … Yeah, and she'd install her fear into me I guess without knowing it, and that would make me anxious, you know. Yeah. Like my brother was sixteen, and he'd go out with his mates, and where we lived there was a lot of accidents and that. But you'd hear an ambulance and my mother would be running screaming through the house saying oh I hope that's not *(brother).* It was like 'oh my goodness', and that would just instantly put anxiety into me.

(P4) P: there were huge anxieties yeah. Wow even just the anxiety of having to go to school or the anxiety of having to sit an exam. When I look back, our life did create anxieties, because it was just like that. Yeah we didn't do stuff like learning ballet and those things. Life was a struggle.

(P8) P: I've always thought, and I don't know if it's exact anxiety as such, but I've always thought if I haven't got something to worry about I'll make something up … yeah my dad's a worrier, his mother was a worrier, you know, it's a bit of a family trait.

(P5): It's so weird [chuckles]. It's all very, very odd, but yeah I … yeah I worry about what people think too much.

(P9) I: When did you first start noticing anxiety?

P: Oh yeah, always been there.

(P6): so I did the same for school. I felt I've got to get out of here. I'm not coping – I'd better get out. So I left school. I had to get out so I ran away. Well I didn't run away but fight or flight. I had to get out because I couldn't handle it. Because when I didn't understand I used to go and hide in the hedge, and I'd just wait until … if I stay in the hedge and just wait, that will be okay, and then I'll come out. And I used to hear Mum saying [name] where are you? Oh no, not yet, I can't handle this.

(P6) I probably couldn't handle the people who used to come to visit, when the nuns used to come up to visit Mum, when there was lots of activity in the house and there was a lot of comings and goings and people talking. Yeah, I just couldn't handle that. I used to have to go away and crawl under the house.

(P7): I think again, seeing my kids is very interesting because I think there's definitely a natural genetic in it that they're sensitive to people. Particularly (son) and (daughter) are both similar to me in that they're very sensitive … well they're all sensitive to other people's feelings, but they are very sensitive to people and what they think and getting things wrong. Yeah so I think for me there's a combination of already being like that naturally…

(P2)P: I recall probably being in *(town location)* so I had to be six, but quite young, and running into the toilet, and shutting myself in the toilet because, yeah, mum was running around screaming something - I can't remember [laughs]. I was in big trouble again [chuckles]. I'd done something without thinking and oh no, here we go again.

(P7): I remember the day I cut my hair short [laughs], and I must have been like in my early 20's then, and it was like I was scared to let them see.

(P7) P: I have to learn to say no, so I'm learning to say no to things.

I: It's a thing you never did?

P: Never did no. I still don't very often [chuckles].

I: What would have happened if you did say no, in your perception?

P: I think it was the fear. It was a fear of upsetting someone.

(P7): I absolutely panicked over exams, just panicked in exams and go completely blank just because of the stress of not doing well, more than anything. … My mum always used to say before exams, 'now we know you've worked really hard so don't worry,' and then if I didn't get anything there or what they thought I should get I was in terrible problems – trouble.

(P4): I can remember I didn't want to sit an exam because I knew I was going to fail it – an interesting point – and I would have. I got more 1's and 2's out of 100 than anyone else I think has ever got in the school. I used to hand in my exam with my name at the top and just a slash through the page, and I'd hand it up and that would be it, because I'd know that if I took that test I would fail, therefore I wouldn't take it.

(P3) P: I couldn't read the machines. Ah, and then I couldn't read an ATM, and I was too nervous cause I was going to make a mistake and the people standing behind me ...to wait for their turn ... turn, I was ...too much pressure, I couldn't cope with it. And then I often found my brain was one step ahead, so instead of thinking, it was ahead then I'd lose things.

(P3): I find it very nervous to ... bring up a fault or a mistake. Maybe I'm scared that I'm going to get in maybe trouble for it. And if I have made a mistake I beat myself up ... to quite some considerable amount….

(P3): And I've got a big thing about being normal and not showing anyone any type of weakness. And if people do find that weakness and sort of make a joke about it, it hits home pretty hard. Not many people do it, but just every now and then you might ... you know, you might spell something wrong.

(P7): And of course … I didn't ask for help. I'd flounder rather than getting help … because if I did anything with them at home it was just a trauma. I'd always end up in tears because I'd be in trouble for not understanding quick enough.

(P6): I think how I processed it all, I processed it all from: 'they don't like me, what's going on here, how do I perform, how do I fit in, what do they want me to do, what am I supposed to be doing, am I doing it right, am I doing it wrong?'

Anger

(P9): And sometimes they'd be just in where you're not supposed to be, and if you're not concentrating... And it'd be a ram lamb and I'd be the wrong way. And my little brothers would be like - oh no, it goes the other way. And it used to really rattle me. Someone younger than me telling me that I was wrong.

(P9): Then it gets difficult, 'cos quite often people like that aren't always right and I'll have to suppress that fury ... I'm not reacting I'll probably need to back off and just take on board other things, you know, instead of just flying off the handle.

(P3): I was 16 then, I used to get terr- ... terribly frustrated. And I had a stutter as well, so I was ... I got a lot of unwanted attention from ... school kids that thought that I was the weaker ... So a lot of my behaviour was ... some people would call it abnormal, but it was just trying to ... it was just my defence in all my weakness.

(P5): And I've got my own self-criticisms on them, as if I'm thinking I'm stupid, well they're going to think I'm stupid … so there was two people at the table I didn't know, and because I didn't know them, I was tense and stressed for at least the first hour or so. Yeah because it was just out of my comfort zone cause I didn't know them. Yeah which is silly – it does seem silly.

