AN EXAMINATION OF BLOOD OXYGEN LEVEL DEPENDENT FUNCTIONAL MAGNETIC RESONANCE IMAGING METHODS IN ANALYSING CHRONIC NON-MALIGNANT PAIN PATIENTS' RESPONSES TO NON-PAINFUL PAIN STIMULI

ANN TAYLOR RGN, MSC MED ED, BN, DIPN (WALES)

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SUPERVISORS:

PROFESSOR RICHARD WISE

PROFESSOR JUDITH HALL

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KEY WORDS

Neuroimaging, BOLD, PHODA, Resting BOLD, Chronic Low Back Pain, Chronic Musculoskeletal Pain, FMRI, Fear, Catastrophising, Anxiety, Depression, Structural imaging, VBM.

SUMMARY

The main focus of this thesis is chronic musculoskeletal pain (CMSKP) as this equates to the largest proportion of patients with chronic non malignant pain and results in the huge burden on the individual, society and health system. Pain interrupts, demands attention, and is difficult to disengage from and fear, anxiety and catastrophising are seen as major factors moderating the attentional demands of pain. Early work with clinical populations indicates considerable promise for fMRI methods to be used in pain diagnosis and therapy which may improve the categorisation of pain conditions in an objective manner based on a better understanding of central mechanisms. Given that treatment for CMSKP has not advanced for many years and behavioural research has not achieved consistent results, fMRI methods may help to provide further understanding of how pain-related attention, fear and catastrophising affect patients. The aim of the thesis was to explore Blood Oxygen Level Dependent (BOLD) signal changes in response to viewing non-painful pain-relevant stimuli. Three neuroimaging studies were undertaken. Two studies involved a population of CMSKP patients where an emotional counting pain and positive Stroop task was used and the other a modified visual task using pictures of activities of daily living (PHODA). One study recruited a population of chronic low back pain patients (CLBP) using a modified picture task and this also include voxel based morphometry and resting BOLD analyses. The main findings were that patients attended to the pain-related stimuli and BOLD region differences in patients compared to controls showed that anxiety, fear and catastrophising were implicated in the large number of regions traditionally involved in the sensory and emotional processing of pain. BOLD differences were greater with the picture stimuli than with a word stimulus. No differences in brain structure was seen in the CLBP group and resting BOLD results are discussed. Implications, limitations and future research directions are presented.

DISSEMINATION OF FINDINGS

ABSTRACTS

Taylor, A., Harris, A., Buck, R., Varnava, A., Hughes, O., Wilkes, A. R., Hall, J., & Wise, R. (2011). Imaging neural responses to affective and pain-related stimuli in chronic non-malignant pain patients vs healthy controls. *British Journal of Anaesthesiology,* **107**(5), 830P-831P.

PUBLICATIONS TO BE SUBMITTED

An fMRI study comparing blood oxygen level dependent (BOLD) responses in patients with chronic low back pain and healthy controls in response to an adaptation of the Photographs of Activities of Daily Living. Ann M Taylor, Ashley D Harris, Alice Varnava, Rhiannon Phillips, Owen Hughes, Antony Wilkes, Judith Hall, Richard Wise

An fMRI study comparing blood oxygen level dependent (BOLD) responses in patients with chronic non-inflammatory musculoskeletal pain and healthy controls in response to a pain-related counting Stroop task Ann M Taylor, Ashley D Harris, Alice Varnava, Rhiannon Phillips, Owen Hughes, Antony Wilkes, Judith Hall, Richard Wise

An fMRI study to compare blood oxygen level dependent (BOLD) responses between patients with chronic non-inflammatory musculoskeletal pain and healthy controls in response to Photographs of Activities of Daily Living. Ann M Taylor, Ashley D Harris, Alice Varnava, Rhiannon Phillips, Owen Hughes, Antony Wilkes, Judith Hall, Richard Wise

PRESENTATIONS

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Taylor, A. Chronic pain: what is it and can education help? Northern Ireland Pain Nurses Forum, May 2011

Taylor, A. Chronic pain: symptom or a disease? South East Kent: Advances in Chronic Pain Management Meeting, October 2011

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GLOSSARY OF ABBREVIATIONS

ACC Anterior cingulate cortex
ASL Arterial spin labelling
BET Brain extraction tool (part of FSL)
BOLD Blood oxygenation level dependent
CBF Cerebral blood flow
CLBP Chronic low back pain
CMSKP Chronic musculoskeletal pain
CNMP Chronic non malignant pain
CNS Central nervous system
CSQ Coping Stategies Questionnaire
CSQ Coping Strategies Questionnaire
DMN Default Mode Network
FA Fear Avoidance
FABQ Fear Avoidance Belief Questionnaire
FEAT FMRIB's expert analysis tool
FILM FMRIB's improved linear model
FLAME FMRIB's local analysis of mixed effects
FLIRT FMRIB's linear registration tool
FMRI Functional magnetic resonance imaging
FMRIB Oxford Centre for Functional Magnetic Resonance Imaging of the Brain
FNIRT FMRIB's tool for small-displacement non-linear registration
FSL FMRIB's software library
GLM General linear model
HRF Haemodynamic response function
IASP International Association for the Study of Pain
MCFLIRT Motion correction using FMRIB's linear image registration tool
MNI Montreal Neurological Institute
MPQ McGill Pain Questionnaire
MRI Magnetic resonance imaging
NRS Numerical rating score
PCC Posterior Cingulate Cortex
PHODA Photographs of Activities of Daily
RT Repetition time
SI Primary somatosensory cortex
SII Secondary somatosensory cortex
SNR Signal to noise ratio
TSK Tampa Scale of Kinesiophobia

CHAPTER 1: INTRODUCTION

1.1 CHRONIC NON-MALIGNANT PAIN

Chronic non-malignant pain (CNMP) poses a large health and socioeconomic burden (Macfarlane et al. 1999; Sprangers et al. 2000; Woolf and Akesson 2001; Torrance et al. 2010) and can be a complex condition to manage (Foster et al. 2003a; Foster et al. 2003b). It appears that it is not just the physical pain itself that results in this complexity but the way in which the individual attends to the pain (Eccleston and Crombez 1999; Buck and Morley 2006), the meaning that the pain has for the individual (Richardson et al. 2006; Foster et al. 2010; Main et al. 2010) and the pain-related behaviours that ensue (Newton-John and Williams 2006; Henschke et al. 2010). Indeed chronic pain has been defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (Merskey and Bogduk 1994).

The management of CNMP is difficult and despite an increased understanding of the factors contributing to the maintenance of pain and disability through behavioural research, there has been only a moderate improvement in treatment outcomes over the last decade (Croft 2000; van der Windt et al. 2008). Significantly interventions have shown at best, only moderate effects in reducing pain and disability in those suffering with chronic pain (CLBP) (Chou and Huffman 2007).

The main focus of this thesis is chronic musculoskeletal pain (CMSKP), including chronic low back pain (CLBP). The reason for this focus is that the largest proportion of patients with CNMP, have CMSKP and/or CLBP and the costs to the individual, society and the health system are great. Approximately 5% of patients develop CLBP following an initial acute back episode and yet these account for 75% of the costs associated with low back

pain (Macfarlane et al. 1999). Based on the latest available statistics from the HSE (2010/11) the total number of people with musculoskeletal disorders in 2010/11 was 508 000 out of a total of 1 152 000 for all work-related illnesses with 158,000 new cases a year. One year after a first episode of back pain 62% of people still have pain and 16% of those initially unable to work are not working after one year (Hestbaek et al. 2003). Estimates for the adult population burden of CLBP include; 11% for disabling back pain in the previous three months, 23% for low back pain lasting more than three months and, 18% for at least moderately troublesome pain in the previous month (Savigny et al. 2009).

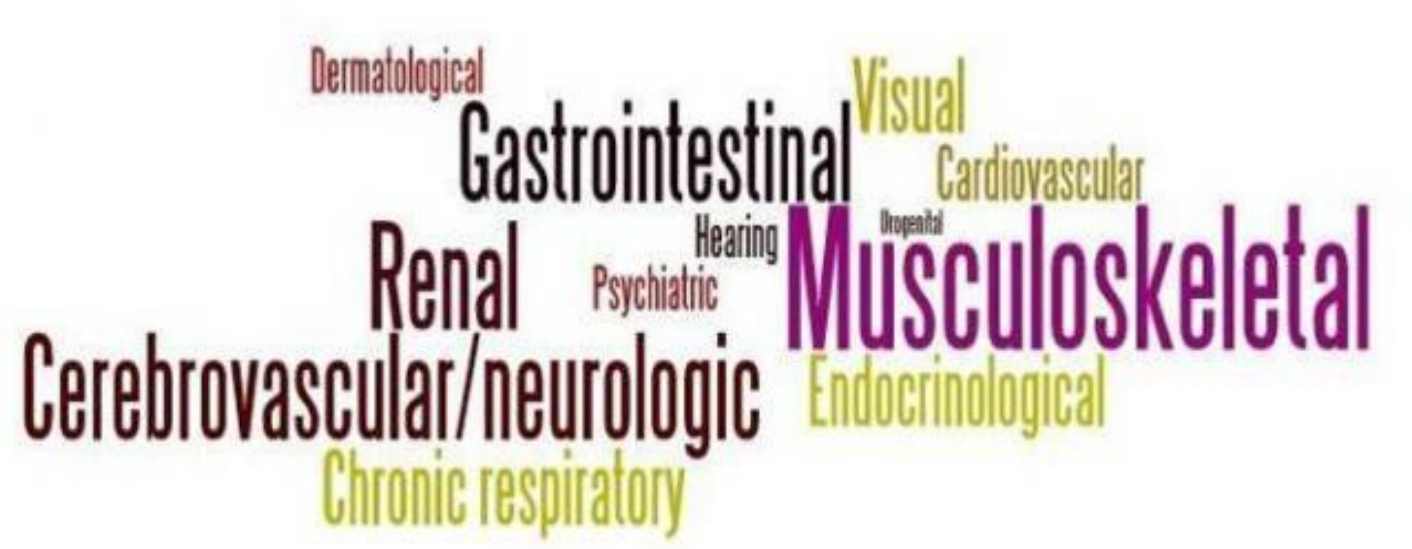


Fig.1.1 Impact of chronic conditions on quality of life.
This word cloud illustrates Sprangers et al (2000) data and shows the impact a number of chronic conditions have on quality of life with musculoskeletal conditions having the greatest. The larger the word, the greater the impact.

In presenting the research, CNMP will relate to studies that have been undertaken in the wider pain population anticipating that a large component of these will have CMSKP and or CLBP if not documented otherwise.

1.2. PAIN AND ATTENTION

Pain interrupts, demands attention, and is difficult to disengage from (Eccleston and Crombez 1999). An attentional bias can be considered as selective attention towards specific information and typically, but not always, these biases are explored in relation to threat and may illustrate a predisposition towards threatening information (Schoth et al. 2012). In an acute situation, pain related-attentional bias is wholly appropriate and serves as a strong survival mechanism, but in people with CNMP it appears not to serve a useful function and can cause harm in itself.

The idea of attention as a potentially important factor in CNMP has been informed by two assumptions; the amount of attention paid to nociceptive stimulation is believed to modulate the experience of pain (Villemure and Bushnell 2002) and CNMP patients are characterised by excessive attention for pain-related information (Pincus and Morley 2001). While these assumptions are useful in explaining the development of CNMP, evidence is inconsistent and inconclusive. Very early work in the fear of pain arena suggested that an individual's past experience with pain, the memory of that pain, and recurrent episodes of pain tend to sensitise the individual to anticipate more pain, influence the amount of fear, and greatly fortify pain–avoidance behaviours (Johnson 1973; Fordyce et al. 1984).

Hypervigilance is a term used to describe those individuals who are excessively attentive to their bodily symptoms (Chapman 1978) and is associated with monitoring bodily sensations for threat. This dysfunctional attentional style has been assumed to maintain and amplify bodily sensations and is seen in the various fear-avoidance models where fearful

patients become increasingly vigilant for signals of bodily threat. This in turn leads to avoidance behaviour and increased disability (Leeuw et al. 2007a).

1.3 MAJOR FACTORS MODIFYING PAIN-RELATED ATTENTION

Several factors are thought to be involved in moderating the attentional demands of pain, the strongest and most consistent effects relate to fear, anxiety, and catastrophising (Eccleston and Crombez 1999). Attentional vigilance for pain-threatening information results in a greater chance of detecting potential sources of threat, exacerbating pain, disability, deterioration in physical health, social isolation and work loss (Schoth et al. 2012). Attentional bias to pain may illustrate a lack of acceptance of having CNMP and may be detrimental to management; acceptance is beneficial in terms of patient functioning (McCracken and Vowles 2007; McCracken and Keogh 2009).

1.3.1 Pain related fear

Pain related fear refers to an excessive and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to pain (Keefe et al. 1991). Pain-related fear and catastrophising are associated with increased attentional interference, awareness of pain, impaired disengagement from pain, and can moderate the effects of attentional coping attempts (Sullivan 1995; Asmundson et al. 1997b; Crombez et al. 1999a; Keogh et al. 2001b; Buck and Morley 2006; Van Damme et al. 2008). Disability and depression may result from activity avoidance, (Heuts et al. 2004; Boersma and Linton 2005; Cook et al. 2006; McCracken and Keogh 2009; Somers et al. 2009). Pain related fear accounts for between 7-31% of the variance in pain severity (Sullivan et al. 2001b).

The Fear Avoidance model (FA model) (Vlaeyen et al. 1995), is commonly accepted as one which integrates the fear-related themes above. It proposes that dysfunctional interpretations give rise to pain-related fear, and associated safety seeking behaviours such as avoidance/ escape and hypervigilance. It also suggests that if the injury/pain experience is perceived as non-threatening, patients positively adapt and cope with their pain (Pincus et al. 2010).

Burton et al (2004) recommend that good quality randomised control trials should be performed on the role of information orientated towards reducing fear avoidance beliefs and improving coping in the prevention of low back pain. However, Pincus et al (2010) felt this statement, in the European Guidelines for the Prevention of Low Back Pain (Burton et al. 2004), was premature as a better understanding is needed of the relationship between beliefs about pain, movement, fear and avoidance and behaviour.

There has been a large amount of research examining the predictive value of fear in developing CMSKP, especially CLBP (Boersma and Linton 2005, 2006; Swinkels-Meewisse et al. 2006; Foster et al. 2010). However, the evidence to support the prognostic value of fear at early stages of pain is inconclusive (Pincus et al. 2006). There appears to be some evidence to suggest that fear may play a role when pain has become persistent pain (Pincus et al. 2006) and therefore we need to better understand those CMSKP patients who have fear avoidance beliefs and behaviours in order to improve clinical assessment and management.

1.3.2 Catastrophising

Ellis (1962) initially introduced the term catastrophising and Beck (1979) subsequently adapted it to usefully describe a maladaptive cognitive style that patients with anxiety and depression use in irrationally and negatively forecasting future events. Catastrophising in the context of pain can be defined as an individual's tendency to exaggerate, ruminate, focus on how threatening pain is, and negatively evaluate their ability to cope with it(Sullivan et al. 1995). It has been conceptualised both as a maladaptive coping strategy and a cognitive appraisal style (Keefe et al. 1989; Keefe et al. 2000). Besides the behavioural data illustrating that pain catastrophising is associated with poor clinical outcomes (Boersma and Linton 2005; Quartana et al. 2009; Bergbom et al. 2011), there appears to be neuro-anatomical evidence proposing that catastrophic thinking can activate brain structures associated with pain-related emotion and behaviour, even after controlling for co-morbid depression (Gracely et al. 2004).

Pain-related fear and catastrophising are associated with increased attentional interference, awareness of pain, impaired disengagement from pain, and can moderate the effects of attentional coping attempts (Heyneman et al. 1990; Sullivan et al. 1995; Asmundson et al. 1997a; Crombez et al. 1999a; Keogh et al. 2001a; Buck and Morley 2006; Main et al. 2007; Van Damme et al. 2008). Unfortunately, it appears that the less advantaged groups in our society are affected most. Low socioeconomic status and educational achievement has been linked to poor pain-related outcomes, maladaptive pain beliefs and coping strategies and more pain-related distress (Dionne et al. 1995; Hoffman et al. 2002; Roth and Geisser 2002; Nguyen et al. 2005; Cano et al. 2006).

1.4 POTENTIAL FOR FMRI IN CMSKP POPULATIONS

Early work with clinical populations indicates considerable promise for fMRI methods to be used in pain diagnosis and therapy (Borsook and Becerra 2006; Schweinhardt et al. 2006; Schweinhardt et al. 2008). Recent advances in functional imaging have transformed the understanding of central processing of pain. Unfortunately, current clinical classifications of CNMP have been so far unhelpful in understanding how pain is processed (Borsook and Becerra 2006). Functional imaging has already redefined chronic pain as a degenerative disease (Apkarian et al. 2004b; Baliki et al. 2008), and has shed some light on complex diseases such as fibromyalgia (Gracely et al. 2004). Therefore, the application of functional imaging may improve the categorisation of pain conditions in an objective manner based on a better understanding of central mechanisms and may lead to improved diagnosis and the identification of more appropriate treatment regimens (Borsook and Becerra 2006).

Functional MRI is a technique that can detect the changes in perfusion caused by brain activity. In fMRI, the capillary changes in blood flow and volume result in a change in deoxyhaemoglobin concentration. The change is reflected in an increase in image intensity at the location of the activity and is called the blood oxygenation level-dependent (BOLD) signal. It does not measure absolute states, rather it needs a reference state to compare to, for example pain needs to be evoked or modulated during an fMRI scan to localize brain activation but it can be used repeatedly in subjects and therefore can be useful in longitudinal studies (Becerra 2006).

There may be a significant potential for use of this method in assessing treatment effects and predicting responsiveness to interventions gleaned from studies in other chronic

disease states. Siegle et al (2006) used fMRI to predict recovery following CBT in patients with unipolar depression. Laatsch et al (2004) used the neurobiological basis of cognitive rehabilitation therapy in mild traumatic brain injury. Finally, de Lange et al (2008) showed that patients with chronic fatigue syndrome who had prefrontal cortical loss compared with healthy controls had a significant increase in grey matter volume following cognitive behavioural therapy.

Neuroimaging has improved our understanding of how cognition, emotion and context can influence pain perception (Avenanti et al. 2006; Baliki et al. 2006; Becerra 2006; Tracey and Mantyh 2007). However, to date, it has not been well utilised in the CMSKP population and this area of research appears to be still in its infancy where there are methodological and ethical challenges that need to be addressed (Wartolowska and Tracey 2009). The majority of fMRI work to date has focused on acute, experimentally induced pain in healthy volunteers, where the meaning of pain is different from CMSKP (Crombez et al. 1999a; Buck and Morley 2006) and the pain-related changes in brain structure and functioning (Apkarian et al. 2004b; Baliki et al. 2008) seen in chronic pain patients are not present in the healthy volunteers. Studies using functional Magnetic Resonance Imaging (fMRI) in acute pain populations have been successful in demonstrating the effects of manipulating attention (primarily distraction), expectation and anticipation, paradoxical sensations and control (Borsook and Becerra 2006).

It has long been proposed that a 'neural matrix' for pain exists which described the dynamic role of networks within the brain responsible for the experience of it. This model suggests that although the processing of pain by the brain is genetically specified, processing is modified by experience (Melzack 1990, 1993, 1999); factors increasing the

sensory flow of pain signals may alter the excitability of central thresholds over time resulting to sensitivity to pain. Therefore, psychological factors thought to amplify pain signals, such as attention, fear and catastrophising may lead to changes in central neural mechanisms leading to central sensitisation and a chronic hyperalgesic state (Melzack 1990, 1993, 1999). Previous studies have shown that people who are fearful and catastrophise attach more threat or harm to non-painful stimuli, such as innocuous electrical currents (Peters et al. 2000; Crombez et al. 2002a) and the neural correlates of this are not clear.

Given that treatment for CMSKP has not advanced for many years and behavioural research has not achieved consistent results, fMRI methods may help to provide further understanding of how pain-related attention, fear and catastrophising affect patients. A number of approaches have been used to study pain in fMRI studies, including block design (Botvinick et al. 2005), event-related (Benuzzi et al. 2008) and percept-related (Davis et al. 2002) paradigms.

Pain has been described in a number of dimensions: the sensory-discriminatory dimension involving SI and SII, thalamus and insular cortex (Bornhovd et al. 2002); the affective-motivational one, including the insular cortex and rostral ventral ACC (Whalen et al. 1998) and the cognitive evaluative involving the parietal and prefrontal cortices and caudal ACC (Vogt et al. 1995). It has been proposed that to consider just the sensory features and not the motivational and affective aspects of pain is to look at only the part, and not even the most important part (Melzack and Casey 1968). The ability to use fMRI to image the whole brain at the same time and to segregate functional circuits allows the central nervous

system (CNS) processes underlying affective and motivational components of pain to be elucidated (Borsook and Becerra 2006).

1.5 THESIS AIMS

The aim of the thesis is to explore Blood Oxygen Level Dependent (BOLD) signal changes in response to viewing non-painful pain-relevant stimuli. It is also intended to examine resting BOLD data and voxel based morphometry in the chronic low back pain group compared to their matched controls. The reasons for undertaking research within this field included the fact that much of the research to date has looked at the impact of nociception in healthy volunteers and inferences are then made about how people with CMNP process painful stimuli. However, patho-physiological processes, such as responses to nociception, do not adequately explain the levels of pain and disability that patients with CNMP report (Waddell 1987; Vlaeyen and Linton 2000, 2012). The research that has been undertaken in fMRI studies has revolved around factors such as attention, fear and catastrophising in healthy populations and has not examined the role of these within the CNMP population in any great depth. Therefore, the research approach in these studies is exploratory and the studies have not been scaled or designed to test hypotheses. The studies included have research aims to reflect the exploratory nature.

We have a growing population likely to experience CNMP; obesity, inactivity and age are all factors in developing osteoarthritis (Betteridge 2004), with factors such as surgery and increasing age being responsible for other types of pain. Behavioural assessment and screening tools lack the sensitivity to be able to accurately predict who will and will not develop CNMP and management in general is not that effective. Therefore, it is important to explore methods that can increase the sensitivity of the assessment process, screen those

who require management and stratify them into appropriate management groups. The neuroimaging research presented in this thesis begins to address the issue of assessment and screening through researching how individuals with CMSKP process pain words and photographs of daily living.

Chapter 2 introduces the key themes from a behavioural perspective and examines attention to pain, fear and catastrophising and illustrates the impact of these psychological factors on pain related disability and outcomes. Chapter 3 examines neuroimaging studies specifically undertaken on patients with CMSKP, including CLBP. The neuroimaging studies reviewed examine the changes that happen as a result of having CNMP and the impact these have on psychological functioning and cognitive ability. Some reference is made to studies that lie outside the main aims for completeness. Chapter 4 introduces the key methods used in this thesis including BOLD fMRI, emotional counting Stroop and Photographs of Daily Activities (PHODA). Chapter 5 presents a Stroop study investigating the role of pain-related attention from a behavioural and neuroimaging perspective. Chapter 6 presents a study using PHODA in patients with CMSKP examining the role of fear in low kinesiophobic patients and using a bespoke task and Chapter 7 investigates PHODA in a high kinesiophobic population of CLBP patients without a bespoke task and includes resting BOLD analysis and voxel based morphometry to investigate structural changes accompanying CLBP. Lastly, Chapter 8 will discuss the findings in terms of possible implications and relate them back to the literature reviewed, discuss the strengths and limitations of the research approach taken in the thesis and identify future research initiatives.

CHAPTER 2: A REVIEW OF BEHAVIOURAL EVIDENCE OF PAIN-RELATED ATTENTION, FEAR AND CATASTROPHISING IN CMSKP

Behavioural evidence examining attention to pain, fear avoidance and catastrophising largely in patients with CMSKP will be reviewed. CMSKP is defined as pain that fulfils International Association of Pain (Merskey and Bogduk 1994) diagnostic criteria and is musculoskeletal pain of non-inflammatory origin. It is important to examine the behavioural approaches to studying the psychological factors of interest in this thesis; attention, fear and catastrophising in order to establish best methods for future research. It may be possible that behavioural research within these topic areas have shown significant outcomes and these have not been replicated in neuro-imaging research and vice versa. It is also important to identify whether adaptations have been made by neuro-imaging researchers to existing behavioural methods or whether the present author needs to adapt behavioural methods for future neuro-imaging studies. Interest in these psychological factors led to the development of methods to research these within the neuro-imaging field in CMSKP populations; these are the psychosocial factors that underpin the research presented later.

2.1 ATTENTION TO PAIN

2.1.1 Introduction

In the field of pain management, there are major implications of having an attentional bias to pain-related information. These implications include increased monitoring of bodily sensations (Pennebaker and Skelton 1981), increases in reported subjective pain intensity (Janssen and Arntz 1996) and the effect biases have on coping strategies (Esteve et al. 2007). These attentional biases may illustrate poor coping strategies in the CMSKP population (Cano et al. 2006). The Schema Enmeshment Model of Pain (Pincus and

Morley 2001) proposes that the enmeshment of pain, illness and self is responsible for information processing biases in CNMP. Its major prediction is that all pain patients, regardless of their emotional state, will demonstrate attentional bias to self-referent sensory pain information. Numerous cognitive paradigms have been used in behavioural studies to explore pain-related attentional bias including Stroop (Stroop 1935b) and visual-probe or dot-probe tasks (Schoth et al. 2012).

The original Stroop task required subjects to name the colour in which words are written whilst ignoring the actual word (Stroop 1935a) (see Fig 2.1). Performance in the task is speeded if the colour and word match, if not and the word conflicts with the colour then performance is slowed.

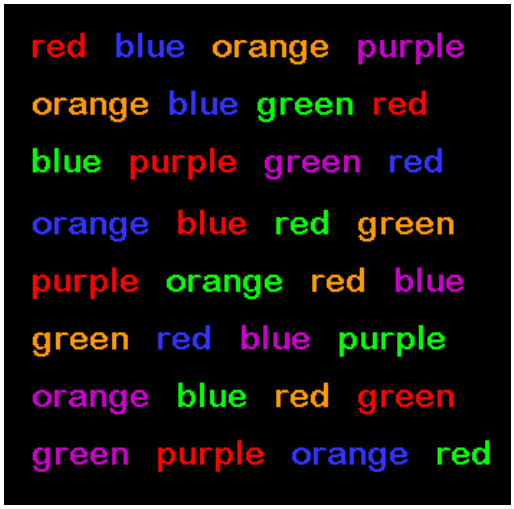


Fig 2.1. Stimulus card illustrating Stroop colour/word congruent and incongruent tasks.
When stating the colour of the ink, reading from left to right, it is relatively easy to complete the first two rows. However, when stating the colour of the ink for the remaining rows, a time lag difference may be perceived as processing the fact that the colour and word are incongruent may lead to processing the information more slowly and errors. The slowing down and error rate is known as the Stroop effect.

The emotional Stroop test (Fig 2.2) has been the most commonly used modification of Stroop in examining attentional bias in patients with CNMP (Roelofs et al. 2002). The subject responds with the number of times an emotional word is displayed compared to a control word. In the emotional Stroop, the meaning of words has been primed (Warren 1974) to ensure it has personal or emotional significance to an individual. The number of accurate responses made is also compared and this is usually used as a secondary outcome for studies.

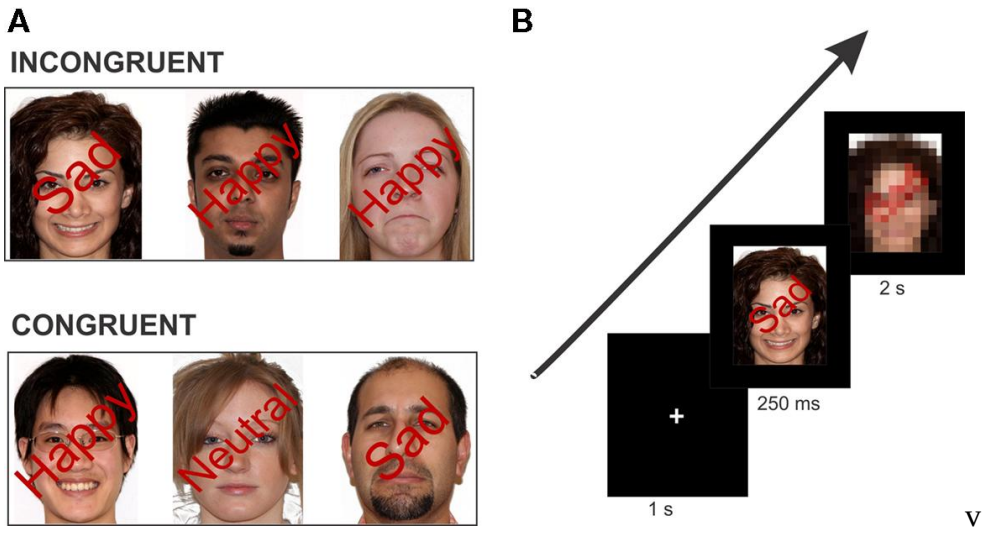


Fig 2.2 An example of a modified emotional, non pain related, Stroop task (Ovaysikia et al. 2011).

The dot-probe task was developed in 1986 (MacLeod et al. 1986) and is a computerised paradigm that records the response time to a series of visually presented stimuli. Stimuli are presented on a computer screen and may consist of words (Fig 2.3) or images (Fig 2.4) that are either threatening/emotional or neutral. Following the presentation, both stimuli are removed and a dot replaces one of the stimuli. Participants are required to locate the dot as quickly as possible with response times being averaged to provide an index of attentional bias for both sets of trials.

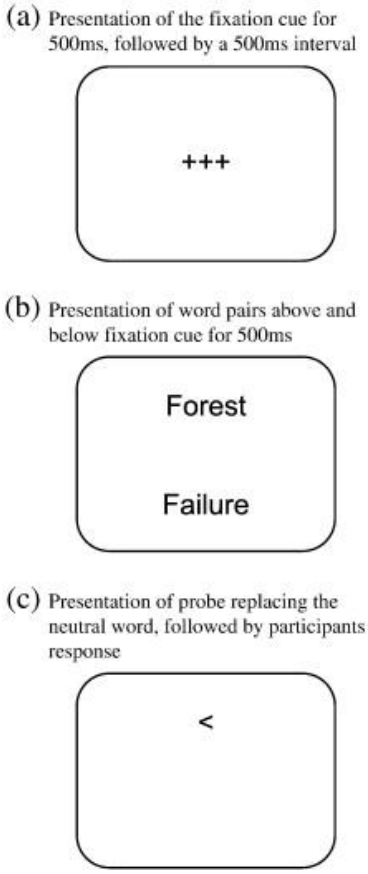


Fig 2.3 An exemplar sequence of events in the modified dot probe word protocol
(Putwain et al. 2011)

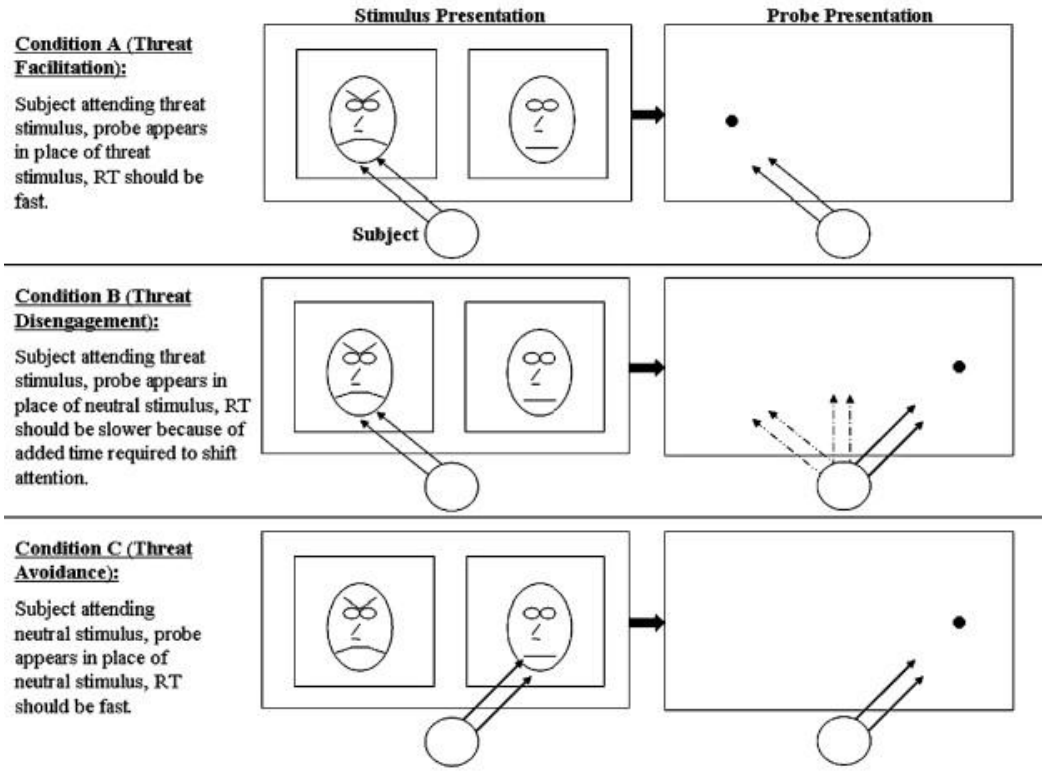


Fig 2.4 Illustration of dot probe image trial and putative mechanisms of vigilance for, difficulty disengaging from, and initial avoidance of threat stimuli
(RT: Response Time) (Frewen et al. 2008).

This section will consider the use of Stroop and dot-probe assessment techniques in studies on attention to pain. This process enabled a decision to be made regarding the most appropriate tools to use in the studies that are core to this research theme. It was important to examine them first within a behavioural context to ensure that a full picture is presented of their utility, before examining the neuro-imaging research.

2.1.2 Attention to pain and the Stroop paradigm

Humans are constantly exposed to a larger number of sensory stimuli than the brain can dedicate processing resources to (Etkin et al. 2006). In order to function, the brain will engage attentional mechanisms to prioritise processing and diminish distraction by stimuli irrelevant to the task being undertaken (Broadbent 1958). The brain is thought to resolve potential 'conflict' and improve performance, by monitoring for any distracters that would produce responses that are not relevant to the task being completed (Botvinick et al. 2001). It has been suggested that emotionally salient stimuli are particularly effective in interfering with ongoing tasks with accompanying conflict (Mathews 1990; LeDoux 2000; Tipples and Sharma 2000).

Investigators have sought, in the past, to establish whether patients suffering with CNMP exhibit specific processing biases through studies which examine whether they process pain-related information differently from normal controls in tasks that involve attentional and memory processes (Pincus et al. 1998). Patients certainly exhibit a recall bias towards pain-related stimuli (Edwards et al. 1992; Pincus et al. 1993; Pincus et al. 1995) and in some, ambiguous information can be processed as pain related (Pincus et al. 1994; Pincus et al. 1996). Several factors are thought to be involved in moderating the attentional

demands of pain, the strongest and most consistent effects relate to fear, anxiety, and catastrophising (Eccleston and Crombez 1999).

A number of studies have examined emotional Stroop in patients with CNMP, comparing their responses with those of healthy controls and reported statistically significant delayed naming latencies for pain words compared to the control words (positive Stroop effect) (Pearce and Morley 1989; Crombez et al. 2000; Snider et al. 2000; Beck et al. 2001). Pain words were combined with non-pain words as controls but while these studies showed delayed naming latencies for sensory words (Pearce and Morley 1989; Crombez et al. 2000; Snider et al. 2000; Beck et al. 2001), the same was not true for affect words and it was only Pearce and Morley (1989) and Snider et al (2000) who found response latencies for both. Crombez et al (2000) found that pain intensity was predictive of the Stroop effect which may account for why a delayed response was seen to sensory and not affect words. Roelofs et al (2002) summarised 5 Stroop studies, not all of which found a pain-related attentional bias, and the summary supports a weak association between delayed naming latencies and pain words. Given the small number of studies available for assessment Roelofs et al (2002) used raw data instead of calculating standardised effect sizes and a markedly stronger effect was found in the study with the lowest rating of methodological quality (Pearce and Morley 1989).

Other studies have reported that pain words do not cause significant response delays between patients with CNMP and controls (Duckworth et al. 1997; Pincus et al. 1998; Andersson and Haldrup 2003). These conflicting findings call into question the role of attentional biases in CMSKP, but methodological decisions taken by authors may have had an impact on their findings. It is possible that the words used for the task were relatively

non-specific and were not salient for the population studied. Granted, all the words came from the McGill Pain Questionnaire (MPQ), but it is not clear which words were actually chosen and only Crombez et al (2000) and Andersson and Haldrup (2003) consider specificity of the task and involved patients in the choice of words (Pincus and Morley 2001). Pincus and Morley (2001) levelled criticism at the MPQ pain descriptors, suggesting that they have a strong metaphorical quality when applied to pain, but are abstract and not always easily imagined or intrinsically self-referent. They suggested that it is important to use stimuli that are more concrete, equate with an individual's own pain description and are more self-referent and these stimuli may then be capable of eliciting attentional bias in a robust manner.

Depression and anxiety has been proposed to have an impact on response times during Stroop testing (Pincus et al. 1998). While some of the above studies did use depression scores as covariates in the statistical analysis (Duckworth et al. 1997; Pincus et al. 1998; Snider et al. 2000; Beck et al. 2001), the remaining studies discussed in this section did not. Consequently, it may not be the attention to pain that causes the delayed responses but the fact that patients had high levels of anxiety and/or depression which explains differences in results.

Reflecting on the Stroop paradigm used in CNMP research, the emotional Stroop effect may not be a Stroop effect at all; not a result of emotional or cognitive conflict. The traditional emotional Stroop task may not provide a measure of emotional conflict comparable to the measure of cognitive conflict provided in the colour-word Stroop task (Etkin et al 2006). Compared to the traditional colour Stroop tasks, the sensory and affect

pain descriptors taken from the MPQ are not colour names and therefore lack validity as congruent items in a colour naming task.

It is also not clear, in the research cited in this section, what pain words were used and whether the control words were appropriate and lexically matched as few included tables or documented methods to lexically balance words. Therefore, the emotional Stroop effect seen in responding to pain words may be mediated by an inhibitory mechanism associated with threat which may be independent from a Stroop effect which is largely a selective-attention mechanism or may be due to lexical bias. Therefore when considering the use of Stroop, outside its original design, it is important to consider what is actually being measured and this may be why there are conflicting results in studies that have revised the original to develop emotional Stoop; attention to pain words may be present, it just may not be seen because the methods are not robust enough, this will be re-visited later in the thesis.

Table 2.1 is an example of a word list used in a Stroop study (1989). The table illustrates the emotive words chosen which are the 'negative emotional Stroop', the 'sensory pain Stroop' and the 'affect pain Stroop'. In rigorous studies using emotional Stroop, to avoid lexical bias, these emotive words should be matched to control words that are not thought to cause any emotional responses and commonly household objects are used (Larsen et al. 2006).

Table 2.1: Example of pain words and matched words in Stroop Studies [taken from Pearce and Morley (1989)]

Negative emotional Stroop	Negative emotional control	Sensory pain Stroop	Sensory pain control	Affect pain Stroop	Affect pain control
failure	develop	throbbing	footnotes	tiring	rattling
hopeless	applause	pounding	coasted	unbearable	astonished
depressed	agreeable	sharp	upper	agonizing	accumulate
grief	rides	aching	sleeve	pumshing	limitless
fear	note	burning	descend	killing	insects
angry	prime	dull	hail	wretched	profusely
irritable	commuting	tender	rendered	dreadful	bleaching
sorrow	accent	sore	flew	exhausting	defining
worried	vehicle	gnawing	mention	nagging	closest
lonely	patrol	hurting	flowed	sickening	boyish

2.1.3 Summary and reflections

Given that more studies found delayed Stroop response times to sensory and affect words in section 2.1 than did not, it suggests that Stroop can be a useful tool to assess pain-related attentional bias in patients with CMSKP. However, the Stroop studies with positive results may be accounted for by mood state rather than pain-patient status. General inconsistencies in the literature may be attributed to the differences between the study methods; differences in the tasks employed and the differences between computerised and non-computerised versions, small samples sizes and in the words used, and presentation of them e.g. block versus randomised. Research must consider these limitations to improve the rigour of future studies on pain-related attentional bias. Roelofs et al (2002) included only a small number of articles, they could not rule out that there were a number of unpublished studies that they had not obtained, the pooled estimation may be

overestimated and the assessment of the research could not be blinded as the authors were familiar with the studies.

2.1.4 Attention to pain studies using visual- or dot-probe task

The dot-probe task (see Fig 2.5 for an example of the task) was designed by MacLeod et al (MacLeod et al. 1986) as they contended that the emotional Stroop was ambiguous and open to errors in responding. Therefore, in examining attention to pain, it was important to synthesise the evidence on the two common approaches to examining this concept, Stroop and dot-probe, in order to justify the method actually chosen for the attention to pain research discussed later in this thesis.

The first study examining the general CNMP population came from Asmundson et al (1997a) but they failed to find selective attention amongst pain patients. They did illustrate that those low in anxiety sensitivity demonstrated a bias away from pain stimuli. Since then a number of studies have been undertaken with some supporting the notion that CMSKP selectively attend to pain related information compared with healthy controls (Dehghani et al. 2003, 2004; Khatibi et al. 2009; Haggman et al. 2010), and others illustrating that this group of patients do not when compared to healthy controls (Asmundson et al. 2005; Roelofs et al. 2005; Asmundson and Hadjistavropoulos 2007; Dear et al. 2011).

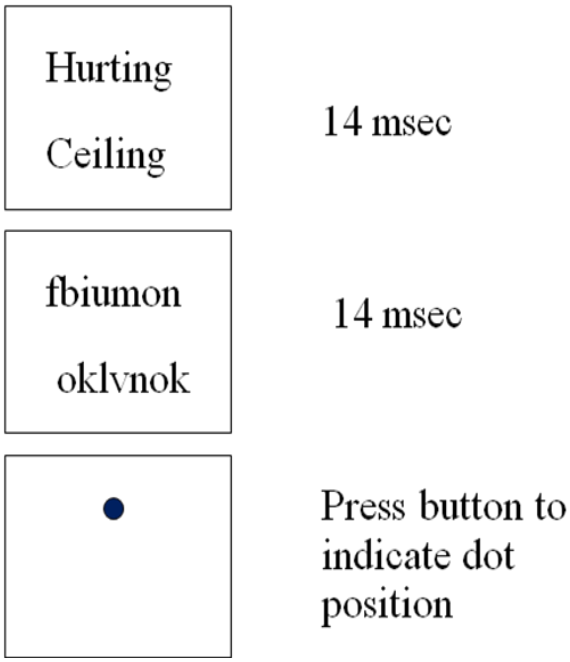


Fig.2.5 Example of a single word dot-probe task

In studies where patients did demonstrate an attentional bias to pain words (Dehghani et al. 2003, 2004; Khatibi et al. 2009; Haggman et al. 2010), it was the sensory words that participants demonstrated significant attentional bias to and not the affective pain words, a similar picture to the Stroop literature. Studies that found an attentional bias to pain words, used sensory and affect words as separate categories. Both categories come from the valid and reliable MPQ but many of the words are ambiguous in that while they are chosen from the affective MPQ domain, some may have sensory connotations also. This ambiguity may have caused a lack of positive bias to affect words. Pain has been defined as a sensory and emotional experience (Merskey and Bogduk 1994) and therefore combining the sensory and affective dimensions of pain possibly reflects better the experience of CMSKP. Future research should consider using combined sensory and affective word dimensions to strength the saliency of the word stimuli in attentional studies.

It is also plausible, however, that affective pain words are processed differently to sensory pain words. From a theoretical perspective, namely fear avoidance (Vlaeyen et al. 1995), it would make sense that hypervigilance is concerned with the avoidance of threat (sensory aspects) rather than the emotional consequences (affective aspects). Pincus and Morley (2001) propose that there are two separate schema relevant to chronic pain: pain schema (response to sensory pain stimuli) and illness schema (response to affective pain words, disability and threat words). This suggestion would help to explain the differences in processing these pain words.

Khatibi, et al (2009) used painful and happy facial expressions, paired with neutral expressions and this may address previous comments made about the saliency of words in attentional pain tasks. The actual viewing of facial expressions of pain may be more emotive for people with CMSKP than for semantic pain words and less ambiguous. Facial expressions of pain convey both sensory and affective information and therefore address the definition of CNMP in a more robust way; pain is a sensory and emotive experience (Merskey and Bogduk 1994). These may account for differences in findings across similar pain groups.

Although, Asmundson et al. (1997a) did not find an attentional bias to pain words, it was interesting to see how those participants with anxiety responded. For those with low anxiety, who shifted attention away from pain, it could suggest that they can distract themselves from or ignore the pain. This may provide clues to how certain people with pain behave. It is therefore important consider the roles of anxiety, and as previously discussed, depression, in pain attention.

Roelofs et al (2005) used 2 dot-probe tasks, linguistic word and picture tasks (using Photographs of Daily Activities – PHODA) (Kugler et al. 1999) and found all participants displayed difficulty in disengaging from the PHODA images, although this was significantly greater in the patient group. The linguistic word task showed no significant results. Dear et al (2011) also used a linguistic and picture task (PHODA) and it is interesting that PHODA engaged pain-related attention in both CMSKP patients and healthy controls. One reason for this could be that the rating of the threat PHODA was perceived to convey before the actual task was undertaken. Consequently, all participants were primed to believe that what they were viewing, i.e. the pictures, could be seen as threatening.

PHODA is an interesting tool and worthy of further study and is discussed in more depth in the methods section of this thesis. However, it may suffer from sensitivity issues in that an individual may perceive pain, threat to physical integrity, re-injury in viewing the photographs; it does not convey just one impact as it is dependent on how the individual views the photograph. Therefore problems in disengaging from the PHODA images in Roelofs et al (2005) may have arisen for a number of different reasons, not solely due to fear of back injury which was the main research target. However, pictures directly depict what patients may fear and therefore may be more emotive for them than words because words are only semantic representations of fear. More work is required to address the role of PHODA in attentional research.

Schoth et al (2012) found, in their systematic review and meta-analysis, that individuals with CNMP show significant greater bias towards pain related information when compared to controls in dot probe tasks and found evidence for significant bias during stages of

initial orienting of attention and maintained attention. The analysis found that bias was more pronounced during the later stages of attention and postulated this was due to the process of rumination. Ten eligible studies were included and they concluded that future research should explore attentional bias and its role in the causation and maintenance of CNMP given the potential consequences bias may have upon quality of life.

Summary and reflections

Research examining pain-related attentional bias in CMSKP patients using the dot-probe paradigm, has produced mixed results. Studies that failed to find an effect were marred by small samples sizes (Asmundson et al. 2005; Asmundson and Hadjistavropoulos 2007), others used large sample sizes and found biases towards sensory pain words (Dehghani et al. 2003, 2004). Differences in findings could be explained by factors that may have influenced the task and were not recorded such as pain (Asmundson et al. 2005), analgesic intake and caffeine (Roelofs et al. 2005); clinicians choosing the stimuli rather than having participant input (Dear et al. 2011) and lack of a control group for comparison (Dehghani et al. 2003, 2004). However, the meta-analysis by Schoth et al (2012) suggested that individuals with CMSKP demonstrate significant attentional bias towards pain-related information compared to healthy controls in the majority of dot-probe research.

2.1.5 Section summary

Evidence that patients with CNMP selectively attend to pain-related stimuli presented in modified Stroop and dot-probe paradigms is mixed. The modified Stroop and dot-probe tasks seem to lack consistency across similar groups of patients. Consequently, drawing firm conclusions from either task using distinct groups of patients needs to be undertaken with caution. Across different populations within the CNMP, it is possible that these tasks

are measuring different phenomena. It appears that general anxiety, anxiety sensitivity, depression, and fear of pain can influence the pattern of findings in dot-probe and Stroop tasks (Pincus and Morley 2001; Pincus et al. 2010).

Reviewing both Stroop and dot-probe studies has provided useful information on word choice, combining sensory and affective words from the MPQ and the consideration of using more self-referential information in pictorial presentations. Fear avoidance models, discussed next, propose that patients with CNMP are hypervigilant to environmental and somatic representations of pain, however the lack of consensus across Stroop and dot-probe tests does not support this.

Pincus and Morley (2001) proposed that Stroop and dot-probe tasks are simply not difficult enough for patients with pain. Experiencing CNMP means that patients have constant pain that competes for attention and thus they have required the skill in managing attentional demands. They suggest that the concurrent demand of CNMP may be sufficient to override the interference effects of these experimental tasks. If this is the case, those with relatively recent CMSKP, may demonstrate an attentional bias to pain related information, whereas those with established pain would not. Therefore, other methods of examining attentional bias may shed more light on the processes involved.

2.2. FEAR AVOIDANCE

2.2.1 Introduction

A number of fear avoidance models have been proposed sharing a common theme that fearful reactions to pain, pain anticipation and/or perceived consequences associated with the pain promotes withdrawal from activities or behaviours that may increase pain (Schoth

et al. 2012). High fear of pain can lead to hypervigilance for both pain and pain-related information (Vlaeyen et al. 1995; Vlaeyen and Crombez 1999; Vlaeyen and Linton 2000).