Physical Sensitivity

(P1) P: Bright lights can, yeah. I mean if I put on a thing that I do to keep the … I like ambience [chuckles].

I: Muted lights?

P: Yeah. [name] always laughs at me because I'm like, "now can we have some ambience please."

(P4):   So I'm sensitive to bright lights. I didn't realise how much I was until now that I understand it.

(P8):   Yeah, well I know I've got sensitivity to light. I don't recall how long that's been going on, but I know ... and that was one of the things that I picked up with (nutritionist) with needing sunglasses on even if it wasn't bright sunlight.

(P6) I: And what about light sensitivity?

P: I like darkness. When I'm at home at night people wonder what on earth I'm doing in there because I sit in the dark. I might have a candle – one of those Himalayan candles which I like just with a tea-light in it. I don't have an electric light. But I might put the little lamp beside me on for a short time then I have to turn it off because it just affects me – I can't handle it. If this was dark, and you had this light, I couldn't sit here with all these lights on. Yeah, like in bed at night, I like to look out at the night, but I don't want the light in my bedroom. That's why I can't live with a lot of TV in bed because it's too bright.

(P6) But yeah like times when the head's really sore I felt extra sensitive, especially to light and noise, especially playful noise.

(P7): I'm massively sensitive to sound. I get very irritated with sound, any kind of repetitive sound. And there's one particular kind of music which … is it house music where it's just like the same beat all the time, I literally feel like I want to hit my head against a wall. Yeah sound is one thing, but then the sound of water or something I really like, but there are certain sounds that can very quickly get me highly irritated.

(P8): I know I've always been startled easily by loud noises, like somebody popping a balloon or oooh! …

(P6):   I didn't like noise of any sort, I didn't like any arguing, I didn't like any loud talking, I didn't like a lot of crowds around me. I wanted them all to go.

(P2) P: Yeah, as long as it's not that screaming and fighting. I guess it's screaming actually, once that scream comes into it. Because even when they were outside screaming and playing I'd come out saying oh no, no, no. Yeah, I can't cope with that screaming noise.

(P1) But too strong - if it's a bad smell, like turps or kerosene - and I can smell burning a mile off but I use it more positively perhaps. I became afraid of smell. There was this man who had a spray can of paint down there. I was going on a walk, and it was a windy day, and he was spraying outside. Well you can imagine what was happening. The smell … I was actually nauseous.

(P5): You know *[chuckles]* and I didn't like admitting that when *(husband)* stroked my arm I didn't like it. I hated it. I wanted him to stop which is not a nice thing to say out loud or to admit to yourself. *[laughs]*

(P2) P: But they brought out chocolate, and everyone said that I've got to have it once [laughs].

I: And what happened?

P: Oh I bounced – oh yeah I bounced. Mum would say to me too much cheese would affect me, but yeah different foods … But I had to be a bit careful, and I think my stomach could have been a problem as a kid.

(P5):   I can't have too much sugar. I didn't know that because I used sugar and stuff as treats. 'You're doing well, you're coping, you're getting through the day – have something sweet.' But yeah I can't have too much or I'll crash.

(P5) I: So have you pinpointed what it is you don't like about certain foods - is it texture or taste or … ?

P: It's the texture and the thought of biting down. I mean I've tried a few new foods but I can't even tell you what they taste like because the anxiety level was so high and the thought of chewing down on them is just … *(screws up face)* … Like I guess when I met *(husband)* I had to cook for him, so I had to touch things normally there's no way I'd touch. Like even now when I roast the chicken I use tongs to pull the meat off, whereas my mother-in-law gets in there with her fingers and it's like ooh … [laughs], cutting up chicken and cutting up things that normally I just don't want a bar of … But yeah like all the foods I don't eat there's no way I'd touch them.

(P6) I: So you say you were emotionally sensitive, and sensitive to all the busy-ness around you.

P: Yeah constantly … Yeah. And to me that's like you're kind of hiding. You're safe. This is safe. All my senses are safe within this … *(indicates cacoon around her).*

(P3): Often in the evenings I will do my fitness, then come home and that's when I tend to just sort of almost like blob out, just watch something and just try and block all things out. And there's often … if I get too over-stimulated I can't get to sleep at night

(P8): so I'd be in bed reading a book and sometimes I'd just about cry when I realised how late it was … Sometimes I just get too tired to go to sleep, and sometimes I can keep reading until half-past 11 even when I've got to get up at six and go to work.

(P8): So yes, and I also get quite – not panicky exactly, but agitated if I've got too much going on in the week.

(P2) P: It doesn't bother me – strong smells [chuckles]. I've worked with sewerage pumps [laughs]. I add spice to my food – yes. Always been a traveller … yeah … like the food … I don't smell things that other people say I smell frequently. But I think I live with people with the best sensory noses in the world. (Wife)'s got an amazing sense of smell and the boys have both got it too.

I: But you don't?

P: No. Just you've really got to think is my nose not working and you just [sniff- sniff - sniff] When I do smell something I know I'll name it quickly, especially spices and stuff like that. I'm good with food smells.

(P3): as an adult when someone asks me to do something I'll say can you please write it down … with words and … mainly words or if they just draw a picture. And now I've learnt to don't be afraid to ask to … or get the person to repeat it.

(P2): I was sitting at the doctor one day with a septic sore in one of my hands, and they were like "oh that's pretty bad." And I'm like "I can't feel it." And they're like "oh can't you?" And I'm like "yeah." And I says "oh if I do this - and I put my finger right into it" - I said "but I can feel that." And they were kind of like "oh," and I think they kind of realised that what I was saying might be true … but no they're not numb. The sensory is not right. The feeling's not right … And when I cut myself I've got to look and see where the blood's come from.

Appendix 5g: Evidence of article 5 submission

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