In 2000, Vlaeyen and Linton (2000) introduced their Fear-Avoidance (FA) model (Fig.2.2.); a model which described how pain disability, affective distress, and physical disuse develop as a result of persistent avoidance behaviours motivated by fear. The FA model has become increasingly popular but one of the unanswered questions, however, is how pain-related fear occurs in the first place (Vlaeyen and Linton 2012). Research has yet to address this but it is clear that activity avoidance is problematic and this section will address this.

Cognitions shape not only psychological outcomes such as emotional functioning but also the nervous system activity underlying pain perception (Villemure and Bushnell 2002; Seminowicz and Davis 2007c). Therefore it is unsurprising that maladaptive pain cognitions are associated with emotional and behavioural responses leading to activity avoidance, disability, depression (Vlaeyen et al. 1995; Goubert et al. 2004b; Peters et al. 2005; Boersma and Linton 2006; Smeets et al. 2009) and predicts future pain (Leeuw et al. 2007a).

There is a large amount of research examining the predictive value of fear avoidance in acute musculoskeletal and back pain (Boersma and Linton 2006; Pincus et al. 2006; Swinkels-Meewisse et al. 2006; Pincus et al. 2010; Wideman and Sullivan 2010). However, the population under consideration here have CMSKP and CLBP and therefore, the predictive fear avoidance literature is not as pertinent as considering fear avoidance and

its impact on those with established chronic pain. Therefore, the focus of this section will be on CMSKP and CLBP.

2.2.2 Fear avoidance: impact

It has been illustrated in this review that while it may be possible to classify patients into groups with similar characteristics, of which fear avoidance is a theme, application of these groups to predict outcomes has been less successful. Fear of movement and (re)injury (Fig 2.6) have been implicated in the development of long-term pain problems leading to avoidance behaviour (Vlaeyen and Linton 2000). Pain related fear and anxiety responses include psycho-physiological (e.g. heightened muscle reactivity), behavioural (e.g. escape and avoidance) and cognitive (e.g. catastrophising) elements (Leeuw et al. 2007a).

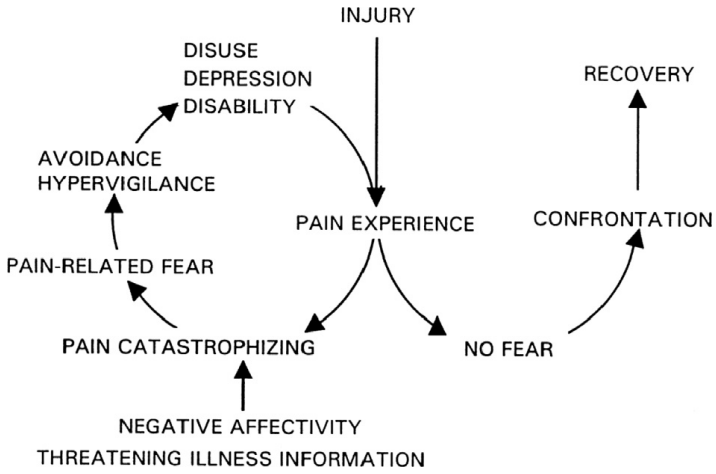


Fig.2.6 The Fear-Avoidance Model (Vlaeyen and Linton 2000)

The FA model proposes that misinterpretation and negative beliefs about early pain experiences lead to fear of movement and of situations associated with movement, resulting in avoidance of such (Vlaeyen and Linton 2000). This leads to hypervigilance and difficulty disengaging from such stimuli (Asmundson et al. 2005; Crombez et al. 2005; Roelofs et al. 2005) contributing to physical dysfunction and increased disability with the

accompanying psychosocial sequelae (Pincus et al. 2010). In this section, the literature will be examined to establish what impact fear of movement/reinjury, fear of pain and fear avoidance has on those with CMSKP and CLBP.

Physical activity

A number of studies have examined the impact of fear and avoidant behaviour on CMSKP patients undertaking physical activities and aimed to investigate the association between pain-related fear and behavioural performance (Crombez et al. 1999b; Reneman et al. 2003; Heuts et al. 2004; Lundberg et al. 2006; Samwel et al. 2006; Elfving et al. 2007; Reneman et al. 2007; Smeets et al. 2007; Leonhardt et al. 2009; Damsgard et al. 2010; Koho et al. 2011). It was found that those participants with high fear of pain and (re)injury [also catastrophising in Elfving et al (2007)] undertook less physical activity (Crombez et al. 1999b; Heuts et al. 2004; Elfving et al. 2007; Koho et al. 2011), had higher activity induced pain (Damsgard et al. 2010), more functional limitations (Heuts et al. 2004) and undertook less leisure-time activity (Koho et al. 2011). However, a number of studies did not find an association between kinesiophobia and physical activity (Reneman et al. 2003; Lundberg et al. 2006; Samwel et al. 2006; Reneman et al. 2007; Smeets et al. 2007; Leonhardt et al. 2009).

The methods used and potential limitations may have resulted in the differences between studies that found kinesiophobia to be predictive of negative outcomes and those that did not. The use of a clinical setting in some of the studies may have meant that some variables were not controlled for (Reneman et al. 2003; Samwel et al. 2006; Reneman et al. 2007). The tasks used in some equated with activities that are seen as part of everyday life (Reneman et al. 2003; Samwel et al. 2006; Reneman et al. 2007; Smeets et al. 2007) and

the relationship between kinesiophobia and everyday physical activities has been shown to be virtually nonexistent (Geisser et al. 2000), possibly due to not being threatening enough.

Many of the studies had limitations with the sample including small sample sizes (Crombez et al. 1999b; Elfving et al. 2007) and representativeness of the sample to the CMSKP population (Reneman et al. 2003; Lundberg et al. 2006; Elfving et al. 2007; Reneman et al. 2007; Leonhardt et al. 2009; Damsgard et al. 2010). Methodological issues included the use of self-report measures (Reneman et al. 2003; Lundberg et al. 2006; Reneman et al. 2007; Leonhardt et al. 2009) and the potential for response bias, cross-sectional methods that could not prove whether pain related fear is a precursor of disability rather than a consequence of it (Crombez et al. 1999b; Heuts et al. 2004; Elfving et al. 2007; Damsgard et al. 2010; Koho et al. 2011).

These studies may be illustrating that increased fear avoidance beliefs are not associated with quantity but rather the quality of activities performed and the choice of salient activities in which to test kinesiophobia is important. They may also illustrate that the tools used to assess fear of movement/(re)injury are not robust or it is not clear what it is that participants are fearful of when they have high ratings of fear. Crombez et al (1999b) found that although patients may have high levels of fear, they do not anticipate more pain than say a group who may not be fearful of an activity and postulated that it may be that a fear of pain is more related to the after-effects of an activity, that patients avoid activities because they fear harm and not pain or they fear that the increases in pain post activity would be difficult to cope with. It may also be the type of activity rather than the amount, a point raised by Leonhardt et al (2009). Future research, it is suggested, will need to specify

the content of stimuli that is anticipated to lead to pain-related fears in CLBP and CMSKP patients.

Over-prediction of pain task

A number of studies have examined CLBP patients' responses to undertaking a physical task to establish whether anticipated pain was over-predicted and whether this was due to self-rated fear (Crombez et al. 1996; Crombez et al. 2002b; Goubert et al. 2002; Goubert et al. 2005b; Trost et al. 2008). Patients were asked to rate expected and experienced pain and the results showed conflicting results; one study found greater pain and harm ratings during the movements in those with high kinesiophobia compared with low (Trost et al. 2008), others found harm ratings were low and pain scores were similar in high and low catastrophisers (Crombez et al. 1999b; Goubert et al. 2002). Therefore, it appears that pain expectancies do not necessarily lead to task induced pain but the results are not conclusive.

Participants' behaviour differed in the studies. Highly kinesiophobic participants over-predicted pain at the beginning of a physical task but with the increasing demands of the task, over-prediction was eliminated and their pain ratings were similar to those with low kinesiophobia in Trost et al (2008). This result agreed with Crombez et al (1996), Goubert et al (2002), Crombez et al (2002b) and Goubert et al's (2005b) in that over-prediction was eliminated with repetition of a similar task but Goubert et al (2002), Crombez et al (2002b) and Goubert et al's (2005b) found that the successful effects of exposure to one movement did not generalize toward a second, dissimilar movement. All but Trost et al (2008), explained this as patients learning as 'an exception to the rule' rather than a fundamental change in their beliefs about movement in general.

The differences in findings here may be due to the fact that Crombez et al (1996), Goubert et al (2002) nor Crombez et al (2002b) included graded exposure elements. Had they included these elements, they may have observed a gradual extinction of the over-prediction responses as seen in Trost et al (2008). Also, in Trost et al (2008), significant differences between high and low kinesiophobic participants may have been obscured by the median split procedure used to organize the groups. Therefore, participants in Trost et al (2008) may not have been as fearful as in the other studies.

The selected movements were not individually tailored to each participant; perceived difficulty with the tasks may not have been equal in all participants (Crombez et al. 1996; Crombez et al. 2002b; Goubert et al. 2002; Goubert et al. 2005b; Trost et al. 2008) and using movements common to everyday life (Trost et al. 2008) may have reduced ecological validity through familiarity of the task. In Goubert et al (2002; 2005b) and Crombez et al (2002b), it was not the high kinesiophobic patients that over-predicted pain compared with the low group but the high catastrophic thinking group compared with the low catastrophic thinking group; possibly illustrating that catastrophising is a more robust way of testing fear of movement than kinesiophobia.

Catastrophising about pain is often considered as a precursor for the development of pain-related fear and pain-related fear has been found to mediate the relationship between pain catastrophising and avoidance behaviour. Although the studies differed in terms of whether it was fear of pain/(re)injury or catastrophising that had an impact on over-prediction, these are both involved in fear avoidance and, for the purpose of this section, add weight to the impact the fear avoidance model has. Catastrophising will be discussed following this section.

Experimental studies using physical tasks

A number of studies have examined lumbar movement and fear of pain in experimental trials (Vlaeyen et al. 1995; Crombez et al. 1998; Al-Obaidi et al. 2000; Geisser et al. 2000; van den Hout et al. 2001; Geisser et al. 2004; Trost et al. 2009). The results of some of these have shown that spinal physical capacity in chronicity is not explained solely by the sensory perception of pain and anticipation of pain and the fear-avoidance belief about physical activities are the strongest predictors of the variation in physical performance (Vlaeyen et al. 1995; Crombez et al. 1998; Al-Obaidi et al. 2000; Geisser et al. 2000; Geisser et al. 2004). However, one study differed in their findings; van den Hout et al (2001) found that pre-lifting pain was the strongest predictor of variation in physical performance with regard to all pain measures studied.

Trost et al (2009) used a modified PHODA, PHODA-M, to assess a sample of patients with CLBP who had high and low levels of kinesiophobia. They used a reaching task where lumbar movements were subjected to increasing load mimicking a graded-exposure type approach. Responses on the PHODA-M were compared to predicted and experienced pain and harm ratings collected during performance of the task. The results distinguished between high and low fear participants on both the reaching task and the PHODA-M. Those with high kinesiophobia legitimated higher pain and harm expectancies in response to the PHODA-M stimuli, supporting the association between TSK and PHODA scores observed by Leeuw et al (2007b).

No study examined muscle activity among persons who did not have CLBP (control group), therefore it is unclear whether the results reflect abnormal muscle activity. Al-Obaidi et al (2000) also classified their participants as ‘chronic’ but the mean duration of

pain experienced was less than 3 months and inclusion criteria specified pain for over 7 weeks, therefore, neither fulfils the IASP definition of CNMP. As with many of the studies, the study method (cross-sectional, correlational) used here does not allow for examination of cause-effect relationships. However, pain-related fear appears to be associated with musculoskeletal abnormalities observed among persons with CLBP and in combination with limited movement may be involved in the development and maintenance of CLBP.

Experimental studies using cognitive tasks

Only three relevant studies could be found that investigated fear of movement and (re)injury using cognitive tasks. Goubert et al (2005a) used vignettes to investigate whether a reluctance to generalise an experience of lesser pain than expected to another, similar situation is associated with pain-related fear and pain catastrophising in patients with CLBP. Leeuw et al (2007c) used two implicit measures, the Extrinsic Affective Simon Task (EAST) and the Go-No-Go-Association Task (GNAT), to study fear of movement/(re)injury without the awareness of the patient. Crombez et al (2012b) used auditory signals to deliver a cue to participants with chronic pain to complete questions about their experiences on a palmtop computer in order to investigate how acceptance of illness affects chronic pain in terms of attention towards pain and fearful thinking of pain.

Goubert et al (2005a) found that pain catastrophising and pain-related fear contributed uniquely in predicting lack of generalisation of corrective experiences and that patients who had high catastrophic and fear thoughts were likely to generalise negative pain-related experiences to other movements and situations, thus becoming more disabled. However, they were less able to generalise positive pain-related experiences. Previous discussions

have postulated that over-prediction correction was seen ‘an exception to the rule’ rather than a fundamental change in their beliefs about movement in general. Here, the interpretation may be that the exception to the rule is the positive pain-related experience and the fundamental ‘change in beliefs’ are in regard to the negative pain-related experiences. Crombez et al (2012b) also found that fear had an impact on the pain experienced; on movements with more intense pain, more negative emotions, and less positive emotions, fearful thinking about pain was increased. Pain therefore was shown to capture attention and elicit fearful thinking about pain.

Leeuw et al (2007c) did not find any differences between CLBP patients and healthy controls in their level of implicit fear of movement/(re)injury and there appeared to be no associations between the cognitive tasks used, or between implicitly measured and self-reported fear of movement/(re)injury. The findings may have been due to the poor reliability of these implicit measures and further research is required on their psychometric properties before using them to assess complex domains such as fear of movement/(re)injury.

These studies are very diverse but it is clear from two of them that pain related fear is a key feature in patients with CMSKP.

2.2.3 Summary and reflections

Crombez et al (2012a), in a recent review, contend that there is now ample evidence to support the validity of the FA model in chronic pain populations, and this section supports this contention. Although changes in cognitive factors (fear avoidance beliefs, catastrophising) are not always found to be significantly associated with changes in pain

intensity their relationship with disability has been shown repeatedly (Crombez et al. 2012a). Research in patients with CMSKP has been undertaken either using experimental measures to introduce physical capacity tasks or in clinical practice and based largely on self-report measures. Several experimental studies have demonstrated the impact of fear avoidance on pain behaviour in laboratory settings but it is difficult to conclude from these studies as there are a number of important limitations that may account for the lack of consistency in outcomes. These have been discussed previously in this section. While the focus of this thesis is around attention to pain, fear and catastrophising, it has to be recognised that other factors are important. Pincus et al (2010) cite, for instance, the patient's motivation, the emotional state of the patient, their level of pain, self-efficacy, and physical de-conditioning as important variables.

One thing to highlight, however, is that the two most commonly used self-report measures TSK and Fear Avoidance Beliefs Questionnaire (FABQ) may lack sensitivity and may account for, in part, the contradictory findings in fear-avoidance studies (Pincus et al. 2010). These tools do not measure fear for specific movements or activities and so a patient could rate a movement as threatening, avoid activity but have a low score. The other methodological issues surround the ecological value of the physical capacity tasks; those that involve replicating activities of daily living may not incur fear because they are constant, potentially unavoidable and familiar. Pincus et al (2010) suggests that research testing specific performance in relation to fear could be improved by obtaining information about what individuals with CMSKP fear and what they avoid and replicating these within a research context.

Clinically, if the results demonstrate that fear is important in chronicity, avoidant behaviours may be limited through defying the harm and danger beliefs about pain and addressing the inaccurate pain expectancies. However, the association between fear and movement may not be conscious (Mincka and Ben Hamida 1998). Self-report measures could both underestimate fear, which is non-conscious and confuse fear with general health beliefs and overestimate it (Pincus et al. 2010). It would seem important for health professionals to understand and be able to differentiate between behaviour that is due to sensory experiences of pain and that which is driven by affect and cognitive factors in order to best address assessment and management strategies. Overall, it appears that the behavioural research to date on fear avoidance, fear of pain, (re)injury and movement has not provided conclusive outcomes and future research is required to help us better understand what these concepts are, how they impact on chronicity and the degree of this impact. Future investigations, for instance, could attempt to ascertain the perceptions and experiences of more extreme portions of the kinesiophobia spectrum, for example, by studying participants scoring at the highest and lowest quartiles of the Tampa Scale of Kinesiophobia.

2.3 CATASTROPHISING

2.3.1 Introduction

According to Lazarus' cognitive theory (Lazarus 1991), catastrophic appraisal serves an adaptive function, in an acute situation, by activating necessary physiological responses to cope with perceived threat. However, when used in conjunction in a chronic situation, it can become maladaptive, promoting physiological and psychosocial behaviours that lead to distress and disability.

Catastrophising has been defined as a set of negative emotional and cognitive processes that serves as a critically important risk factor for poor pain-related outcomes (Sullivan et al. 2001b; Edwards et al. 2006; Quartana et al. 2009). It is central to the fear avoidance model, and can be defined as an individual's tendency to exaggerate, ruminate, focus on how threatening pain is, and negatively evaluate their ability to cope with it (Sullivan 1995). It is the cognitive route through which fear of pain develops (Vlaeyen et al. 1995) and the resultant fear has been conceptualised both as a maladaptive coping strategy and a cognitive appraisal style (Keefe et al. 1990). Catastrophising is strongly associated with depression and both augment pain perception through increased attention to the pain and heightened emotional responses (Gracely et al. 2004).

A number of models have been put forward to explain catastrophising (Sullivan et al. 2001b):

- The Schema-activation model; catastrophisers may possess "pain schema" containing excessively negative information about pain-related experiences, and pessimistic beliefs about pain or the ability to cope with pain.
- The Appraisal model, related to the schema-activation theory and characterising catastrophising as an appraisal system.
- The Attentional model, both the schema-activation model and the appraisal model propose that individuals who exaggerate the threat value of pain will increase their attentional focus on pain. This model proposes that catastrophising is an attentional orientation activity
- The Coping model, pain catastrophising acts as a coping mechanism
    - Communal coping model, catastrophising represents a behavioural coping strategy employed by individuals experiencing pain to elicit emotional

and/or tangible support from others, thereby positively reinforcing pain and illness behaviours and undermining successful adaptation to pain.

Sullivan et al (2001b) suggests that these models can provide useful frameworks for understanding the relationship between catastrophising and pain and they are not necessarily incompatible. It is conceivable that these models may account for different domains of the relation between catastrophising and pain and may prove useful in addressing differences in how catastrophising manifests itself in different pain populations and in different individuals.

As already discussed, fear of movement or (re)injury is related to chronicity but pain catastrophising and general emotional distress (depressed mood and anxiety) also have been shown to have an impact on pain-related disability (Pincus et al. 2002; Leeuw et al. 2007a). The Coping Strategies Questionnaire (CSQ) (Rosenstiel and Keefe 1983) and the Pain Catastrophising Scale (PCS) (Sullivan et al. 1995) are typically used to obtain information about catastrophising. The PCS assesses three domains believed to comprise much of the pain catastrophising construct, while the CSQ only evaluates the helplessness dimension. An area of assessment that is currently underdeveloped is that which needs to consider the behavioural elements of pain catastrophising. To date, there exists no means of systematically assessing pain catastrophising behaviours (Quartana et al. 2009). Such research would likely have important implications for more clearly characterising the interpersonal consequences and determinants of catastrophising (Quartana et al. 2009). This section will examine the evidence for catastrophising within a CMSKP pain population.

2.3.2 Catastrophising: impact

The majority of studies examining pain interference in CMSKP patients are based on self-report data. While experimental research within a laboratory setting may produce more objective data, this has mainly involved healthy controls and as already discussed, making assumptions about CMSKP from healthy volunteer data may not be appropriate. However, laboratory research is important as it may generate theoretical perspectives that are then refined through clinical research. Research in the clinical setting, may also be limited in that results are mainly generated through self-reports of pain experiences which are necessary to formulate individual treatment plans but from a research perspective, recall of these experiences may be inaccurate.

Laboratory based research

Laboratory based research in catastrophising resulted from concerns, that various authors proposed, regarding reliance on self-report measures (Sullivan et al. 2001b; France et al. 2002; Edwards et al. 2005; Campbell et al. 2010) with inherent problems associated with recall bias and accuracy of the responder (Jamison et al. 1989; Keefe et al. 2000; Crombez et al. 2002a; Bergbom et al. 2011). The majority of experimental studies discussed in this section have used cognitive tasks combined with painful stimuli (Crombez et al. 2002a; Giesecke et al. 2003; Richardson et al. 2009; Campbell et al. 2010; Quartana et al. 2010; Richardson et al. 2010) in a diverse number of CMSKP groups.

From these laboratory based studies, it appears that there are mixed results. Pain catastrophising had a negative impact on induced pain in a number of studies; increased catastrophising led to increased attention to pain and pain intensity (Crombez et al. 2002a; Giesecke et al. 2003; Campbell et al. 2010) but not in others (Richardson et al. 2009;

Quartana et al. 2010; Richardson et al. 2010). Richardson et al (2009) and Quartana et al (2010) found that pain catastrophising was not associated with induced pain ratings. Richardson et al (2010) initially found a difference but when a concept called 'pain willingness' (the degree to which an individual focuses on the pain) was controlled for, the relationship between catastrophising and task interference did not survive.

Catastrophising was more strongly related to self-reported daily interference compared to observed interference from experimentally induced pain in Campbell et al (2010) and Richardson et al (2010) indicating that differences occur when catastrophising is measured in a laboratory setting compared with a clinical setting. It therefore appears that CMSKP patients differ in pain catastrophising depending on whether the assessment is undertaken situationally (measured during or directly after administration of a noxious stimulus) or using dispositional measures (those obtained by self-assessed measures based on recall). They also differ within proposed homogeneous groups, such as seen above (Giesecke et al. 2003). These differences may be due to what is actually being measured; measuring a general tendency to catastrophise (trait) compared with measuring an individual's response to a specific situation over a certain time-span (state).

Pain catastrophising has most typically been conceptualized and assessed as a trait like or dispositional variable but trait measures of pain catastrophising have been criticised as not adequately capturing variance in pain because measures of pain catastrophising (CSQ or PCS) rely on recall of a pain event (Quartana et al. 2009). This may be true in studies involving healthy controls, who may have to recall over many years to identify a pain scenario but not necessarily so in studies using CMSKP participants in whom pain tends to be persistent. Quartana et al (2009) document a number of weaknesses associated with the

state pain catastrophising literature including lack of established validity and reliability of state measures, correlations between state and trait measures of pain catastrophising have ranged from small to moderate in magnitude and state pain catastrophising may be confounded with the pain experience itself. Moreover, catastrophising might represent a type of latent construct, requiring sufficient activation to exert its effects (Buenaver et al. 2008); in laboratory settings, the task may not be sufficient to activate the catastrophising constructs and informed consent informs the patient that there will be no harm, whereas previous and current pain experiences might well involve such threats.

In the above studies, there was no assessment of the fear of pain and while, Crombez et al (2002a), Giesecke et al (2003) and Richardson et al (2010) investigated other potentially overlapping cognitive factors, others did not (Campbell et al. 2010; Quartana et al. 2010). Evidence suggests that other cognitive factors, including fear of pain, work in tandem with catastrophising in shaping pain behaviours (Goubert et al. 2004b; Sullivan et al. 2004; Peters et al. 2005) and a more accurate psychological profile may have been obtained had fear of pain been assessed. Despite observing no association between pain catastrophising and induced pain, Quartana et al (2010) suggested a significant association between pain catastrophising and cortisol responses to pain. This may have resulted from failing to assess such factors as fear of pain, pain-related distress and hypervigilance which may increase stress more than pain catastrophising. It may be that sensory pain experience per se does not drive the catastrophising-cortisol association. Instead, it might be the affective component of pain is exaggerated in those that catastrophise triggering the stress response. These findings emphasise the importance of assessing catastrophising from a multidimensional perspective and suggest that pain-related catastrophising should be assessed in relation to specific and definable events.

In a number of other laboratory based research studies, observation of physical capacity tasks were used (Keefe et al. 2000; Somers et al. 2009). These studies both used a population of OA knee pain patients and found that pain cognitions, particularly pain catastrophising, were important variables in understanding pain, pain behaviour, disability, and functional ability (after controlling for pain). Fear was not assessed in Keefe et al (2000) but it was in Somers et al (2009) and they found that pain catastrophising explained a higher proportion of variance in pain and psychological disability than pain-related fear. This has previously been shown in both the OA population and in other CMSKP groups (Keefe et al. 1991; Cook et al. 2006; Edwards et al. 2006).

In people with chronic pain, tendencies to ruminate upon pain and feel helpless about it (pain catastrophising) may be more important in explaining physical disability than fear of movement. Fear did explain the significance variance in one of the tasks, 'walking fast' (Somers et al. 2009) and may reinforce the previous discussion about these psychological variables being assessed in relation to specific and definable events.

From these studies, it is clear that catastrophising and pain are intrinsically linked. The results concur with the majority of laboratory based research despite the data having been collected by self-report measures and the studies were cross-sectional. These studies underscore the need to recognise psychological factors as being the main drivers for chronicity in CMSKP patients and not physical pain per se.

Clinical research

Clinical research has shed considerable light on the role of catastrophising compared with other factors in CMSKP and pain-related disability (Sullivan et al. 1998; Vienneau et al. 1999; Severeijns et al. 2001; Peters et al. 2005; Borsbo et al. 2009; Borsbo et al. 2010; Ong et al. 2010; Bergbom et al. 2011; Linton et al. 2011; Buenaver et al. 2012). These factors include depressed mood (Geisser et al. 1994b; Borsbo et al. 2009; Bergbom et al. 2011; Linton et al. 2011), self-efficacy (Borsbo et al. 2010), psychological resilience and positive emotions (Ong et al. 2010), sleep (Buenaver et al. 2012), work status (Sullivan et al. 1998; Wideman and Sullivan 2010), physical pathology (Severeijns et al. 2001; Peters et al. 2005) and psychological distress (Severeijns et al. 2001).

Findings from all of the above studies illustrate that quality of life and disability are associated with catastrophising, with factors such as self-efficacy (Borsbo et al. 2010; Wideman and Sullivan 2010) and high resilience (Ong et al. 2010) correlating positively with the outcomes tested in the studies e.g. quality of life and general health variables, medication use and negatively with pain (Sullivan et al. 1998; Vienneau et al. 1999; Severeijns et al. 2001; Borsbo et al. 2009; Borsbo et al. 2010; Ong et al. 2010; Wideman and Sullivan 2010; Bergbom et al. 2011; Linton et al. 2011; Buenaver et al. 2012). Based on depressed mood and high levels of catastrophising, treatment outcomes have been shown to be poor (Bergbom et al. 2011) as has sleep (Buenaver et al. 2012) and catastrophising has been shown to be a potent predictor of psychological distress (Severeijns et al. 2001). Physical pathology and pain catastrophising have also been found to be significantly related to pain intensity (Vienneau et al. 1999; Severeijns et al. 2001; Peters et al. 2005).

A number of studies have examined pain catastrophising in homogeneous, disease specific CMSKP patient populations including fibromyalgia (Crombez et al. 2004; van Wilgen et al. 2008; Rodero et al. 2010), spinal cord injury (Turner et al. 2002; Hirsh et al. 2011), multiple sclerosis (Hirsh et al. 2011), temporomandibular disorder (Turner et al. 2004) and chronic whiplash (Thompson et al. 2010) and all studies found that pain-catastrophising affected the participants negatively. Greater catastrophising was significantly related to greater levels of disability and other outcome measures tested in these studies. In van Wilgen et al (2008) an inability to understand the experienced fibromyalgic symptoms probably increased the tendency to catastrophise; this included experiencing cyclical and changing symptoms that are unpredictable, have emotional consequences and perceived to be a serious disease.

Rodero et al (2010) examined patients with fibromyalgia who were grouped using duration of pain and found that catastrophising had more impact on pain and quality of life at 2 years and helplessness at 4 years; similar finding have been demonstrated in other studies (Sullivan et al. 1998; Vienneau et al. 1999). However, catastrophising was a stronger predictor of fibromyalgia impact than pain itself across all duration groups and remained constant over time, despite the fact that fibromyalgia impact increased (Rodero et al. 2010). Turner et al (2004) also illustrated that catastrophising was stable in a study undertaken over a 2-week period and also found that the variability was similar from the first to the second week. These studies suggest that in the absence of an intervention targeting catastrophising or a substantial reduction in pain or depression, patients with CMSKP tend to be stable in their degree of pain-related catastrophising.

Thompson et al (2010) was the only study not to find that pain intensity was significantly related to any of the cognitive factors studied, including catastrophising. The differences in findings may be related to the different groups of patients studied, the fact that pain intensity was only assessed at one time point in Thompson et al (2010) and/or the differences in the cognitive variables other than catastrophising studied. In Thompson et al (2010) data was only available for 44% of the patients and those that participated may be a different group from those that did not.

Much of the evidence linking catastrophising with increased distress and perceived disability has been undertaken in clinical settings with study participants suffering from a range of pain-related disorders. However, it is known that those who seek care have a high prevalence of co-morbid psychiatric conditions which may alter the association between catastrophising, distress and disability (Ciccone et al. 2010). In the absence of screening for mental health problems or factoring these into the analysis, generalisations to clinical practice should be made cautiously.

These studies illustrate that there is a complex interaction of psychological factors on disability, quality of life and health. Much of the research in catastrophising, as in fear, is cross-sectional in nature and thus causality cannot be determined; catastrophising may produce high pain levels or be a consequence of severe pain (Keefe et al. 2000). While there is a correlation between pain and catastrophising, it appears that they are separate but related constructs.

Several studies have shown that when pain is controlled for, catastrophising still explains important study outcomes (Keefe et al. 1989; Affleck et al. 1992; Sullivan et al. 1998).

Therefore, if catastrophising was indistinguishable from pain, the effect of controlling for current pain would have made catastrophising non-significant (Keefe et al. 2000). The same is true for depression and catastrophising, they are separate but related constructs (Geisser et al. 1994b; Linton et al. 2011).

It is important to assess catastrophising alongside other cognitive factors as although catastrophising and depression are related (Severeijns et al. 2004), several authors have suggested that catastrophising is a separate phenomenon (Keefe et al. 1989; Geisser et al. 1994a; Geisser et al. 1994b; Sullivan et al. 1998; Keefe et al. 2000; Sullivan et al. 2001a; Wideman and Sullivan 2010; Linton et al. 2011). Linton et al (2011) found a small to moderate correlation between catastrophising and depression. They identified individuals with one but not the other problem and found that having one or the other was associated with current pain problems and outcome, while having both increased the associations substantially. Therefore, while pain catastrophising and heightened depressed mood are separate phenomena, they do have an additive and adverse effect on the impact of pain, relative to either alone.

Similar discussions centre on negative affect with some suggesting that catastrophising is a part of neuroticism (Turner and Aaron 2001). Others suggest catastrophising is related to negative affect but it is a better predictor of several pain-related outcome variables over negative affect (Affleck et al. 1992; Sullivan et al. 1995; Martin et al. 1996) and therefore unlikely to be part of negative affect. Therefore, it appears that catastrophising is an independent concept but highly linked to other major psychological factors that lead to increased disability and distress in patients with CMSKP.

Community-based research

A number of studies have examined catastrophising in community samples of individuals not being managed within a health care environment and not studied within a laboratory setting (Cano 2004; Linton 2005; Karoly and Ruehlman 2006, 2007; Ciccone et al. 2010; Day and Thorn 2010; Kratz et al. 2011). Different samples of people participated, including working populations (Linton 2005; Ciccone et al. 2010), rural populations (Day and Thorn 2010), CNMP (large percentage being CMSKP) populations (Severeijns et al. 2002; Severeijns et al. 2004; Karoly and Ruehlman 2007; Kratz et al. 2011), married couples (Cano 2004) and resilient versus non resilient populations (Karoly and Ruehlman 2006).

All but Linton (2005), who examined predictive capabilities of catastrophising, found that pain-related catastrophising accounted for substantial variance in measure of psychological distress and physical impairment in a negative manner. These findings were independent of pain duration (Ciccone et al. 2010; Day and Thorn 2010), not seen in participants who were assessed as being 'resilient' (Karoly and Ruehlman 2006), seen in individuals with longer durations of pain and who perceived less spousal support (Cano 2004) or who had attachment anxiety (Kratz et al. 2011) and were significantly associated with impaired mental health (Severeijns et al. 2002; Severeijns et al. 2004; Ciccone et al. 2010). Linton (2005) found that the most potent risk factors for developing chronic spinal pain were psychological distress and poor function with catastrophising having the highest odds ratio.

High levels of catastrophising were also associated with more frequent use of pain medication, work disability, limitations in social activities and specialist consultation in some (Severeijns et al. 2002; Severeijns et al. 2004) but not all studies (Severeijns et al.

2005). Severeijns et al (2005) subsequently followed up their 2004 cohort, no evidence was found that pain catastrophising predicted specialist consultation, the use of pain medication, or absenteeism. They found a low level of catastrophising in the community sample and a small but significant effect of catastrophising on the development of chronic pain complaints but no significant effects of catastrophising on health index values. They concluded that the findings were difficult to explain but offered that catastrophising in the general population is low. However, the findings may have been attributed to only 51.1% of the original population returning their postal questionnaires.

Despite the fact that catastrophising was uniquely associated with mental health, Severeijns et al (2002) did not screen their sample for psychiatric illness; therefore, it may not have been the pain that led to mental health problems; these may have already existed. Other studies also had issues with mental health status in participants, Severeijns et al (2004) and Kratz et al (2011) did not screen for depression – their results could therefore have been due to depression in their populations rather than pain; Karoly and Ruehlman (2006) limited participation to those reporting high levels of psychological distress – therefore they may not have been a true representation of a community pain sample, and in Ciccone et al (2010) psychiatric 'diagnoses' were based on screening instruments and not on structured clinical interviews, therefore diagnosis may not have been accurate.

Therefore, while pain-related catastrophising is seen within the community, the participants in the above studies must be coping with this in ways that are not seen in those who seek medical care. It is not clear whether the participants then go onto seek support as the studies are cross-sectional rather than longitudinal but there are research opportunities in establishing what mediates the process of seeking medical support.

2.3.3 Summary and reflections

There appear to be consistent and robust associations between pain catastrophising and an array of clinical pain-related outcomes, including measures of clinical pain severity, pain-related activity interference, disability, depression (and other negative mood indices) and alterations in social support networks. It has been linked to increased behavioural expression of pain, as well as a variety of illness behaviours and Quartana et al (2009), in their critical review note that the magnitude of these relationships is variable, with catastrophising accounting for minimal variance in pain severity in some studies but not others. As indicated in this section, pain catastrophising has been linked to exaggerated negative mood and depression and appears to be a rather potent predictor of a variety of pain related outcomes. However, the role of pain catastrophising in CMSKP is very complex and not self-evident and the type of setting in which research takes place is important (Severeijns et al. 2005) as seen in the discussions regarding laboratory versus clinical research above.

In the introduction to this section, a number of catastrophising models were highlighted. The literature review has illustrated that there are reasons to believe that catastrophising is part of an appraisal system (Severeijns et al. 2001; Somers et al. 2009), supports the Schema-activation model (van Wilgen et al. 2008; Somers et al. 2009), supports the attention model (Crombez et al. 2002a; Giesecke et al. 2003; Campbell et al. 2010), may reflect coping (Karoly and Ruehlman 2006; Borsbo et al. 2010; Ong et al. 2010) and especially communal coping (Cano 2004; Kratz et al. 2011). There appears to be substantial overlap between the models and whether these models of catastrophising work interactively to predict behaviour has not been examined in a systematic fashion.

The research on catastrophising in CMSKP has limitations which need to be considered, lack of comparison to a control group meant that impact of catastrophising in CMSKP patients could not be fully explored as healthy controls may well have catastrophic thoughts but in the absence of pain, it has no impact (Quartana et al. 2010). Studies were mainly cross sectional and so cause and effect relationships could not be made (Keefe et al. 2000; Crombez et al. 2004; Borsbo et al. 2009; Borsbo et al. 2010; Ciccone et al. 2010; Day and Thorn 2010; Thompson et al. 2010; Buenaver et al. 2012). Lack of description about the physical tests that were used in some of the studies meant generalisations to practice are limited (Bergbom et al. 2011). Some studies lacked power due to small sample sizes (Campbell et al. 2010) and low response rates (Borsbo et al. 2009; Borsbo et al. 2010; Thompson et al. 2010) and other studies suffered from selection biases (Giesecke et al. 2003; Karoly and Ruehlman 2006). Self-report measures were used in many and could have led to response bias (Borsbo et al. 2009; Borsbo et al. 2010; Day and Thorn 2010; Bergbom et al. 2011). That said, the research generally concurred that pain-related catastrophising was a problem and had a negative impact on pain, disability and mood.

2.4 CHAPTER SUMMARY

It is clear from this chapter that attention, fear and catastrophising are major psychological factors influencing chronicity. Some work has been undertaken on classifying groups of patients who are thought to respond in similar ways to these cognitive factors but the clinical applications of these has not been realised. The quality of life for patients, with psychological barriers to recovery, is large and impacts greatly on them, their family and health and social care. Pain intensity and duration have a minor role to play in quality of life in the largely cross-sectional research that has been undertaken.

There are inherent weaknesses in some of the ways attention, fear and catastrophising are measured and there remains controversy in research findings as to how these concepts impact on individuals. Elevated levels of psychological factors appear to be useful indicators of an increased risk for unfavourable outcomes and need to be given more attention within the research arena and in clinical practice. Elevated levels of these differ in significant areas, suggesting the need for flexible ways of managing and researching psychological factors to systematically assess the behavioural impact of them. Early identification of key differences in those that have a successful treatment outcome and those that do not could help clinicians make decisions about which patients should receive 'normally' effective treatments and those that require enhanced management. In order to advance the field of research in attention, fear and catastrophising, further research is needed. One of the barriers that appear to reduce our understanding of these factors is the use of current assessment methods which are global, non-specific and based on self-report. These tell us little about the processes involved and lack context; there is a need to characterise the determinants and consequences of these factors in particular contexts. Self-report measures may lack specificity, individual behaviour may be unconscious and these measures do not tap into this and there may be report bias in recalling of events or providing answers that the individual thinks is appropriate rather than what is accurate.

It is clear that behavioural research has shed considerable light on the role of attention, fear and catastrophising but there is still a lack of understanding about these factors. Neuro-imaging may provide some insight into how the brain responds to pain-related attention, fear and catastrophising and whether changes occur in how the brain functions in response to these in patients with CMSKP. The next chapter will investigate the role of neuro-imaging research in further understanding these factors.

CHAPTER 3: A NEUROIMAGING REVIEW OF PAIN-RELATED PSYCHOLOGICAL FACTORS IN CMSKP

Neuroimaging evidence primarily examining studies that have included CMSKP and CLBP patients is reviewed. There is not a large body of neuroimaging research on the psychological influences outlined in the Chapter 2. However, there is research available examining the impact that persistent pain has on broader cognitive and psychological functioning in CMSKP and that which can be extrapolated from other CNMP groups. This provides important information about how pain can alter general brain functioning and also, can change brain structure. Therefore this chapter will present the research that has been undertaken in CMSKP patients examining cognitive and psychological changes that occur with persistent pain. Some discussion around healthy volunteer studies and other pain conditions will be entered into where pertinent to the sub-headings and for completeness.

Patients with CNMP are known to have prefrontal cortical and thalamic loss (Apkarian et al. 2004b) and show widespread disruption which impacts on overall brain function (Acerra and Moseley 2005; Baliki et al. 2008). Therefore to maximise the potential of using fMRI to further understand attention, fear and catastrophising, there is a need to develop methods to allow for the investigation of clinical, persistent pain in the scanning environment. The previous chapter reviewed the behavioural research on these factors and illustrated that while they do impact on the pain experience, there are still many gaps in our understanding of these factors, how best to research them and how they affect clinical outcomes. Analysing neuro-imaging studies to assess what has been undertaken in the CNMP field pertinent to patients with CLBP and CMSKP motivates the research focus taken in the studies discussed later.

It has long been proposed that a 'neural matrix' for pain exists which described the dynamic role of networks within the brain responsible for the experience of it. There is increasing evidence that neural structure as well as function can alter over short periods of time; as little as 17 days (Gauthier et al. 2008); highlighting how dynamic brain function can be. The 'neural matrix' model suggests that although the processing of pain by the brain is genetically specified, processing is modified by experience. The 'pain network' theory has been criticised recently but it appears that factors increasing the sensory flow of pain signals may alter the excitability of central thresholds over time resulting in sensitivity to pain. Therefore, psychological factors thought to amplify pain signals, such as attention, fear and catastrophising may lead to changes in central neural mechanisms leading to central sensitisation and a chronic hyperalgesic state (Melzack 1990, 1993, 1999). Previous studies have shown that people who are fearful and catastrophise attach more threat or harm to non-painful stimuli (Peters et al. 2000; Crombez et al. 2002a) and the neural correlates of this are not clear.

Neuro-imaging has improved our understanding of how cognition, emotion and context influence pain perception in experimental pain (Apkarian et al. 2004b; Tracey and Mantyh 2007; Baliki et al. 2008) and has important potential diagnostic and therapeutic applications for pain. However, it has not been exploited, especially within the CMSKP population, as this area of research is still in its infancy and there are methodological and ethical challenges that need to be addressed (Wartolowska and Tracey 2009).

The majority of fMRI research to date has focused on acute, experimentally induced pain in healthy volunteers, where the meaning of pain is different from CMSKP (Crombez et al. 1999a; Buck and Morley 2006) and many of the pain-related changes in brain structure and

functioning (Apkarian et al. 2004b; Baliki et al. 2008) seen in chronic pain patients appear not to be present in healthy volunteers. This raises the question as to how well findings can be generalised from data obtained in experimentally induced pain research to explain clinical pain (Richardson et al. 2010). The following sections will consider the structural and functional brain changes that occur as a result of having CNMP and the impact these have on psychological functioning, leading to a section examining neuroimaging studies of psychological functioning that may impact on chronicity.

3.1 STRUCTURAL CHANGES AND PAIN

Until recently, it was not clear how persistent pain affected the brain and how it functions with much of research having been in animal models (Woolf and Salter 2000; Hunt and Mantyh 2001; Julius and Basbaum 2001). These have shown cerebral reorganisation of nociceptive coding by peripheral afferents and spinal cord neurons providing evidence for apoptosis of spinal cord cells (Whiteside and Munglani 2001; Moore et al. 2002; de Novellis et al. 2004); changes commonly seen in both inflammatory and neuropathic pain. Despite individuals experiencing reduction in quality of life and heightened anxiety and depression (Asmundson et al. 2005; Ang et al. 2010; Bergbom et al. 2011), it was thought that cortical responses to spinal changes were passive and once the pain abated then the cerebral cortex reverts to a normal state (Price 2000; Mendell and Sahenk 2003). It is now clear that these changes are not passive, they impact on the structure and function of the brain and are accompanied by abnormal brain chemistry (Grachev et al. 2000) illustrative of neuronal loss and dysfunction and reduced cognitive abilities (Apkarian et al. 2004a).

In comparing brain metabolites in healthy controls and CLBP patients, N-acetyl-aspartate was shown to be diminished in multiple prefrontal regions in patients (Grachev et al.

2000) suggesting that brain atrophy may be caused by decreased neural density in these regions. This was directly tested and it was found that decreased grey matter was apparent in dorsolateral prefrontal cortex and thalamus and these were related to the duration and severity of CLBP (Apkarian et al. 2004b). Other studies have followed suit in a number of different clinical pain conditions including complex regional pain syndrome (Geha et al. 2008). This condition falls outside the remit of the thesis but is included because research showed similar regions, as the conditions discussed below, with grey and white matter atrophy in medial prefrontal cortex, ventral striatum portion of basal ganglia, insula, and ACC (Geha et al. 2008) and this reorganisation seems to re-normalise with therapy (Maihofner et al. 2004).

A number of studies have been performed examining cortical structural changes accompanying CMSKP (Apkarian et al. 2004b; Kuchinad et al. 2007; Gerstner et al. 2011) and while different regions appear to be implicated in different chronic pain states, there appears to be overlap in the cingulate cortex, insula, and dorsolateral prefrontal cortex. These studies have illustrated a link between duration of the condition and amount of cortical loss and have focused structural loss in the following regions:

- CLBP - bilateral reductions in dorsolateral pre-frontal cortices and right thalamus (Apkarian et al. 2004b), brainstem and the somatosensory cortex (Schmidt-Wilcke et al. 2006a). Correlation analysis of pain unpleasantness and the intensity of pain on the day of scanning revealed a strong negative correlation in these areas. Additionally, a significant increase in gray matter bilaterally in the basal ganglia and the left thalamus was found.
- Fibromyalgia - observed loss in cingulate, insular and medial frontal cortices, and parahippocampal gyri (Kuchinad et al. 2007); in right superior temporal gyrus, the

left posterior thalamus (Hsu et al. 2009) and postcentral gyri, amygdalae, hippocampi, superior frontal gyri, and anterior cingulate gyri (Lutz et al. 2008). However, Hsu et al (Hsu et al. 2009) found that when affective disorders were controlled for, such as trait anxiety, there was no difference between those with fibromyalgia who did not have affective disorders and healthy controls.

- Temporormandibular disorders with decreases in grey matter volume occurring in the left anterior cingulate and inferior frontal gyri, the right posterior cingulate gyrus and anterior insular cortex, and bilaterally in the superior temporal gyrus and in regional white matter volume in the medial prefrontal cortex bilaterally (Gerstner et al. 2011).

In patients with fibromyalgia, grey matter loss occurred mainly in regions related to stress [parahippocampal gyrus (Herman et al. 2005)] and in all groups in pain processing regions [cingulate, insular, and prefrontal cortices (Apkarian et al. 2005)], which might reflect their long-term experience of these symptoms. Given that cingulate and prefrontal cortices are particularly implicated in pain modulation (Apkarian et al. 2005) structural changes in these regions may be implicated in chronicity and deficits in regions such as the parahippocampal and frontal cortices also may account for cognitive deficits. However, in irritable bowel disease, Seminowicz et al (2010) found that the disease was associated with decreased gray matter density (GMD) in widespread areas of the brain, including medial prefrontal and ventrolateral prefrontal cortex, posterior parietal cortex, ventral striatum, and thalamus. Compared with controls, they observed increased GMD in patients with IBS in the pregenual anterior cingulate cortex and the orbitofrontal cortex, as well as trends in the posterior insula/secondary somatosensory cortex, (para)hippocampus, and left dorsolateral prefrontal cortex. In accounting for anxiety and depression, they found that

several of the regions involved in affective processing no longer differed between patients with IBS and controls, whereas the differences in prefrontal and posterior parietal cortices remained. They authors concluded that changes in density of grey matter among regions involved in cognitive/evaluative functions are specifically observed in patients with IBS, whereas changes in other areas of the brain can be explained by levels of anxiety and depression. Differences in findings between patients with musculoskeletal pain and irritable bowel disease may reflect differences in somatic and visceral pain.

The impact of this cortical loss can be seen in a couple of studies (Buckalew et al. 2008; Luerding et al. 2008). Patients with fibromyalgia were seen to be impaired in a non-verbal working memory task and a non-verbal long-term memory task in the free recall condition (Luerding et al. 2008). In CLBP, older adults were impaired on attention and mental flexibility tasks (Buckalew et al. 2008). Therefore, it appears that in addition to chronic pain, patients suffer from neurocognitive deficits that correlate with local brain morphology. There appears to be accumulating evidence now indicating that a number of CNMP conditions are characterised by grey and white matter reductions, which can affect cognitive functioning; the specific regions involved differ among syndromes and this may explain differences in symptoms. Reasons for the cortical thinning have been postulated; genetic (Zubieta et al. 2003), abnormal brain chemistry (Grachev et al. 2000) and/or experiential (Perkins and Kehlet 2000) factors. Others include cell atrophy or synaptic loss and decreases in cell size or blood volume (Draganski and May 2008; May 2008).

Opioid use may also be implicated in loss of cortical density (Upadhyay et al. 2010; Younger et al. 2011) and have been shown to cause brain atrophy in non-pain patients (Upadhyay et al. 2010) and patient receiving experimental morphine (Younger et al. 2011);

bilateral volumetric loss in the amygdala, decreased anisotropy in axonal pathways specific to the amygdala, and decreases in functional connectivity in regions that included the anterior insula, nucleus accumbens and amygdala subdivisions (Upadhyay et al. 2010). In Apkarian et al (2004b), the authors did control for drug consumption which showed no relationship to global or local measures of grey matter. However, drug use was converted into a unitary scale which may have obscured the effect of opioids. In other studies it appears that they were not controlled for (Schmidt-Wilcke et al. 2006a; Kuchinad et al. 2007; Schmidt-Wilcke et al. 2007; Hsu et al. 2009; Gerstner et al. 2011).

Many of these studies are cross-sectional and the causality cannot be confirmed, just the relationship, there is evidence that if chronic pain resolves, cortical atrophy reverses (Rodriguez-Raecke et al. 2009; Gwilym et al. 2010; Seminowicz et al. 2011). Therefore, it is likely that the pain has caused the atrophy rather than the atrophy leading to the pain.

There also may be genetic and other predisposing factors that lead to brain atrophy in patients with chronic pain. Apkarian et al (2004b) found that only 18% of whole-brain gray matter variance could be explained by pain duration and proposed genetic and experiential predispositions contributed to the observed atrophy. However, the relationship between pain characteristics and dorsolateral prefrontal cortex atrophy was much stronger.

Reason for whole-brain atrophy may be general disuse in that patients can be physically inactive due to pain or accompanying cognitive sequalea of having pain. However, Rodriguez-Raecke et al (2009) found no changes in motor areas between patients and controls in their study. They proposed that while chronic pain hinders physical exercise, research investigating pain and brain morphometry report changes in pain-transmitting

regions but not in motor areas. Apkarian and colleagues observed that the regional pattern of atrophy was distinct from that seen in chronic depression or anxiety and showed a minimal relationship with anxiety and depression traits (Apkarian et al. 2004b).

Atrophy in areas of the brain involved in pain perception may dictate the properties of the pain state and as this progresses, the pain condition may become more irreversible and less responsive to therapy.

3.2 FUNCTIONAL CHANGES

Living with CNMP can lead to maladaptive thinking and behaviour and is thought to be associated with physiological and psychological modifications, yet there was, until recently, a lack of knowledge regarding the brain elements involved in such conditions (Baliki et al. 2006). Findings of studies reported here will be largely discussed in terms of the impact on those with CNMP rather than entering into lengthy discussions about the implications for acute pain. While the latter is interesting, it is not pertinent to the aims of the dissertation per se. However, a brief overview will be provided in order to illustrate differences between the two types of pain in later discussions.

The insula and the ACC are the two cortical structures most consistently activated in acute pain studies with the thalamus and basal ganglion being the common sub-cortical regions (Apkarian et al. 2005). Additionally, a number of other regions have been observed responding to acute pain and these include SI, SII, lateral prefrontal and posterior parietal cortices and the cerebellum (Apkarian 2008). Within the brainstem, periaqueductal grey, ventral tegmental area, rostral ventromedial medulla and parabrachial nuclei have been found to be activated for the anticipation and perception of pain (Dunckley et al. 2005);

regions corresponding to the descending modulatory pathways involved in controlling nociceptive information transmission from the spinal cord (Apkarian 2008).

The ACC and insula are involved with the affective dimensions of pain; the ACC more consistently than the insula (Rainville et al. 1997) and the somatosensory regions have been thought to better reflect sensory dimensions, such as intensity and location (Apkarian 2008). However, Oshiro et al (2007) challenge this as other regions outside the somatosensory cortex are involved in the evaluation of spatial locations of noxious stimuli. Similarly, the ACC and insula are not just involved with affective dimensions of pain and have been shown to be involved with autonomic control and representation (Brooks et al. 2005; Critchley 2005).

Apkarian et al (2005) proposed an increased activation in the prefrontal cortical regions in CNMP and suggests that this pain distorts cognitive and emotional perception and processing of everyday experiences which lead to anxiety and depression with a reduced quality of life (Apkarian 2008). CNMP is characterised by the experience of spontaneous pain (pain perceived in the absence of physical stimuli) and exaggerated responses to physical stimuli such as hyperalgesia and allodynia (Apkarian 2008). Studies have compared spontaneous pain and acute painful stimuli and illustrated that these pains are processed and modulated differently (see Section 3.2.1). In examining CLBP (Baliki et al. 2006), osteoarthritis (Kulkarni et al. 2007; Schweinhardt et al. 2008) and postherpetic neuralgia (Geha et al. 2007) it has been observed that distinct brain regions are involved in spontaneous pain.

In CLBP (Baliki et al. 2006) and in osteoarthritis (Kulkarni et al. 2007) the medial prefrontal cortex represented the spontaneous pain (further details are provided in 3.2.1) and where it best represented the integration of pain and depression the amygdala and basal ganglia were also implicated (Schweinhardt et al. 2008). In post herpetic neuralgia, the amygdala and the ventral striatum portion of the basal ganglion reflected best spontaneous pain. Post herpetic neuralgia is not pertinent to the aims of the thesis as such but is discussed here to illustrate that, although the regions are different in these two groups, they are closely connected and have been implicated in hedonics, addiction and emotional learning and memory (Bechara et al. 2000; Volkow and Fowler 2000; Kringelbach 2005). This suggests that in CNMP, the emotional and hedonic regions are better related to spontaneous pain than brain regions more commonly seen in acute nociceptive pain.

3.2.1 Modulation of acute and chronic pain

Several studies have examined different responses to experimental pain between CLBP patients and healthy controls using fMRI (Gracely et al. 2002; Giesecke et al. 2004; Baliki et al. 2006; Baliki et al. 2010). Gracely et al (2002) compared pain pressure sensitivity in patients with fibromyalgia and healthy controls and Giesecke et al (2004), using the same experimental pain stimulus compared patients with CLBP, fibromyalgia patients and healthy controls. Baliki and colleagues initially investigated the brain regions involved in spontaneous CLBP (high sustained pain and increasing pain) compared with thermal pain in healthy subjects (Baliki et al. 2006). Latterly, they studied the temporal characteristics of the motivation/valuation circuit during acute pain between healthy volunteers and CLBP patients, the effect of acute noxious thermal stimuli on chronic pain, and modulation of pleasantness/unpleasantness by this interaction (Baliki et al. 2010).

Gracely et al (2002) and Giesecke et al (2004) found that the patients with chronic pain differed at equal levels of pressure to the healthy volunteers in that they experienced greater pain levels. Gracely et al (2002) observed activation in the contralateral primary and secondary sensory cortices in both groups, activations were more pronounced in patients and the activation in the secondary somatosensory cortex in patients was also observed on the ipsilateral side. Both groups also showed a common significant decrease in signal in the ipsilateral primary somatosensory cortex. Giesecke et al (2004) found that while contralateral SII was seen in all groups, regions that were activated in patients and not controls included ipsilateral SII and cerebellum, and in the contralateral SI and inferior parietal lobule. When stimuli that elicited equally painful responses were applied (requiring significantly lower pressure in both patient groups as compared with the control group), neuronal activations were similar among all groups studied (contralateral SI and SII, ipsilateral SII, cerebellum, and the contralateral inferior parietal lobule, contralateral ACC) although the magnitude of these was greater in the patient groups. In Giesecke et al (2004) in all three groups, the contralateral insula was activated but the locality differed in patients with fibromyalgia compared with the other two groups, the anterior insular; activation is involved in affective pain responses and may be associated with their higher level of distress in fibromyalgia patients. These studies illustrated that much lower levels of stimulation led to higher pain reports in the patient groups but not controls and yet both activated similar pain regions illustrating central augmentation of pain in those with existing and persistent pain.

Baliki et al (2006) found that sustained high CLBP resulted in increased activity in the medial prefrontal cortex (including rostral anterior cingulate) which was strongly related to

CLBP intensity. Increasing pain appeared to transiently activate brain regions commonly observed in acute pain; best represented by the insula and reflected CLBP duration. When spontaneous CLBP was contrasted to thermal stimulation, the medial prefrontal cortex correlated only to the intensity of spontaneous pain and the insula only to the pain intensity for the thermal stimulation.

Baliki et al (2010) compared brain activations in response to acute noxious thermal stimuli in controls and CBP patients. While the groups were similar in terms of pain perception and related cortical activation, the nucleus accumbens activity differentiated the groups very accurately and revealed tonic and phasic responses with distinct properties. Positive phasic accumbens activations at stimulus onset and offset tracked stimulus salience and, in normal subjects, predicted reward (pain relief) magnitude at stimulus offset. In CBP, accumbens activity correlated with different cortical circuitry from that of normals and phasic activity at stimulus offset was negative in polarity, suggesting that the acute pain relieves the ongoing back pain. The relieving effect was confirmed in a separate psychophysical study in CBP. The authors concluded that in contrast to somatosensory pathways, which reflect sensory properties of acute noxious stimuli, accumbens activity in humans encodes its predicted value and anticipates its analgesic potential on chronic pain.

The nucleus acumbens appears to have a role in both reward- and pain-predictive cues (Harris et al. 2007; Becerra and Borsook 2008; Delgado et al. 2008; Platt and Huettel 2008). The uncertaintly regarding the motivational or hedonic valence of nucleus acumben signals generated by transient noxious stimuli is confounded by the issues around onset and offset of the stimuli. The onset and maintenance of a noxious stimulus is aversive and acts as a punisher, but the offset is potentially rewarding and so responses to transient

noxious stimuli can comprise of both aversive and appetitive components. However, neither the potential role of phasic and tonic NAc activity in the evaluation and prediction of pain and its relief, nor possible changes in activity in the presence of chronic pain, have been explicitly addressed and hence the reason Baliki et al (2010) performed the study.

The above are interesting studies illustrating, in part, that acute and chronic pain appears not to be processed in the same way and patients with CNMP may not process experimental pain as healthy volunteers do. These findings are consistent with the occurrence of augmented central pain processing in patients with CNMP.

A meta-analysis of fMRI studies illustrates that the frequency of brain areas activated in normal subjects during experimental pain is ACC, 81%; SI, 79%; SII, 81%; insula, 100%, thalamus 81% and prefrontal cortex, 70% (Apkarian et al. 2005). However, in patients with clinical pain conditions, the frequency of brain areas active are ACC, 45%; SI, 28%; SII, 20%; insula, 58%; thalamus, 59% and prefrontal cortex (Apkarian et al. 2005). This was a large and convincing meta-analysis which included 68 studies of experimental pain in normal subjects, 30 in clinical pain conditions and 30 using neuroelectrical methods. Another 24 articles were identified where brain neurochemistry of pain was examined. Therefore, it appears that sensory/discriminatory structures seem to activate less frequently in patients than controls but the opposite is true for affective/emotional regions (Apkarian et al. 2005). The difference between CNMP patients and controls appears to relate to the variation in patterns of activation, rather than involving different sets of brain regions.

3.2.2 Learning, memory and executive functioning

Executive control is a global term for cognitive processes that involve the maintenance of long-term goals, planning, the ability to ignore distracting information, and to suppress

inappropriate responses. It is an important part of the working memory system and is responsible for maintaining relevant items in the short-term memory store, removing items no longer needed, and ignoring items that are not relevant to the task at hand (Glass et al. 2011).

Concerns over how fibromyalgia influences brain function led to Glass et al (2011) undertaking a study on working memory and executive function in patients age matched to healthy controls. They found no difference in behavioural responses, time or accuracy, between groups but revealed that patients with fibromyalgia had substantial differences in the neuroimaging findings compared with controls. Patients with fibromyalgia had lower activation in the right premotor cortex, supplementary motor area, midcingulate cortex, putamen and after controlling for anxiety but not depression, right insular cortex and right inferior frontal gyrus. Also present was hyper-activation seen in the right inferior temporal gyrus/fusiform gyrus. Despite no differences in reaction time and accuracy, fibromyalgia patients showed less brain activation in cortical structures in the inhibition network, specifically those within the selection/motor preparation areas, and the attention network with increased activations in brain areas not normally part of the inhibition network. Therefore, it appears that response inhibition and pain perception may rely on partially overlapping networks and resources taken up by experiencing persistent pain may not be available for executive functioning tasks such as response inhibition and thus compensatory cortical plasticity is required for task performance.

The medial frontal wall, which includes the supplementary motor area, the pre-supplementary motor area and ACC, the premotor cortex, right ventrolateral cortex (especially the inferior frontal cortex) and subcortical structures such as the caudate and

sub-thalamic nucleus are most commonly associated with response inhibition (Corbetta et al. 2008; Nakata et al. 2008; Duann et al. 2009). However, many of these regions involved in this inhibition network, have similar and distinct roles in other networks which add to the difficulties in making sense of findings. Glass et al (2011) cites the following as examples, the ACC and insula are both parts of the pain network, the salience network, and a control network (Dosenbach et al. 2006); the right anterior insula and inferior frontal gyrus are part of the ventral attention system; the right frontal eye field (in premotor cortex) and the inferior parietal lobule are involved in the dorsal attention system and the middle frontal gyrus, at resting, appears to be a link between the two networks (Corbetta et al. 2008). The role of the medial frontal wall in both inhibition and pain perception has previously been established (Glass et al. 2011) therefore it is unsurprising that anomalies were seen in patients with fibromyalgia in this region.

One of the areas (not confirmed by the authors so it is unclear which area this is) showing less activation in the fibromyalgia group projected to the posterior ACC, mid cingulate cortex and supplementary motor area. These areas are involved in planning of motor action (supplementary motor area), action control and response selection (pre-supplementary motor cortex), task-relevant parameters such as attention, control, and error detection (ACC) and pain perception (ACC). Therefore, the decreased response associated with inhibition may have resulted from the ongoing neural activity associated with persistent pain using up resources. Also seen was a decrease in BOLD response in the regions involved in the dorsal attention network (premotor cortex, projecting to the right frontal eye field, right inferior parietal cortex) and in the inferior frontal gyrus and insula, part of the ventral attention system, illustrating poor responses in areas responsible for attention.

The inferior temporal gyrus and fusiform gyrus are part of the visual association cortex and both involved in object recognition and activation, and in the latter, has been reported with the task used in Glass et al (2011), Go-No-Go task (Simmonds et al. 2008). In a study of mild cognitive impairment, where there may be changes in regional cerebral blood flow, patients have been shown to have increased activation in the fusiform gyrus within different working memory paradigms which Yetkin et al (2006) interpreted as employment of additional neural resources to improve task performance. Therefore, recruitment by the fibromyalgia patients, of the inferior temporal gyrus/fusiform gyrus may be a compensation mechanism for decreased neural resources in the medial frontal wall and premotor areas. This study suggests that complex neural processes combine to compensate for the presence of pain and possibly because of the cortical loss discussed previously.

Part of the survival value of pain is its intimate association with learning (Apkarian et al. 2009) and this learning can develop a pain memory that can last throughout an individual's life. Although simplistic, Pavlovian paradigms of learning and memory, especially in fear conditioning, support the contention that the more painful the stimulus, the fewer trials it takes to establish an aversive, negative and emotional association to the stimulus (conditioning) (Schafe et al. 2001). Extinguishing aversive associations of fearful events is important in normal living and if this cannot be achieved, leads to reduction in quality of life as seen in those with phobias and panic disorders. However, extinction is difficult in people with CNMP as when re-exposed to the condition that caused fear, the chances are the person is still in pain and this becomes a reinforcement of the aversive association (Apkarian et al. 2009). Disentangling these associations is difficult, especially, as previously discussed in relation to fear of movement, they may not even be conscious but they may account for the suffering experienced by those with persistent pain.

Recently, interest has been directed to the issue of reward and punishment especially in relation to goal pursuits (Becerra and Borsook 2008) and may explain the nucleus accumbens role discussed in Section 3.2.1 (Baliki et al. 2010). If CNMP is seen as the presence of a stimulus that is difficult to extinguish in relation to its link with random events, then the brain networks underlying reward and punishment-induced learning are engaged and would interfere with or decrease the ability of learning in terms of other events especially if mediated through emotional cues (Apkarian et al. 2009).

3.2.3 Concentration

It has been shown in a number of fMRI studies that the ability to concentrate on a task is reduced in those with CNMP (Buffington et al. 2005). Sustained attention can be problematic; defined as the ability to maintain a consistent response over an extended time during continuous and repetitive activity (Sohlberg and Mateer 1987). It appears to be vulnerable to pain which can interrupt cognitive processing and capture attention (Eccleston et al. 1997; Eccleston and Crombez 1999). The ACC appears to be important for sustained attention and may modulate an individual's ability to attend to something over time and is also involved in pain perception (Buffington et al. 2005), responding directly to noxious stimuli and becoming more active the more intense and longer the duration of pain (Rainville et al. 1997; Casey 1999).

Buffington et al (2005) used fMRI to examine the differences in activations in ACC between healthy participants and those with CMSKP (using Osteoarthritis (OA) of the knee as a model) while completing a sustained attention task with and without exposure to an acute painful stimulus. In all participants, two distinct spatial patterns within the ACC

were isolated; one that reflected the disrupted ACC activity when a painful stimulus was applied and the other reflected the emergent ACC activity when a painful stimulus was applied. A broadly distributed cluster of voxels in the ACC were seen in the healthy group modulated by painful stimulation compared to the CMSKP group where a discrete focal region of the ACC was modulated by pain. This demonstrates that ACC activity is modulated differently during tasks of sustained attention and pain with chronic pain resulting in significantly different ACC activation patterns. Although imaging revealed differences, performance on the sustained activity task between groups did not. The results suggest that ACC activity is modulated differently during tasks of sustained attention and pain, both acute and persistent pain impact on it, and that acute and persistent pain result in different ACC activations.

A study in patients with post-herpetic neuralgia illustrates that brain activity during a visual attentional task is modulated by the intensity of ongoing pain at the time of performing the task (Geha et al. 2007). This is not one of the conditions under consideration in this thesis but it does provide some interesting perspectives on the adjustments the brain in persistent pain undergoes to compensate and hence its inclusion here. The results of this study illustrate that even in a simple, non-emotional attentional activity, the medial prefrontal cortex shows increased activation and the motor and posterior parietal cortical activity is decreased in proportion to the intensity of the experienced pain. What actually controls this compensation is unclear but there are important implications. Research using any task will be distorted by the ongoing presence of pain and studies that compare healthy volunteers with CNMP patients may obtain results because of this distortion and not because of differences in neuronal processing that are task related. This may explain the inconsistent results seen in studies that use acute

pain stimuli to understand distinctions in pain processing between healthy controls and various clinical pain conditions (Apkarian et al. 2005). Simple non-painful tasks can study and demonstrate differences between CNMP patients and healthy controls but using subtractions to form contrast maps may be misleading (Apkarian et al. 2009). Future research needs to carefully consider methods to address these issues.

3.2.4 Default Mode Network (DMN)

A 'resting' brain may be defined as one where the subject is awake but not engaged in any demanding sensory, motor, or intellectual activity (Apkarian et al. 2009). It is an important state for neuroimaging studies because it defines the baseline or control against which tasks are often, by default, measured. The medial prefrontal cortex, precuneus, PCC and hippocampus (Rameson et al. 2010) are commonly observed in resting state networks and also are sensitive to cognitive states in self-referential tasks (Kong et al. 2010). Resting state networks are proposed to be involved in attending to environmental stimuli, both internally and externally generated (Raichle et al. 2001), in reviewing past knowledge to prepare for future actions (Binder et al. 1999), in episodic memory processing (Greicius et al. 2004) and has been proposed to be the neural correlate of the 'stream of consciousness' and in daydreaming (Greicius and Menon 2004).

In the Default Mode Network, one of these resting state networks, research has illustrated that when undertaking a task, in healthy controls, it should decrease its activity during task performance when compared to the average brain activity at rest (Baliki et al. 2008; Mantini et al. 2009; Kong et al. 2010). Recently, the angular gyrus has also been implicated in the DMN (Qiu et al. 2011). Several studies have provided insight into the DMN either by identifying decreases in brain activity during a task or by studying the

correlation patterns of spontaneous brain activity at rest (Raichle et al. 2001; Greicius et al. 2003; Fox et al. 2005; Fox and Raichle 2007). The fact that these regions are more active at rest than during a task suggests that when resting the brain remains active in an organized manner (Raichle et al. 2001).

In a number of chronic neurological conditions, the DMN has been shown to be disordered (Greicius et al. 2004; Kennedy et al. 2006; Greicius et al. 2007) and recently this has also been shown to be abnormal in CLBP (Baliki et al. 2008) and may be related to the ongoing symptoms of depression, anxiety, sleep disturbances and decision making abnormalities (Apkarian et al. 2004a) seen in this population.

Baliki et al (2008) found, using a non-pain attention task, that CLBP patients exhibited pronounced alterations in the functional connectivity between brain regions implicated in the DMN compared with healthy controls. Given that patients experience unrelenting pain, it is to be expected that they will have altered brain resting states. The DMN is believed to enhance the process of interpreting information, responding to it and even predicting environmental demands (Raichle 2006) but it would seem that in patients with CLBP, the DMN is disrupted leading to these functions being compromised. The study could not shed light on the mechanisms behind the disruption but it may be implicated in the fact that patients with CLBP have cortical atrophy (Apkarian et al. 2004b). In conclusion, the authors offer that 'the brain of a chronic pain patient is not simply a healthy brain processing pain information, but rather is altered by the persistent pain in a manner reminiscent of other neurological conditions associated with cognitive impairments' (pg 1402).

These findings are important in again highlighting the fact that the effects of acute pain on brain dynamics seem opposite and or different to those observed in CNMP. Therefore studying the brain in acute pain may in fact provide the wrong clues when making generalisations as to the impact of CNMP on the brain (Apkarian et al. 2009).

3.3 PSYCHOLOGICAL FUNCTIONING

A number of different approaches have been taken to examine psychological and cognitive changes that occur with CNMP to better understand how people with CMSKP differ in their psychological profiles; attention, fear, catastrophising and depression will be discussed as studies were found in CMSKP populations.

3.3.1 Pain-related attention

Studies have shown interactions between brain networks supporting pain and cognition (Craig 2002; Seminowicz and Davis 2007b; Luerding et al. 2008); pain can capture attention to adjust behaviour (Crombez et al. 1997; Eccleston and Crombez 1999; Legrain et al. 2009) mediated by areas that are implicated in pain salience detection such as the mid ACC and insula (Downar et al. 2003; Albanese et al. 2007) (bottom-up process). A top-down process has also been observed during distraction with a noxious stimulus when performing a goal-directed task and involves activation of the mid ACC and is driven by prefrontal and parietal cortical areas to engage attention (Corbetta and Shulman 2002). Effective connectivity between these regions is therefore necessary for goal-directed task performance (Botvinick et al. 2001). Attentional load can also modulate pain with top-down processes that involve the anti-nociceptive system (Wiech et al. 2008).

Hypervigilance to CNMP may limit the amount of resources available to perform goal-directed cognitive tasks (Eccleston et al. 1997; Crombez et al. 2004; Crombez et al. 2005) and this may manifest by slower responses during experimentally induced pain (Seminowicz and Davis 2007a) and in chronic pain conditions (Eccleston 1994, 1995). Effective cognitive functioning may be aided through protective mechanisms that filter out emotional interference and this depends on the top-down modulation from the prefrontal cortex to the pregenual ACC, which subsequently modulates amygdala activity (Bishop et al. 2004b; Ochsner et al. 2006; Whalen et al. 2006). Successful cognitive function therefore depends on functional connectivity between the pregenual ACC and the amygdala. As discussed in Chapter 2, the valence of emotionally salient stimuli has been shown to affect task performance in CMSKP.

Wasan et al (2011) used arterial spin labelling and fMRI to determine cortical brain regions that were activated by manoeuvres, including noxious heat stimuli and techniques to increase spontaneous pain, that aggravated CLBP and compared this with the same manoeuvres in healthy controls. The clinically significant worsening of ongoing CLBP was associated with significant regional blood flow increases within brain regions known to activate with experimental pain (somatosensory, prefrontal, and insular cortices) and in other structures observed less frequently in experimental pain studies, such as the superior parietal lobule, SII and supramarginal gyrus. This effect was specific to changes in ongoing CLBP as it was observed during worsening pain, but not observed after thermal pain application, or in matched, pain-free healthy controls.

The regions activated during worsening pain encompass the sensory-discriminative and affective pain processing regions related to pain. Importantly, from the perspective of this

thesis, a number of regions that are involved in attentional aspects of pain had increased blood flow. These included the superior parietal lobules (Corbetta and Shulman 2002; Duncan and Albanese 2003; Villemure and Bushnell 2009; Iannetti and Mouraux 2010), the supramarginal gyrus (Duncan and Albanese 2003), the medial prefrontal (Gusnard et al. 2001; Benuzzi et al. 2008) and insular cortices (Ploghaus et al. 1999; Jackson et al. 2006a; Lamm et al. 2007; Ogino et al. 2007).

In a counting Stroop task, Weissman-Fogel et al (2011) examined patients with temporomandibular disorders matched to healthy controls responding to an attention-demanding Stroop that involved cognitive and emotional interference. The counting Stroop tasks comprised neutral words, incongruent numbers, or emotional words, including temporomandibular disorder-specific words. The patients demonstrated abnormal brain responses; and while not significant, the authors reported that patients also had slower response times, more pronounced task-evoked fMRI responses in brain areas implicated in attention and cognition as well as emotional and salience processes, abnormal DMN activity and reduced connectivity within the prefrontal-cingulate and amygdale-cingulate pairs of brain regions that are normally coupled during cognitive interference and increased connectivity of these pairs during emotional interference. Reduced connectivity appears to be context dependent and these results may illustrate differential normal physiological responses during the task and reflect the importance of the regions for the particular cognitive operations having a primary role in the task.

Compared to controls, patients showed increased task-evoked responses in brain areas implicated in attention (e.g., lateral prefrontal, inferior parietal), emotional processes (e.g., amygdala, pregenual anterior cingulate), motor planning and performance (e.g.,

supplementary and primary motor areas), and activation of the default-mode network (medial prefrontal and posterior cingulate).

The slower emotional word response times may have resulted from the attentional demands of the CNMP leading to attenuated, slower, and/or unsynchronized neural recruitment or patients may be using different brain processes to balance attention, salient and emotional needs. CNMP may compromise the ability to effectively attend to and properly balance cognitive needs more so in a negative emotional context (Eccleston 1995; Eccleston and Crombez 1999; Apkarian et al. 2004a). Patients, and not controls, were affected by the emotional words illustrated also by the activation of brain regions involved in emotional processing; medial prefrontal cortex, pregenual ACC (Devinsky et al. 1995; Whalen et al. 1998; Whalen et al. 2006) and parahippocampus/amygdala (Pessoa 2008). The pregenual ACC and amygdala activity did correlate but it did not show down-regulation of parahippocampal/amygdala activity and this suggests a weak or inefficient functional connectivity between these two regions. Top-down regulation by the dorsolateral prefrontal cortex can also modulate the pregenual ACC-amygdala connectivity and involves fronto-parietal regions to control attention and minimise emotional salience and this may have been evoked by the emotional Stroop. The fact that mid ACC activity was correlated to the dorsolateral prefrontal cortex activity in the patients strengthens the top-down regulation. Therefore, these activities may normally facilitate task performance by inhibiting emotion-related behaviours. Unfortunately, psychological distress levels were not measured in these patients, so the fact that co-morbid depression or anxiety disorders were present and could affect the results cannot be ruled out.

During the emotional interference task, the PCC was also more activated in patients than in controls; this region mediating interactions of emotional and memory-related processes and is activated by emotionally salient stimuli (Maddock 1999; Maddock et al. 2003). It may also be involved with contextualising painful stimuli as the dorsal PCC is involved in visuospatial orientation towards innocuous and noxious somatosensory stimuli (Vogt 2005). Activation of this region may tap into the sensory qualities of the pain, therefore and this is supported by the rostral splenial cortical activation, which has a function in memory access (Maddock 1999) and also showed abnormal activation in the patient group.

The cognitive interference task showed no behavioural differences between patients and controls despite different brain activations in the mid ACC, dorsolateral prefrontal cortex, SII and supplementary motor area. These prefrontal regions play a role in attention and executive cognitive control (Miller and Cohen 2001). In the control group, mid ACC was highly correlated with activity in the dorsolateral prefrontal cortex; the ACC having a role in conflict monitoring (Carter et al. 1999) and the dorsolateral prefrontal cortex having a role in exerting attentional control to reduce conflict (MacDonald et al. 2000; Kerns et al. 2004). Task related activity in the dorsolateral prefrontal cortex correlated with the degree of behavioural interference. The pregenual ACC and amygdala showed nonspecific deactivation during the cognitive interference task. In the patient group, these 2 networks became decoupled and dissociated with the behavioural output and medial prefrontal cortex/pregenual ACC and amygdala were activated, these normally being engaged by emotional stimuli (Devinsky et al. 1995; Bush et al. 2000) and activated during evoked/spontaneous pain (Peyron et al. 2000; Baliki et al. 2006). These results suggest that attentional and emotional networks are engaged by the patient's pain and therefore not able to be recruited for goal-directed cognitive tasks.

The majority of work on attention has been undertaken in healthy controls with early behavioural work showing that directing attention to a painful stimulus can increase its perceived intensity and unpleasantness (Miron et al. 1989). Researchers, using healthy volunteers have also shown that the pain experience can also be reduced if a cognitive task is performed during the pain exposure (Petrovic et al. 2000). In healthy populations, attentional modulation of pain has been shown in brain regions such as the thalamus, SI, ACC and insula (Petrovic et al. 2000; Longe et al. 2001; Bantick et al. 2002; Brooks et al. 2002; Dunckley et al. 2005; Coen et al. 2008). Increased SI activity is commonly seen in response to painful stimulus in these attention studies (Bushnell et al. 1999; Peyron et al. 1999; Seminowicz et al. 2004; Dunckley et al. 2005) as well as heightened anterior insula cortex activation (Peyron et al. 1999; Dunckley et al. 2005) and an inverse correlation between mid ACC and pain intensity ratings (Dunckley et al. 2005).

Distraction studies in healthy volunteers complement the above findings. Reduction in activity during a distraction task during noxious stimulation has shown activity reduction in ACC (Frankenstein et al. 2001); in right ACC and right prefrontal cortex (Coen et al. 2008); in SI, SII-insula (Petrovic et al. 2000; Qiu et al. 2004), cingulate cortex and medial temporal area (Qiu et al. 2004) and in SII, insula and thalamus, but with simultaneous increased activity in parts of cingulate cortex and orbitofrontal cortex (Valet et al. 2004). While these were admittedly not all fMRI studies they are included to illustrate the consensus on the importance of these regions in attention to acute, experimental pain. The reduction of experimental pain via distraction has also been undertaken with a Stroop task and was associated with reduced activation in the insula, thalamus and mid-cingulate region while the perigenual ACC and orbitofrontal cortex showed increased activation

(Bantick et al. 2002), suggesting that these regions are involved in the modulatory effects of attention. Another region that has been shown to increase activation in distraction tasks is the periaqueductal grey illustrating that top-down modulation contributes to the pain reducing effects of distraction (Tracey et al. 2002).

These studies suggest that when healthy volunteers attend a painful stimulus there is increased activity in the 'pain neuromatrix' (e.g., in the anterior insula and SI) whereas distraction reduces pain-related brain activity (e.g., in SI, SII, thalamus, insula, perigenual ACC). What is not clear is whether this occurs as a linear function of the degree of attention and distraction. Distraction also activates the orbitofrontal cortex, perigenual ACC and periaqueductal grey suggesting that these are involved in modulating attentional effects in the context of pain, although it is unlikely to be specific to pain. Added to the complexity is the fact that emotional states can influence pain perception and enhance nociceptive activity in the limbic regions such as the ACC and insula (Phillips et al. 2003). The ACC, accompanying SI, periaqueductal grey, insula, prefrontal cortex and cerebellum, are also activated in anticipation or expectation of pain in the absence of a physical stimulus (Porro et al. 2002; Villemure and Bushnell 2002).

More research is needed to clarify the mechanisms underlying this complex situation, especially in relation to CNMP where research is sparse. As already discussed, patient with CNMP become preoccupied with their pain and pain-related attention is problematic in this group of patients from a behavioural viewpoint with some studies suggesting that persistent pain may worsen in response to distraction attempts (Keefe and Williams 1990; Goubert et al. 2004a).

3.3.2 Fear

As previously discussed, in Section 2.2, numerous studies have supported the avoidance component of the FA model and it has been illustrated that those with CLBP/CMSKP perform less well in movement orientated tasks than patients with low fear avoidance. Those with high fear avoidance also anticipate more pain than controls or those with low fear avoidance and the model has shown some success in predicting self-reported disability. An fMRI study in humans reported actual LBP-related cerebral substrates (Kobayashi et al. 2009) in which the authors stated that abnormal activations were identified in the prefrontal cortex, insula, thalamus, PCC, supplementary motor area and premotor areas – predominantly in the right hemisphere. It may be reasonable to suggest that these abnormalities arise from psychological factors such as fear and given the impact of the FA model, it is surprising that nothing, until very recently, was known about its neural correlates.

Shimo et al (2011) hypothesized that visualization of a painful event may trigger painful memories, thus provoking the affective dimension of pain. They investigated neural correlates of affect processing in subjects with LBP and subjects without LBP using a virtual LBP stimuli; a picture of a man carrying luggage in a half-crouching position. All subjects with LBP reported experiencing discomfort and some reported experiencing pain. In contrast to subjects without LBP, subjects with LBP displayed activation of the cortical area related to pain and emotions: the insula, supplementary motor area, premotor area, thalamus, pulvinar, posterior cingulate cortex, hippocampus, fusiform gyrus, and cerebellum. This suggests that the virtual LBP stimuli caused memory retrieval of unpleasant experiences and the authors concluded that this may be associated with prolonged chronic LBP conditions.

Barke et al (2012) investigated the neural correlates of fear of movement in women who had CLBP and compared fear responses to those with arachnophobia and healthy controls. The authors tested two groups of patients with CLBP (high and low avoidance) and compared them to healthy controls and those with a spider phobia. Functional MRI data were collected while subjects viewed images; including those that were thought to cause fear in general, spider pictures, a selection from PHODA of back straining movements and neutral control pictures. High avoidance pain patients did not show increased activation (compared with low fear avoidant participants or compared to neutral pictures) in areas presumed to respond to phobias and fear; amygdala, insula and anterior cingulate among others (Etkin and Wager 2007). These findings contrasted with the activations in 'fear regions' seen when avoidant patients viewed general fear-related pictures or when spider phobics viewed pictures of spiders. Based on their findings, the authors concluded that the results did not support the fear component of the fear avoidance model.

Barke et al (2012) proposed a number of explanations for their findings and discussed why these were unlikely to impact on the results. The reasons discussed included: the selection of stimuli was inappropriate; the stimulation paradigm was not suitable for evoking fear-related activations; the statistical power was too low to detect the effect; the high fear-avoidant patients suffered from impaired fear processing; the participants in the high fear-avoidance group were not really highly fear-avoidant; the patients did not relate the movements to themselves; context-based effects influenced the perception of the movement pictures; the concept of fear of movement as postulated in the model was not really a fearful emotional state, but something different. These were all well argued

however, there was no resolution offered as to why there were no neuronal fear responses to PHODA.

Some points that appear to be missing from the authors' discussion need highlighting. The pictures were not rated in the scanner and participants passively observed them so it is unclear what the impact of them was in the scanner. While in Shimo et al (2011), participants also passively viewed photographs, the virtual pain picture did resonate with the LBP participants who admitted to having pain when undertaking the action in the photograph but no pain when standing, which was the baseline photograph, therefore the media was salient to someone with LBP. Participants were asked to indicate the positive/negative and arousal properties of the photographs post scanning, as were participants who previously rated the photographs in a pilot. There was no context for the participants in terms of how they were to consider the pictures and how to attach meaning; negative, positive and arousing in what respect? The results may be due to the fact that they did not incur fear, as participants knew that they would avoid these activities and hence they did not fear them. These comments have also been highlighted and discussed in Salomons and Davis' (2012) commentary. They proposed that to demonstrate that the motivation for avoidant behaviour is a psychological state other than fear, it would be necessary to generate a state capable of motivating avoidant behaviour. The use of the rating system led to the testing of an unspecified affective state which may not have been power enough to motivate fear avoidance.

Salomons and Davis (2012) also raised the limitations of the research in terms of reverse inference (e.g. 'pain elicits response in the insula, task X elicits activation in the insula, therefore task X is painful') and suggest that it cannot be used as the basis of strong

deductive conclusions; it is used to generate new hypothesis and research questions, however. Salomons and Davis (2012) suggest that the probability of a reverse inference being true is a function of the degree to which the region of interest is exclusively activated by the proposed psychological state (i.e. 'is insula only activated by pain?') and in the context of the Barke paper, the insula, anterior cingulate and amygdala are not specific to the construct being tested (fear) but are associated with numerous cognitive and affective states (Hudson 2000; Bornhovd et al. 2002; Davidson 2002). Salomons and Davis (2012) conclude that while lack of activation in these regions might suggest that fear was not elicited, such findings could be used as evidence against any number of other motivationally relevant states and this, in turn, leads to questions about the salience of the task and its validity as a test of the fear avoidance model.

Fear is another concept not well researched in patients with CNMP in the neuroimaging field and warrants further attention especially given the issues raised in Chapter 2 regarding what it is that individuals fear and the limitations associated with fear assessment.

3.3.3 Catastrophising

Pain catastrophising is associated with exaggerated negative affective responses to pain and maladaptive cognitive modulation of pain, as discussed previously, and therefore investigators have focused particularly on those brain regions involved in processing and regulation of the unpleasantness dimension of pain (Rainville 2002) and emotion more broadly (Wager et al. 2008) such as the ACC, and the dorsolateral and ventromedial prefrontal cortex. The impact of pain-related catastrophising on neural mechanisms will be discussed to establish if these differ in patients with CNMP compared to healthy controls.

Two studies have examined the neural correlates of catastrophising in patients with fibromyalgia compared to healthy controls (Gracely et al. 2004; Burgmer et al. 2011). Gracely et al (2004) examined the association between catastrophising and brain responses to blunt pressure in patients with fibromyalgia; healthy volunteers and patients were divided into high or low catastrophisers, based on a median split of residual catastrophising scores. Bergmer et al (2011) compared the activation pattern of patients with fibromyalgia and healthy controls during the time of pain anticipation correlating catastrophising as a modulating cognitive factor and assessed catastrophising both as a trait and as a state characteristic during an experimental pain procedure.

After controlling for depression, both studies found activation within the dorsolateral prefrontal cortex but differed in their findings of other regions and this may just reflect the differences in methods; actual experimental pain and anticipation of experimental pain. Gracely et al (2004) also found activation within the dorsal ACC, medial prefrontal cortex and motor areas and Burgmer et al (2011), the periaqueductal grey and PCC during anticipation of an experimental pain where subjects were informed about the level of pain to be expected.

Both studies discussed some of the findings in relation to attention to pain being maladaptive in fibromyalgia. Gracely et al (2002) found that catastrophising activated brain structures found to be associated not only with pain processing, but also with the attention, expectation and emotional aspects of pain. These regions included the lentiform nuclei (Sullivan et al. 2001b), the cerebellum and medial frontal gyrus (Ploghaus et al. 1999), SII and rostral ACC (Davis et al. 2000; Sawamoto et al. 2000; Davidson 2002).

Burgmer et al (2011) cited Keltner et al (2006) and Koyama et al (2005) as studies previously showing that prior knowledge of a painful stimuli influences neural processing of pain in the dorsolateral prefrontal cortex, PCC and periaqueductal grey due to an increased attentional load and less ability to distract from the pain.

These data suggest that pain catastrophising is related to greater activity in areas implicated in affective processing of pain, attention to pain, and perhaps with pre-motor and motor regions with associated pain behaviours, suggesting that catastrophising may influence pain perception though its influence on attention. Except for the dorsolateral prefrontal cortex being the only common region of activation, these authors reached similar conclusions regarding the issues of catastrophising and attention illustrating that these brain regions are broadly implicated in a variety of emotional and cognitive processes.

The experimental pain stimulus did not result in significant findings despite the presence of greater catastrophising in regard to clinical pain in those with high catastrophising in Gracely et al (2002) or compared with the healthy volunteers in Burgmer et al (2011). Reasons for this may be that during the consent process, patients were reassured that no harm would come of having the pain, clinical catastrophising was stronger than the experimental stimulus and/or catastrophising as a trait dimension in CNMP seems to be independent of pain coping implemented during acute or experimental pain.

These studies are cross-sectional so the causal nature of these relationships remains to be determined; it is unclear whether altered CNS mechanisms may cause an individual to catastrophise about pain or catastrophising changes CNS mechanisms or persistent pain leads to catastrophising. It is also unclear whether altered CNS pain modulation pathways

are uniquely associated with pain catastrophising, or whether it is part of the negative affect or other negative-related cognitions associated with persistent pain.

Pain catastrophising taps into a negative pain schema (Quartana et al. 2009) and shares statistically significant variance with broader negative affect concepts such as anxiety and depression (Sullivan et al. 2001b). There is some debate as to whether catastrophising is a separate construct beyond negative affect in general (Quartana et al. 2009) but given it is one of the strongest predictors of negative pain-related outcomes (see Chapter 2), it is reasonable to think of it as a separate construct.

It has been suggested that the cognitive-affective processes of pain catastrophising enhance the experience of pain by altering central thresholds of excitability which over time increases pain sensitivity (Sullivan et al. 2001b). However, this has not been confirmed as there is no association between pain catastrophising and the nociceptive flexion reflex (a reflex that facilitates withdrawal from a potentially noxious stimulus) (France et al. 2002).

Alterations in supraspinal endogenous pain inhibitory and facilitatory processes may be associated with pain catastrophising (Quartana et al. 2009) and this was illustrated in Weissman-Fogel et al (2011) discussed previously (see section 3.3.1) and in a study on catastrophising in healthy volunteers (Seminowicz and Davis 2006). The latter study found that during mild pain, in healthy volunteers, activity involved regions linked to the affective, attentional and motor aspects of pain, such as the insula, rostral ACC, prefrontal cortex and SII, to be positively correlated with pain catastrophising scores. However, more intense pain showed that catastrophising was negatively correlated with prefrontal areas involved in pain control, the dorsolateral prefrontal cortex suggesting that difficulty

disengaging in pain catastrophisers may be due to lack of top-down control. Amygdala, right temporal lobe, posterior parietal and lateral SI were negatively correlated with the catastrophising score during moderate pain (Seminowicz and Davis 2006).

It appears that catastrophising is associated with activity in brain areas related to attention to pain, emotion and motor activity. However, more research is required to determine how catastrophising influences neural networks and if it can be distinguished from attention and negative emotions.

3.3.4 Depression

The processing of pain information in the brain is influenced by multiple factors including mood (Villemure et al. 2003; Rainville et al. 2005), attention (Asmundson and Hadjistavropoulos 2007; Brown et al. 2008) and cognitive factors, such as pain-related attitudes and beliefs (Ang et al. 2010; Asenlof and Soderlund 2010). In CNMP, depressed mood is an important psychological variable involved in the pain experience (Schweinhardt et al. 2008) and appears to be a co-morbid condition accompanying chronic pain (Bair et al. 2003).

Symptoms associated with this combination include heightened pain experience (Linton and Gotestam 1985; Doan and Wadden 1989) and negative mood (Turner et al. 2004; Sitges et al. 2007); both known risk factors for the onset of CNMP (Currie and Wang 2005). Functional brain imaging may offer the chance to determine the interaction between negative affect and the cerebral processing of pain and relate this to the degree of pain experienced.

Schweinhardt et al (2008) investigated the neurophysiological interactions between depressive symptoms and disease-relevant pain in rheumatoid arthritis patients relating to joint pain and depressive symptoms and contrasted this with experimental heat pain. Provoked joint pain correlated with medial prefrontal cortex activation and the association between depression scores and tender-to-swollen joint ratio was partly mediated by activation in this region. Medial prefrontal activation also varied significantly with the fMRI signal in limbic areas and in areas that process self-relevant information. This suggests that the medial prefrontal cortex may have a role in mediating the relationship between depressive symptoms and pain severity in those with rheumatoid arthritis through engaging brain areas that are important in affective and self-referential processing.

The medial prefrontal cortex is involved in the detection of adverse outcomes (Ridderinkhof et al. 2004), self-referential activity (Gusnard et al. 2001; Rameson et al. 2010) and is an important site of emotional processing (Phan et al. 2003; Kober et al. 2008). It also appears to be a neural correlate of sustained 'high' pain in patients with CLBP (Baliki et al. 2006) and of joint pain in patients with osteoarthritis (Kulkarni et al. 2007). This region is also involved in encoding anxiety during pain (Ochsner et al. 2006), given that the authors did not separately assess anxiety and the Beck Depression Inventory is relatively non-specific the specificity of the relationship between depressive symptoms and brain activation is not clear.

In patients with fibromyalgia, Giesecke et al (2005) found that depression did not modulate the sensory dimension of pain processing, as measured by fMRI and quantitative sensory testing. However, depression was correlated with increased activity in neural regions (i.e., amygdala, and contralateral anterior insula) that process the affective dimension of pain.

The differences in findings here may be due to the fact that fibromyalgia may have a greater affect pain component to the condition than a sensory one, as seen in the rheumatoid arthritis group (Giesecke et al. 2005).

While depression has been discussed in relation to heightened pain with depression, the converse has also be found with reports of normal or reduced pain sensitivity in clinically depressed patients (Dickens et al. 2003; Bar et al. 2006; Bar et al. 2007). However, again, this must be seen in context of experimental pain stimuli. It has yet to be established what the mechanisms are connecting pain and depression; a biological link has been muted (Stahl 2002; Chan et al. 2009) involving the serotonin and norepinephrine system which is dysfunctional in depression (Chan et al. 2009) and which modulates the descending pathways in pain (Stahl 2002).

Neuroimaging studies show that regions involved in pain perception overlap with the abnormal activity of neural structures of patients suffering from depression; the prefrontal cortex, thalamus, amygdala, ACC and insula (Mayberg 2003; Wagner et al. 2006). The left ventrolateral thalamus, the right ventrolateral and the dorsolateral prefrontal cortices (areas responsible for the sensory-discriminatory and cognitive-evaluative aspects of pain) have been shown to be hyperactive in depressed patients compared to healthy controls during experimental pain (Bar et al. 2007). Symptom severity correlated positively with activity in the left ventrolateral nucleus of the thalamus, suggesting that depressed patients experience greater 'pain activity' in the brain than healthy people.

Depressed patients may also have greater emotional processing before they experience pain as when anticipating experimental pain the right anterior insula, dorsal ACC and the

right amygdala showed increased activation, areas responsible for the affective-motivational aspect of pain (Strigo et al. 2008). During painful stimulation there was greater activity in the right amygdala and decreased activity in the periaqueductal grey, rostral ACC and prefrontal cortex compared to healthy controls (Strigo et al. 2008). Therefore, depressed patients, who may have increased emotional reactivity, have impaired pain modulation when anticipating it (Strigo et al. 2008) and this may be linked to hypervigilance and increased pain with increased attention.

Dysfunctional emotional regulation has been hypothesised in studies as modulating the pain experience in depressed individuals, including Giesecke et al (2005) and in healthy volunteers (Berna et al. 2010). During the pain stimulus and after induction of a negative mood, healthy volunteers showed increased activation in insula, thalamus, hippocampus, dorsolateral prefrontal cortex, orbitofrontal cortex , and subgenual ACC areas of the 'pain neuromatrix' (Berna et al. 2010). Those who reported the highest degree of pain unpleasantness during negative mood showed higher activity in the amygdala and inferior frontal gyrus. These regions are involved in the emotional regulation of pain and therefore may form part of the mechanisms that affect pain processing during depressed mood and enhance the pain experience (Knudsen et al. 2011); it is not merely a question of pain attentional bias but impaired emotional regulation.

Imaging studies suggest that the negative mood of depressed individuals impairs pain modulation in neural structures involved in emotion regulation (Knudsen et al. 2011). However, little is known about how depression influences the neural modulation of pain due to the limited amount of research. Research on depression and pain suggests a role for

the affective elements of pain processing but this requires further exploration especially in regard to enhancing pain perception.

3.4 CHAPTER SUMMARY

The brain imaging studies discussed in this chapter indicate cortical and sub-cortical networks that underlie pain perception. Rather than one 'pain centre' in the brain, studies have identified a number of pathways of somatosensory (SI, SII and insula), limbic (insula and ACC) and associative (prefrontal cortex) structures that involve inputs from multiple other networks. Dysregulation in the function of these networks may underlie the development and maintenance of CNMP.

It is apparent that the processing of nociceptive information is complex, it differs in terms of the context (experimental versus spontaneous pain) and that the experience of pain can be modulated by a variety of factors that either facilitate or inhibit pain-related information. CNMP can alter structural and functional systems and negative affect, such as depression, fear and pain related catastrophising, generally increase the experience of pain and increase activity in areas of the 'pain neuromatrix'. Pain related attention also can enhance pain and increase activity within the 'pain neuromatrix' while distraction decreases its perceived intensity and associated cortical activity in healthy volunteers, but this function in CNMP populations has not been addressed. The neural changes that occur in patients with CNMP lead to a variety of problems in concentration, memory, learning and task completion. Neuroimaging has illustrated that the changes experienced by someone suffering CNMP are likely to cause reduction in the quality of life, more negative mood and promote chronicity.

Findings from imaging studies discussed in this chapter illustrate that mechanisms responsible for structural and functional changes and those driving psychological and cognitive responses are often complex, reflecting activation or deactivation at numerous brain sites with sometimes contradictory results. It is also not clear what specific tasks regions in the brain are responsible for as there are so many overlaps in roles. To infer something about a particular pattern of brain activation will require studies to control for other potential influences on brain responses prior to assessing the specific influence on pain; within CNMP, this may not be possible. The pattern of brain activation (or deactivation) between an experimental and control condition is assumed to reflect the activity of a particular pain mechanism, however, in patients with CNMP, underlying spontaneous pain will always make interpretation problematic.

Globally, very little research has been undertaken within CNMP populations, especially in CMSKP and CLBP, but the situation is changing. Reasons for not depending on acute and experimental pain research to make inferences about CNMP populations have been driven by the neurological changes seen in imaging research. Techniques commonly used in behavioural studies in CNMP populations have been modified for neuroimaging studies but have yet to be widely used, for instance the counting Stroop has been used in a number of healthy volunteer studies but only in 1 study of CNMP and dot-probe methods have yet to be used in this population.

It is clear that research needs to be undertaken to better understand how psychological factors that maintain chronicity within the CMSKP population effects neural functioning and this may lead to better understanding of the role of these factors leading to more robust ways of assessing and managing these patients. The management of CNMP is difficult and

despite an increased understanding of the factors contributing to the maintenance of pain and disability through behavioural research, there has been only a moderate improvement in treatment outcomes (Croft 2000; van der Windt et al. 2008).

Early work with clinical populations suggests considerable promise for the use of fMRI in pain diagnosis and therapy. The application of functional imaging may improve the categorisation of pain conditions in an objective manner based on a better understanding of central mechanisms and may lead to improved diagnosis and the identification of more appropriate treatment regimens.

CHAPTER 4: METHODS AND METHOD DEVELOPMENT

This chapter will provide an overview of the methods chosen to undertake the studies presented later in this thesis. Each study, presented in Chapters 5, 6 and 7 will have individual method sections which are pertinent to the study aims but to complete this, background is required to further support them. It was clear from the literature review that little has been undertaken to help identify the neural correlates of attention, fear and catastrophising within CMSK patients. Research undertaken on attention has used a Stroop paradigm but dot probe research has not been undertaken in the scanner environment. PHODA has been used to examine fear and catastrophising in behavioural research. We decided that as Stroop had already been adapted for fMRI research, it was reasonable to utilise this and behavioural studies supported its use. The research on fear and catastrophising appeared to suggest that more salient stimuli needed to be used to assess these concepts and so pictorial methods such as PHODA appeared to be a more robust way to assess pain and movement related fear. It seemed reasonable to consider these as methods to include in the research portfolio. Therefore, this chapter will examine fMRI as a research tool and discuss the use of the counting or numerical Stroop and PHODA within this environment.

4.1 FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI)

Functional MRI (fMRI) allows us the opportunity of observing neural activity non-invasively in the human brain. It has provided exciting opportunities to study topics that have seemed impossible to research previously in a rigorous scientific way. However, using fMRI in a research paradigm leads to notable challenges when faced with analysing data which is complex and present in large amounts.

Magnetic resonance imaging uses the magnetic properties of certain molecules to allow the study of structure and function of the brain. The first human MRI scanner was built in 1977 and in 1985 the Food and Drug Administration approved MRI for clinical use. Hospitals throughout the Western World installed scanners and MRI is now seen as a routine investigative tool in medical care, given its low risk profile and non-invasive nature.

The image that is obtained with MRI maps of the net local transverse magnetisation of the hydrogen nuclei and this depends on several intrinsic properties of the tissue. Transverse magnetisation is a transient phenomenon and does not exist until the MRI processes activates it. Image contrast is manipulated during image acquisition by adjusting several parameters, such as repetition time (TR) and the echo time (TE) which control the sensitivity of the signal to the local tissue relaxation times (T_1, T_2 - discussed later).

This section will discuss the blood oxygenation level dependent signal (BOLD) and fMRI in relation to techniques used in pain and emotion research.

4.1.1 The Blood Oxygenation Level dependent signal

The goal of fMRI is to observe the brain as it functions in as close to real time as possible and the ideal would be that neural activity would be measured with high spatial resolution in real time but this has not been realised yet. The typical fMRI experiment records a sluggish, indirect measure of neural activity; nevertheless, this imperfect technology has dramatically influenced the study of the brain. It visualises brain function by measuring the haemodynamic response to neural activation and records BOLD activity and contrast is

obtained from natural changes in the oxygen saturation of blood in cerebral capillaries and veins as a response to activity (Ashby 2011).

The physics of the BOLD signal response is complex but for the purpose of this thesis, the BOLD signal is a measure of the amount of oxygenated haemoglobin present (see Fig 4.1). This BOLD effect arises because of two distinct phenomena. Firstly, when haemoglobin loses oxygen to become deoxyhaemaglobin, the magnetic properties change with respect to the surrounding tissue, reducing the MRI signal slightly. Conversely, this signal is increased when the blood becomes more oxygenated. This is combined with the second phenomena to make it useful scientifically. This involves blood flow to the area of activation in the brain. The blood flow increases much more than the metabolic rate for oxygen and leads to a reduction of the oxygen extraction fraction and a decrease in the amount of deoxyhaemoglobin (increase in oxyhaemoglobin) in venous blood. These two phenomena produce the BOLD effect, a local increase of the MR signal owing to a reduction of the oxygen extraction fraction during increased neural activity (Buxton 2002).

Active brain areas consume more oxygen than inactive areas and when neural activity increases in an area, metabolic demands rise and the vasculature increases delivery of oxygenated haemoglobin to the area. Immediately after neural activity, typically there is an oxygen debt and so the ratio of oxygenated to deoxygenated haemoglobin (the BOLD signal) can fall to below baseline levels. The vasculature responds by overcompensating in order to get more oxygen laden haemoglobin to the area so that there is a peak, well above baseline, at around 6 seconds after the neural activity that elicited these responses. After this peak, the BOLD signal returns back to baseline over a period of 10-25 seconds, in some brain regions with a so-called ‘undershoot’.

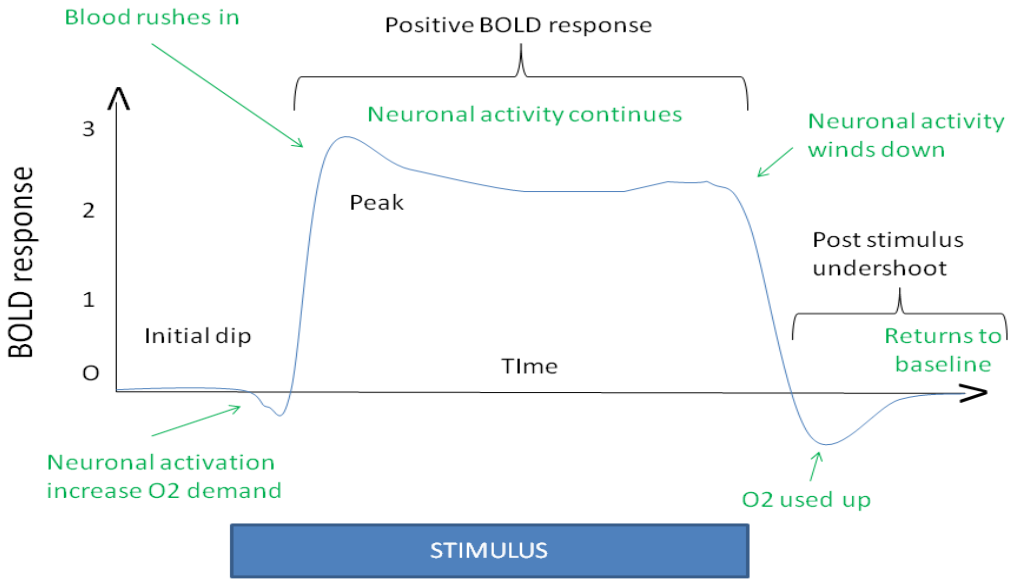


Fig.4.1 Diagrammatic representation of the BOLD signal
(Adapated from Buxton (2002))

4.1.2 Principles

Precessing

Precession is a change in the orientation of the rotational axis of a rotating body. The source of resonance in an fMRI experiment comes from the fact that the protons and neutrons that make up a nucleus posses an intrinsic angular momentum called 'spin'. This 'spin' should not be confused with that of something spinning on an axis as it is a purely quantum mechanical phenomenon. Protons, neutrons and electrons have the same magnitude of angular momentum which cannot be increased or decreased, unlike a physical entity spinning on an axis, but the axis of spin can be changed (Buxton 2002). Nuclei with an even number of protons and neutrons have no net spin but those with an odd number do. Hydrogen, with only a single proton as its nucleus therefore, has a net spin and is the primary focus of MRI due to its abundance in the body. The hydrogen nucleus

acts like a tiny magnet with the north-south axis parallel to the spin axis and this is known as the magnetic dipole moment and is associated with the spin of the proton. When the proton is placed in a magnetic field, a proton with this magnetic dipole moment will precess around the field of axis and the frequency of this precession is the resonant frequency of the MR.

Relaxation

Relaxation is the other important process that affects the orientation of the proton's spin. When a proton is placed in a large magnetic field, the precession rate is very fast and if the angle of the axis could be observed for a few rotations, it would appear as a pure precession with no tendency for alignment with the magnetic field. However, if multiple rotations were observed, the axis alignment will creep to line up with the magnetic field. The time constant for this relaxation process is called T_1 and after a time that is several times longer than T_1 the axis is essentially aligned. Relaxation is an example of energy equilibration; lowest energy is expended when aligned to a magnetic field, highest when it is not. As orientation to the magnetic field is undertaken, energy is dissipated as heat. A typical value for T_1 in the human body is about 1s.

Equilibrium magnetisation

A lower energy state is preferred according to the second law of thermodynamics, it is important to determine how many hydrogen nuclei are in higher states and how many are in lower states. The differences between the numbers of hydrogen nuclei in the two states depend on the energy differences between the states and on the temperature. Temperature is important because the hydrogen nuclei and of course the water or lipids they are in, also have thermal energy and the random thermal motion tends to push the nuclei out of

alignment. When all of these factors are balanced, the hydrogen nuclei are in a state of equilibrium. This means that more are aligned in one direction than another and body water is magnetised, albeit weakly, when in the MR scanner. Magnetisation refers to the net magnetic moment per unit volume and is the sum of all the individual magnetic moments of the hydrogen nuclei. The resulting magnetisation is parallel to the magnetic field of the MR system (Stroman 2011) and this magnitude is directly proportional to the local proton density or spin density (Buxton 2002). The total magnetic field of the excess protons forms a vector which is called the net magnetic vector.

Radiofrequency pulse

The local value of the net differences between hydrogen nuclei aligned to the magnetic field and those that are not is not directly observable because it is much weaker than the externally applied magnetic field. However, if they could all be tipped to 90° they would all precess around the field at the same rate and so would the net magnetic vector. Tipping over the magnetisation produces a measurable, transient signal and this tipping is accomplished by the RF pulse.

Free induction decay signal

Once the RF signal is removed, the nuclei will re-align themselves such that their net magnetic moment is again parallel with the magnetic field in the scanner. The signal decays because the precessing component of the magnetisation itself decays (Buxton 2002); the individual dipoles are no longer precessing at precisely the same time. Therefore, the longitudinal relaxation time T_1 which has already been discussed as the longitudinal relaxation time, is joined by the transverse relaxation time T_2. This indicates

the time required for the free induction decay response signal from a given tissue type to decay.

The MR image contrast depends on these two tissue-specific parameters; T_1 and T_2. When MR images are acquired, the RF pulse is repeated at a predetermined rate and the RF sequence is known as repetition time (TR). The free induction decay response signal can be measured at various times within the TR interval and the time between which the RF pulse is applied and the response signal is measured is the echo delay time (TE). By manipulating TR and TE, the acquired MR image can be made to contrast various tissue types.

If the TR is long, the signal generated by the second RF pulse will be equal to the magnitude of the first RF response but as the TR is shortened, the signal generated by the second RF pulse becomes weaker. To generate a second, full amplitude signal, a recovery time a number of times greater than T_1 is required to allow the spins to relax back to equilibrium. The relaxation time also varies among tissues.

A voxel is a volume element representing a value in the three dimensional space, corresponding to a pixel for a given slice thickness. The voxel intensity of a given tissue type (i.e. white matter compared with grey matter) depends on the proton density of the tissue; the higher the proton density, the stronger the free induction decay response signal. To produce constrast in an image the operator can manipulate TR and the spin echo time (TE). These control how strongly the local tissue relaxation times T_1 and T_2 affect the signal. By lengthening the TE, there is more time from transverse delay (T_2). The TR controls how much longitudinal relaxation is allowed to happen before the magnetisation is tipped over again when the pulse sequence is repeated (T_1). If tissues have equal T_1 and T_2

these will tend to cancel each other out and produce poor tissue contrast. Therefore, to produce a strong signal with T_1 weighting, the sensitivity to T_2 must be suppressed.

Small changes in venous oxygen saturation cause a change in magnetic susceptibility that affects the BOLD signal. Increases in T_2-weighted MR signal are seen with the small increases in venous oxygen saturations (decrease in deoxyhaemaglobin) during neural activation. This is accompanied by a decrease in the field gradients around blood vessels that further acts to increase the T_2-weighted signal during decreased deoxyhaemaglobin and by repeatedly acquiring rapid T_2-weighted images, changes in the MR signal close to the region of activation can be observed.

Pulse sequencing

Given that longer TR in RF pulse sequencing allows for complete recovery, it might appear that the optimal parameter would be pulse sequencing that maximises the signal. However, the MR signal is weak and a limitation on spatial resolution is noise in the image. The contrast to noise ratio determines whether one tissue can be distinguished from another in an image (Buxton 2002).

The simplest pulse sequence is the free induction decay sequence; a series of RF pulses creates a precessing magnetisation transfer and a measurable signal. When used for imaging, it is called a gradient recalled echo pulse sequence. The research contained in this thesis comes from work involving gradient echo, echo planar imaging. Echo planar imaging is a rapid magnetic resonance imaging technique which records an entire image in a TR period and measures all lines of k-space in a single TR period. In practice, k-space often refers to the temporary image space, usually a matrix, in which data from digitised

MR signals are stored during data acquisition. When k-space is full (at the end of the scan) the data are mathematically processed to produce a final image. Thus k-space holds raw data before reconstruction.

4.1.3 BOLD FMRI experimental design

In fMRI studies, subjects are usually required to perform a task which is observed via a mirror on the top of the bore to direct the subject's eyes to a computer screen and often uses a hand held device for responses. A full safety check is necessary to ensure that subjects are safe to be placed within the MR bore and it is essential that no incompatable material and/or devices are introduced into the imaging room; ferromagentic metal objects and electronic devices are not permitted. An initial patient screening questionnaire is completed prior to scanning and immediately before scanning a shorter questionnaire is given to the subject. All personnel have to be trained and assessed on their safety knowledge.

Stimuli are repeatedly presented as the MR images are acquired and because neuronal activation causes a relatively small signal change, it is necessary to repeat the stimulus a number of times to increase the contrast to noise ratio. Experiments use either a block design or an event-related design. During scanning, as well as the task, there is other information that is collected, structural scans, fieldmaps, resting BOLD, cerebral blood flow and physiological data, etc.

In block design (Fig 4.2), the functional run consists of a series of blocks lasting for around 30s to a couple of minutes. During the course of the block, subjects are instructed to perform the same activity continuously and in between these activity blocks there will be

rest blocks where nothing is required of the subject. In an event related design (see Fig 4.3), the functional run is divided into discrete trials. Frequently, each trial is one of several types of stimuli and each type is repeated at least 20 times over the course of the experiment and presentation order of the trial is usually randomised. Jittering may also be undertaken which is the practice of varying the timing of the TR relative to stimulus presentation to vary the inter-trial interval. Jittering is a necessary design feature of any rapid event-related design as without it, it would not be possible to separate BOLD signal responses from successive events or to obtain a unique estimate of model parameters. When analysing data from even-related designs, it is critical to know exactly when the presentation of each stimulus occurred relative to TR onset and this is often undertaken by synchronising stimulus presentation with the onset of the stimulus using a timing (TTL) pulse.

Slow event-related designs include long rests between each pair of successive trials to allow the BOLD response to decay back to baseline. While statistically this makes sense, it is costly in terms of reducing the number of trials that can be completed in any functional run and may cause participants to drift their attention away from the task causing unwanted BOLD responses (Ashby 2011).

Rapid event-related designs contain much shorter delays and have been made possible by sophisticated statistics that allow for the overlapping BOLD responses in regions where BOLD has not completely decayed prior to another stimulus presentation. As BOLD signal change only gives a relative estimation of change in neural activity, it is necessary to have a baseline or "resting" condition for comparison.

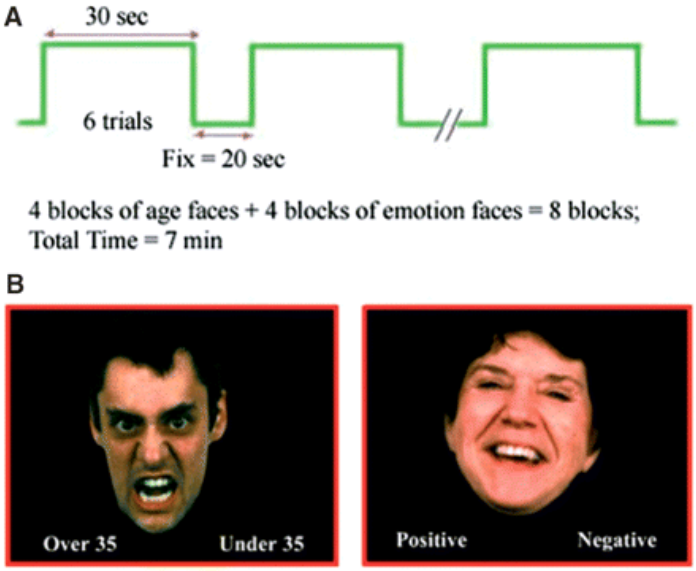


Fig.4.2 Example of a block design
(A) Incidental and directed conditions block design. (B) Examples of face stimulus displays used for the incidental condition (on the left) and for the directed condition (on the right) (Passarotti et al. 2009).

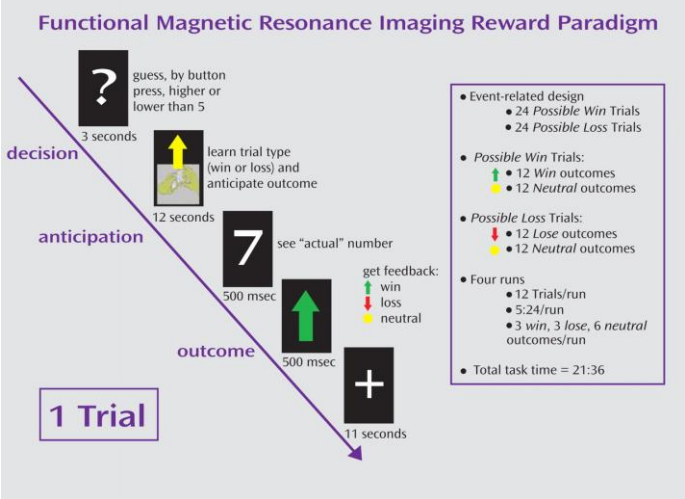


Fig.4.3 Example of event-related design
In this event-related paradigm, each trial included both an anticipation period and an outcome period, and participants received win, loss, or no-change feedback for each trial. The participants were told that their performance would determine a monetary reward to be received after the scan (Forbes et al. 2009).

4.1.4 Data analysis: pre-processing

Data produced from fMRI research can be challenging to analyse due to the large amount produced, the substantial spatial and temporal correlations and the noisy nature of the data

(Ashby 2011). Typically, the signal that the analysis is trying to find is 2-3% of the baseline MRI signal; the effect sizes are small. Thermal motion and physiological factors (same metabolic demand in the same region does not always produce the same BOLD response) can be seen as 'true' noise. Head motion, scanner drift and uncontrolled cognitive activity in the participant can be seen as unaccounted for signal.

Pre-processing includes a number of steps that are required before statistical analysis can be undertaken and include:

- Slice-timing correction: corrects for variability in BOLD.
    - Slice-time correction is not a critical problem in block designs where the repetition of tasks supports relatively constant brain activation as tasks are undertaken for several minutes until the block ends and after which the BOLD signal decays back to baseline.
    - Slice-time differences are problematic in event-related designs where subjects alternate between task and rest rapidly causing the BOLD responses in task sensitive voxels to change frequently. Slice timing can be corrected during pre-processing or be accounted for in the statistical methods used
- Motion correction: during scanning, there is movement of the brain which unless corrected can lead to a single voxel in the time series not being represented in the same volume of brain tissue throughout the experiment. Motion correction algorithms are used to address this problem (Jenkinson et al. 2002)
- Spatial smoothing:
    - increases the signal to noise ratio reducing, in principle, random noise

    - will make the distribution of the BOLD response more normal; the statistical models that dominate fMRI data analysis assume normally distributed noise
    - is also required by a number of commonly used methods to protect against multiple comparison problems and the chance of too many false positives. Several of the most commonly used methods for solving this problem are derived from the Gaussian Random Field Theory and the significant thresholds recommended by these methods assume spatial smoothing with a Gaussian kernel (Jenkinson et al. 2002). Areas of activation should not be cancelled out to the same extent as the noise as long as the smoothing kernel is a similar size as or smaller than the areas of activation. However, if small areas of activation are to be expected, the size of the smoothing kernel should be carefully chosen.
- Temporal filtering: smoothes data at each voxel across neighbouring TRs unlike spatial filtering which smoothes data at each TR.
    - High pass filtering removes scanner drifts and some cardio-respiratory effects. A filter cut-off will prevent filtering out of the variations related to the experimental paradigm and should be equal to approximately one and a half times the paradigm period.
    - Low pass filtering can cause an increase in temporal autocorrelation and is therefore not generally used. In the data, temporal smoothness is calculated and removed during 'pre-whitening'. Pre-whitening renders noise 'white' or random rather than correlated. Noise is heavily correlated with itself, each timepoint is not an independent observation so smoothing estimates the

degree of correlation between one time point and the next and removes the amount of noise that is correlated to the signal.

- Co-registering functional and structural data: aligns the functional and structural images.
    - Accurate image registration is essential for the analysis of multi-subject studies. The traditional approach is to use software that uses linear algorithms (e.g. FLIRT) (Jenkinson and Smith 2001), but recently non-linear registration software (e.g. FNIRT) (Andersson et al. 2007) has been made available that specifically optimises registration from high resolution structural images to standard space.
- Normalisation: corrects for the differences in individual sizes and shapes of brains and facilitates group analyses. If not performed, it is difficult to assign task related activation observed in some cluster of voxels to specific neuro-anatomical brain regions.
    - Historically the Talairach atlas was almost universally used because of lack of an alternative. Much dissatisfaction has been levelled at this because it is derived from one, rather unrepresentative brain (Ashby 2011).
    - The Montreal Neurological Institute (MNI) atlas is a more popular altas being based on the average of high resolution structural scans from 152 brains.
- Correction of magnetic field inhomogeneities: sinus cavities can cause inhomogeneties that are not easily corrected via shimming. These cause spatial distortions and signal dropout in echo-planar imaging, particularly in the frontal lobes due to their proximity to the air sinuses. Without correction, this will affect the registration of the echo-planar imaging to the subjects T_1 structural scans.

- These distortions are corrected with the aid of fieldmaps which ‘unwarps’ the echo-planar images. Fieldmaps are acquired as separate scans and measure the strength of the magnetic field at each voxel (Jenkinson 2003).

4.1.5 Data analysis: statistical analysis and the general linear model

Statistical modelling of the data correlates the MR signal with the paradigm performed in the scanner. A simple way of undertaking this is to average the signal during the ‘on’ periods and contrast these with the ‘off’ periods using a t-test. However, this ignores the temporal structure of the signal. A more robust way to analyse the data is to compare the time-course for each voxel with the time-course of the paradigm or to the expected haemodynamic response function; termed boxcar and boxcar convolved with haemodynamic response function respectively. FEAT, FMRIB’s expert analysis tool, uses GLM, otherwise known as multiple regression on first-level (time-series) data known as FILM (FMRIB's Improved Linear Model). FILM uses a robust and accurate nonparametric estimation of time series autocorrelation to prewhiten each voxel's time series; this gives improved estimation efficiency compared with methods that do not prewhiten.

Statistical parameters are assigned to each voxel associated with probability (*P* value). Given the large number of voxels within the brain, a correction is required to address multiple comparisons. The Bonferonni method is overly conservative because voxels tend not be independent of each other. Cluster based thresholding using Gaussian Random Field Theory defines probability values based on cluster size and the initial statistical threshold chosen (Woolrich et al. 2001) and hence has been used for the studies in this thesis.

Analysing for group responses is important in order to be able to infer meaning for populations and to improve signal to noise ratio of activation maps as data from single subjects may be difficult to interpret due to noise. For higher-level analysis FEAT uses FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann et al. 2003; Woolrich et al. 2004; Woolrich 2008). FLAME models and estimates the random-effects component of the measured inter-session mixed-effects variance, using Bayesian random approach (Markov chain Monte Carlo (MCMC)) sampling to get an accurate estimation of the true random-effects variance and degrees of freedom at each voxel.

Statistical methods include 'fixed' effects which only consider within subject variances and 'mixed' effects which also consider between subject variance. Mixed effects is used in the majority of the analyses in this thesis. It allows conclusions to be drawn about the population from which subjects were drawn rather than just that specific group of subjects.

4.1.6 Resting BOLD

Identification of objective markers that could simultaneously validate CNMP symptoms and be useful in elucidating underlying pathological processes have eluded researchers because chronic pain has been notoriously difficult to elicit in a controlled way and can fluctuate in magnitude.

Resting-state functional-connectivity magnetic resonance imaging is a relatively recent adaptation of fMRI and has been used to sample spontaneous fluctuating pain with specific network activity; notably the DMN, Executive Attention Network and the Medial Visual Network. This method examines intrinsic connectivity which is defined as ongoing neural and metabolic activity that occurs in the resting basal state.

Resting BOLD investigations aim to show correlated activity in the resting state and the networks involved in this activity are referred to as intrinsic connectivity networks. The data derived from these investigations can then be analysed with independent component analysis (ICA). ICA is a data driven method of isolating independent brain networks that have temporally correlated fMRI findings on time-series scans(Napadow et al. 2010). These brain networks are thought to be connected synaptically since the fMRI signal between brain areas in these networks are correlated over time and follow structural monosynaptic and polysynaptic pathways (Krienen and Buckner 2009; van den Heuvel et al. 2009). This is likely to reflect meaningful neurophysiological activity.

4.1.7 Voxel based morphometry (VBM)

Voxel-based morphometry (VBM), in its simplest form, involves a voxel-wise comparison of the local concentration of gray matter between two groups of subjects. The procedure involves spatially normalising high resolution images from study participants into the same stereotactic space, segmenting the grey matter from the spatially normalised images and smoothing the grey matter segments. Voxel-wise parametric statistical tests which compare the smoothed grey-matter images are then conducted to produce maps illustrating where grey matter concentrations differ significantly between groups.

Statistical analysis of VBM is performed using the GLM. However, a number of assumptions need to hold in order for VBM to be valid (Ashburner and Friston 2000):

- The segmentation must correctly identify grey and white matter
- Any confounding effects must be eliminated or modelled as far as possible

- The nature of the data must be considered and the assumptions required by the statistical tests, if there is doubt about the validity of the assumptions, non-parametric statistical analysis should be used.

Unfortunately VBM, currently, is not powerful enough to detect subtle brain abnormalities in individuals, even with many hundreds of subjects in a database of controls.

4.1.8 Summary

Neuroimaging, specifically fMRI, offers an opportunity to further study psychological and cognitive variables to build on existing behavioural research. The BOLD response only provides an indirect measure of neural activation and an understanding of how this and the pattern of neural responses are related is integral to refining neuroimaging techniques.

Pre-processing is an incredibly important step in data analysis and decisions around quality assurance are important as some of these processes can be undertaken during pre-processing or during statistical analysis. Other processes are dependent on the facilities available and these need to be weighed up and decided upon at the beginning of any neuro-imaging study.

Statistical analysis is a complex process and many factors also need to be considered including decision about the most robust way of handling data and producing valid and reliable outcomes. FEAT is based around the GLM and offers the researcher a simple way of using statistical methods to process complex data sets. Further detail of statistical analysis is provided in Chapters 5, 6 and 7.

VBM and resting BOLD are useful additions to understanding the results produced by fMRI studies. VBM may help elucidate whether the results found may be due to structural differences between controls and patients and resting BOLD can help to establish the connectivity of 'pain centres' to the DMN in those with chronic pain.

4.2 COUNTING STROOP

In the MRI scanner, head movements confound the experiment and therefore spoken words are not appropriate resulting in Bush et al. (1998) developing a counting Stroop task for fMRI use. The Stroop task has been used for over half a century in various behavioural studies before entering the neuroimaging field. It has been validated in different guises also and this section will briefly examine its historical development before discussing the counting or numerical Stroop.

4.2.1 Historical perspective

Stroop focuses on the fact that cognitive interference occurs when the processing of one stimulus feature impedes the simultaneous processing of a second stimulus attribute. The colour Stroop became the prototypical interference task following a study by Stroop published in 1935 (Stroop 1935b). It was popular in behavioural research because it was seen as elegant in its simplicity and extremely reliable (Smith and Nyman 1974; Schobo and Hentshcel 1977) and provided information about the essential mechanisms of attention and cognition in both healthy volunteers and those with neuro-physiological impairments (Treisman and Fearnley 1969; Dyer and Severance 1973; MacLeod 1991).

The Stroop interference effect, reported as the second of three different tasks in the original paper (Stroop 1935b), describes an effect where it took longer for subjects to name the

colour of the ink that the colour words were written in when the ink colour and the naming of the colour word did not match than it did naming the colour of coloured squares.

The Stroop paradigm has been re-designed in many formats to address the needs of behavioural and neuro-imaging researchers. The following provides a brief discussion of these approaches in order to contextualise the counting or numeric Stroop paradigm. The standard Stroop colour-word interference test involves subjects naming colours of incongruous words (colour of the word and the name do not match) and of control colour patches. Interference is measured as the differences in times between these two. Although some authors have been doubtful about the reliability and validity of the Stroop colour-word text others have been more optimistic arguing that reliability was quite good (Smith and Nyman 1974; Schobo and Hentshcel 1977).

Modifications have been undertaken, in terms of how the words and colour have been presented, but have made little difference in interference scores. As a psychometric tool, the Stroop colour-word test appears to have reasonable reliability and validity and coupled with the ease of administration, it has been widely used. Many versions of the test have been developed and tested (MacLeod 1991):

- The individual stimulus version of the colour-word task: those studying intereference wanted a more analytical method where individual stimuli could be presented and timed and this version also modified the format of the stimulus with robust interference resulting.
- Sorting and matching versions of the colour-word task: rather than naming or reading stimuli aloud, subjects were asked to sort stimuli into categories with

sorting categories of colour only card being faster than sorting incongruent colour-word cards into categories identified by colour patches.

- Picture word interference task: the naming of colours and pictures was found to be slower than reading aloud corresponding words. This led to words being embedded inside line drawings and required subjects to name the pictures. It has been questioned whether this measured the same phenomenon as Stroop.
- Auditory analogues of the Stroop task: this was based on the proposal that if individuals could selectively filter by modality, then there ought not to be much cross-modality interference. An example of such would be the word 'low' being presented with a low pitch auditory signal, 'high' with a high pitched signal and the incongruence would be the word 'low' with a high pitch of vice versa. This suffered from the lack of a neutral-word control condition and the sum of facilitation and interference is unknown.

Therefore, historically, it can been seen that Stroop has been subjected to a number of variations, the above list is not exhaustive and the next sections will introduce the concept of the emotional Stroop and the counting Stroop as it is the combination of emotional words in a counting Stroop format that was chosen to test pain related attention in the study outlined in Chapter 4.

4.2.3 Counting Stroop

As discussed earlier, cognitive interference occurs when the processing of one stimulus impedes the simultaneous processing of a second. Interference is minimal when there is congruence and is increased as incongruence is entered into the Stroop paradigm. In cognitive fMRI experiments, the traditional Stroop has a number of drawbacks that limited

its use, and yet objective measures of task performance are necessary in illustrating that subjects are actually engaged in a task. This then allows researchers to examine changes in neuronal functioning as it relates to the performance of participants enrolled in neuroimaging studies.

One of the major drawbacks of colour-word naming is head movements, only 2-3mm of movement can seriously affect the image produced. Bush et al (1998) proposed an alternative strategy; the counting Stroop. They proposed that using an arbitrarily labelled button box with colour names was not optimal because it added an undesired layer of cognitive complexity and required training of participants. The counting Stroop was designed as a button-press Stroop interference task that allowed online response measurement in the absence of speech. In this counting Stroop task, participants are asked to report on a button box the number of words they see in the screen regardless of the meaning of the words. Neutral or control block are presented containing non-number words, such as common animals and the interferences blocks are number words 'one', 'two', 'three' and 'four'.

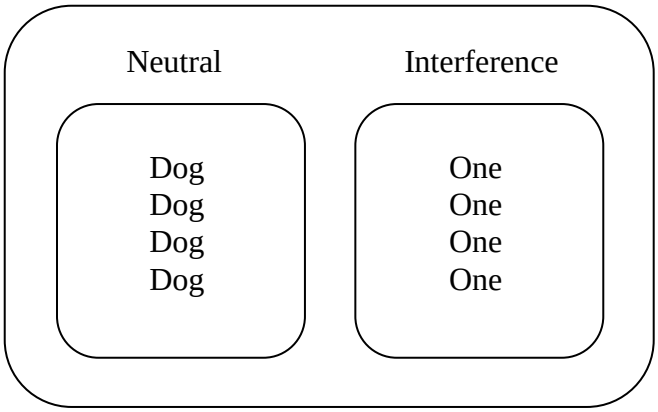


Fig.4.4 Counting Stroop trial example, example of single trials for the two types of stimuli.
Both sets of word stimuli were common words from a single semantic category. During 'neutral' trials, common animal names (dog, cat, bird, or mouse) were used. During 'interference' blocks, the words consisted of number names (one, two, three, or four). In both examples, the correct answer would be to press button number 4 (Bush et al. 2006).

The counting Stroop introduces two cognitive processes, reading and counting, into competition during the interference (incongruent) trials. In contrast, the word stimuli used in the neutral trials do not interfere significantly with the counting process. Reaction time required to count and respond to the words measures the degree of cognitive interference.

In an initial validation study (Bush et al. 1998) the counting Stroop was used to identify and characterise the mediating neural substrate of cognitive interference and specifically examined the role of the dorsal anterior midcingulate cortex. This region was seen to have highly significant activation during the counting Stroop as were the lateral prefrontal, premotor and parietal cortices. Behaviourally, participants also showed cognitive interference with longer response times for interference trials than for neutral ones. Learning effects were noted with response times and dorsolateral midcingulate activity decreasing with practice of the interference trials (issues around learning effects in relation to the Stroop study performed in this thesis are discussed in Chapter 5). This provided some insight into how the brain responds to learning and provided an example of how performance data can prove to be useful in analysing imaging data. Bush et al (2006) propose that given this learning effect, the counting Stroop is not recommended for longitudinal studies.

The counting Stroop and its variants have been used in a number of studies, in healthy volunteers (Chen 1998; Bantick et al. 2002; Hayward et al. 2004; Kemmotsu et al. 2005) and in clinical conditions (Bush et al. 1999; Tamm et al. 2002; Parry et al. 2003; Wagner et al. 2006; Wagner et al. 2010; Tlustos et al. 2011). Bush et al (2006) proposed that accuracy in healthy volunteers should be high and response times greater for interference trials compared with neutral ones. Using data from their group (Bush et al. 1998; Bush et al.

1999), they projected that interference minus neutral subtractions can be expected to activate a network of brain regions involved in attention, response selection, motor planning and output (dorsolateral midcingulate, middle frontal gyri, premotor and primary motor cortex, inferior temporal gyrus and superior parietal lobule). They also proposed that the ACC would coincide with greater response latencies and healthy participants would show a typical 'deactivation' in the pregenual/subgenual ventral ACC, PCC and hippocampus. It is not clear from their published protocol why they expected this typical 'deactivation' and this has been discussed in Chapter 5, discussion section.

4.2.4 The emotional counting Stroop

Performance can be slowed by contradictory sensory information, as the Stroop tasks have illustrated, but in everyday life there are sources of interference that may be more complex. In everyday living, there are numerous opportunities for intrusions on primary task performance because of factors that grab the attention such as emotional information, and in relation to this thesis, pain-related information. Therefore, while the counting Stroop is useful for fMRI research, it needs to be more related to examining emotional components. Further modification of the Stroop paradigm has been undertaken by cognitive scientists in order to establish whether emotional information is more likely to produce task interference in groups of participants where this emotional information is salient (Mathews and MacLeod 1994). A delay in response when emotional versus non-emotional information is presented during a cognitive task can be interpreted as emotional interference.

As discussed previously, neuroimaging studies offer the opportunity to identify neural substrates of behavioural phenomena, such as task interference; implicating the ACC as a

critical component of balancing the competing information presented in the counting Stroop. To address the emotional component in an fMRI attentional paradigm, Whalen and colleagues developed the emotional Stroop or ecStroop (Whalen et al. 2006) to allow for the assessment of the impact of emotional information on button-press performance.

In a variation of Bush et al (2006), the ecStroop presents one, two, three or four repeated words on a screen. Half the words used will be neutral and half are emotional in nature. The ecStroop is designed with psychopathology in mind and therefore the words usually consist of items related to a particular diagnosed condition as well as more generally negative words that are implemented as a comparison condition to reveal the disorder-specific nature of any observed Stroop effect. It would be anticipated that reaction times to disorder-specific versus general-negative or neutral words would be expected to be increased in the patient population; healthy controls would not be expected to reveal such differences. Healthy volunteers can display an emotional Stroop effect in the absence of a diagnosable disorder if the words are salient to that individual (Williams et al. 1996), therefore, care must be taken to choose words that are not salient to all participants.

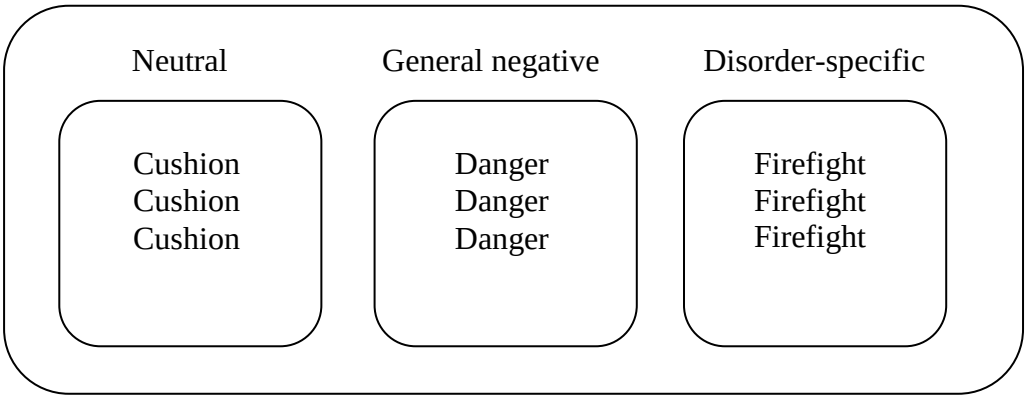


Fig.4.5 Example of emotional counting Stroop
Example of single trials, used in post traumatic stress disorder, for the three types of stimulus. In all examples, the correct answer would be to press button number 3 (Whalen et al. 2006).

Whalen et al (1998) had previously validated the ecStroop in a study using fMRI to recruit the ACC. In healthy volunteers, the ecStroop activated the more dorsal anterior cingulate cognitive division and also showed the overall decrease in ACC affective division signal intensity. The participants demonstrated a reliable reaction time effect. Taken together, the authors concluded that these data offer a within-group spatial dissociation of ACC function based upon information content (i.e., cognitive vs. emotional) and/or presence of behavioural interference. They proposed that the ecStroop would be a useful fMRI probe of the affective division of the ACC function in anxiety disorders. Since the initial validation study, it has been used in a number of psychopathological or potentially psychopathological condition studies (Shin et al. 2001; Mannie et al. 2008; Britton et al. 2009; Weissman-Fogel et al. 2011).

Whalen et al (2006) and Bush et al (2006) published fMRI protocols of which the major principles are used in the methods section of the Stroop research outlined in Chapter 5.

4.2.5 Stroop pilot study

To obtain the most appropriate words for use in a fMRI Stroop study examining pain-related attention between patients with CMSKP and healthy controls, as advised by Whalen et al (2006), a pilot study was undertaken outside the scanning environment. This section describes the pilot study and its findings.

Introduction

A few studies have been undertaken using an emotional Stroop paradigm in patients with chronic pain (Pearce and Morley 1989; Duckworth 1997; Pincus et al. 1998; Crombez et al. 2000; Snider et al. 2000; Beck et al. 2001; Andersson and Haldrup 2003). Some studies

have shown an attentional bias, albeit weak, to sensory and/or affect pain words (Pearce and Morley 1989; Crombez et al. 2000; Beck et al. 2001; Andersson and Haldrup 2003) or in specific groups of pain patients (Duckworth 1997; Snider et al. 2000) and others have not (Pincus et al. 1998). The existing research has a number of limitations; some studies have relied on non-computerized versions of the Stroop task, some have small samples, some have not controlled for multiple data sets, or have lacked a control group (Roelofs et al. 2002).

In previous studies, pain words were largely chosen from the McGill Pain Questionnaire (MPQ). However, it was not always clear how the pain words were chosen and whether they were appropriately lexically matched to control words. Therefore word bias cannot be ruled out; words may not have been salient and/or may not have been robustly matched. Using words that are salient can be difficult to achieve; either the study risks primacy bias if participants are asked to choose the words prior to the study or words may have to be chosen in a similar population but not that involved in the main study. This latter approach avoids primacy bias but there are risks that the chosen population may differ from the main study group in the use of pain descriptors.

Previously, pain words were compared to negative and controls words in many of the studies discussed in the literature review and this comparison did not lead to convincing Stroop behavioural results. An interesting study on anxiety by Mathews and Klug (1993) examined colour naming words in clinical anxiety using word sets that were varied in valence and in their judged relationship to the concerns of anxious patients. The rationale was that positive words may be semantically linked to negative ones and serve as primers or that the positive words were ideals, that the patients were fearful that they would never

be able to achieve the states the positive words described. They found that positive emotional words can cause as much interference with colour naming performance of anxious patients as negative words. When positive words were found to cause interference, it appeared this may have been because some of them were semantically linked with a perceived threat or current concern. The authors suggested that the mixed results obtained were attributable to varying degrees of match between the words and the concerns of the patients and may have been obtained because little attention has been paid in the past to the semantic associates of the stimuli used that has been judged as non-threatening.

Validity of an emotional Stroop task hinges on equivalence between the emotion and the control words in terms of lexical features related to word recognition (Larsen et al. 2006). If the pain words presented are significantly lower in frequency of use, longer in length, and have smaller orthographic neighbourhoods than words used as controls this could lead to a slowdown as Larsen et al (2006) found with emotional words. This would suggest that if the words used in Stroop research are not lexically balanced, the study results are due to the words used and not due to the effect the words have on the participants (Larsen et al. 2006; Estes and Adelman 2008; Larsen et al. 2008).

Aims

The aim was to identify the most salient words to use in a proposed fMRI Stroop study. The words to be investigated were pain words and positive words which needed to be lexically matched to control or neutral words.

Participants

Following approval from Dyfed Powys Local Research Ethics Committee, twenty patients with diagnosed CNMP, awaiting treatment for their pain and twenty age and gender

matched controls obtained from a volunteer panel were recruited. Participants had to be able to read English and this was their primary language. All had to understand and be able to provide informed consent. Patients had to also have a diagnosis of chronic pain that was due to a musculoskeletal condition and had an average pain score of 50 and above on a numerical rating scale of 0-100 ('No' – 'Worst Possible Pain') over the 3 months prior to enrolment. Exclusion criteria for all participants were those with: serious metabolic, rheumatoid, vascular or diagnosed psychiatric disorders; dyslexia or inability to read written English and inability to give informed consent.

Procedure

In order to establish the words that may produce the most intereference in patients but not controls, participants were asked to read the list of pain words from the McGill Pain Questionnaire (MPQ) (Melzack 1975). Pain-related words (affective and sensory) and a list of words that represented positive emotional states e.g. 'confident', 'motivated', 'able' were rated for salience. Patients were asked to rate the words that best described their pain (affective and sensory words, 0 'does not describe my pain', 1 'mildly accurate description of my pain', 2 'moderately accurate description of my pain', 3 'exact description of my pain') and these were ranked from the highest scoring down to the lowest scoring across the patient group. Controls did not experience any pain. The positive emotional words were rated using the same 0-3 scale by both patients and the controls (0 'does not describe how I feel' to 3 'exact description of how I feel') and these were scored by ranking those that scored highest for the control group and lowest for the patient group to provide a word bias. The top 16 words from each word group were to be used in the imaging study.

Positive, sensory and affective (collectively interference) words were then matched with neutral words (household objects) based on the how often they were used in the English language, word length, and the number of orthographic neighbours (the number of words that are similar to the actual word used after changing a letter) using the English Lexical Project (Balota et al. 2007). Quality of matching was to be confirmed with statistical analysis (Mann Whitney U test). If no lexically balanced household objects existed within the top 16 ranked words, then interference words would be substituted with words placed below the top ranked 16.

Results

There were no statistically significant differences in lexical characteristics tested between the control and interference words. A few of the interference words had to be substituted with words that were placed below the top 16 ranked words as no lexically balanced household object words existed. The sensory words that were rated the highest in the patient group were: Aching, Hurting, Stabbing, Throbbing, Sharp, Shooting, Tender, Dull, Sore, Gnawing, Burning, Pressing, Cramping, Hot, Heavy, Tingling. The affective rated the highest in the patient group were: Tingling, Gruelling, Exhausting, Wretched, Vicious, Nagging, Penetrating, Agonizing, Dreadful, Piercing, Radiating, Intense, Troublesome, Miserable, Annoying, Unbearable

For the positive words, those that scored highest in the control group and lowest in the patient group were: Capable, Motivated, Able, Positive, Enthusiastic, Healthy, Well, Optimistic, Cheerful, Content, Confident, Fit, Active, Achieving, Enjoying, Bright.

The words obtained were then lexically matched to control words and due to lack of appropriate lexical matches, pain words ‘gruelling’, ‘unbearable’ and ‘penetrating’ were substituted with ‘sickening’, ‘killing’ and ‘torturing’. Positive words lost were ‘motivated’, ‘able’, ‘positive’, ‘well’, ‘confident’, ‘fit’, ‘active’ and ‘bright’, substituted with ‘robust’, ‘outgoing’, ‘relaxed’, ‘peaceful’, ‘lively’, ‘rested’, ‘liberated’, comforted’. The final word list with the matched controls is included in the following table (Table 4.1)

Table 4.1: Final word list for Stroop study

Interference Block	*Control Block*	*Interference Block*	*Control Block*	*Interference Block*	*Control Block*
Sensory Interference (Sen Inter)	Sensory Control (Sen Con)	Affective Interference (Aff Inter)	Affective Control (Aff Con)	Positive Interference (Pos Inter)	Positive Control (Pos Con)
1 aching	1 kettle	1 tiring	1 funnel	1 lively	1 fridge
2 tingling	2 armchair	2 torturing	2 saucers	2 comforted	2 lampshade
3 penetrating	3 bookshelves	3 exhausting	3 letterbox	3 liberated	3 calendars
4 hurting	4 ceiling	4 wretched	4 shelves	4 outgoing	4 cabinet
5 tender	5 plates	5 vicious	5 bucket	5 robust	5 ladder
6 pulsing	6 balcony	6 nagging	6 bedding	6 rested	6 sponge
7 stabbing	7 cupboard	7 sickening	7 polishing	7 cheerful	7 textiles
8 cramping	8 carpeted	8 agonising	8 dispenser	8 optimistic	8 appliances
9 tearing	9 laundry	9 dreadful	9 boarding	9 peaceful	9 painting
10 pressing	10 calendar	10 piercing	10 bathroom	10 enjoying	10 bedroom
11 wrenching	11 radiators	11 radiating	11 barometer	11 contented	11 bookcase
12 burning	12 glasses	12 intense	12 mirrors	12 relaxed	12 barrels
13 lacerating	13 tablecloth	13 troublesome	13 screwdriver	13 enthusiastic	13 refrigerator
14 throbbing	14 fireplace	14 miserable	14 fencing	14 achieving	14 container
15 sharp	15 chair	15 annoying	15 clothing	15 healthy	15 crystal
16 heavy	16 frame	16 killing	16 surface	16 capable	16 license

4.2.6 Summary

The ecStroop has resulted from the need to assess cognitive interference and emotional interference within neuroimaging research. It has evolved from a long standing paradigm which has been subjected to a number of different modifications and appears to be a suitable method to use in fMRI studies.

Chapter 5 will illustrate how it has been used to look at pain-related attention in CMSKP and whether it has been a suitable tool to examine this will be presented in the discussion

chapter. A pilot prepared the words to be used attempting to improve the rigor of the study and to address the lack of salience and lexical balancing discussed in previous research.

4.3 PHODA

The stimuli that are developed to address attentional bias, fear and catastrophising must reflect the degree to which stimuli represent an individual's concerns and the stimuli needs to be concrete, unambiguous and posses qualities that reflect real life (Roelofs et al. 2005). There has been support in the anxiety-related literature for pictorial stimuli as they offer advantages over word-stimuli. Pictures are likely to possess greater threat value if chosen appropriately, they can avoid confounds between stimulus threat and familiarity or words and can overcome any ambiguity in the nature of words (Dear et al. 2011).

4.3.1 PHODA development

PHODA was originally developed as a diagnostic tool to determine the perceived harmfulness of different physical activities and movement (Kugler et al. 1999). The tool was developed from 8 possible movements which included lifting, bending, turning, reaching, falling, intermittent load, unexpected movement and long-lasting load in stance or sit with limited dynamics. These were derived from basic movements which included extending, inflecting, rotating, lateral inflecting, compression and traction and 2 manners of moving which were static and dynamic. The 8 possible movements were set against 4 areas of daily occupations which included activities of daily living, housekeeping, work, and sport and leisure time and converted into recognisable and frequent activities instead of in terms of their biomechanics. The list of movements and activities was then tested, corrected and supplemented by several experts on CLBP. This resulted in 100 photographs of daily activities.

Further development of PHODA was undertaken by Leeuw et al (2007b) who developed a shortened electronic version of the PHODA (the PHODA-SeV) consisting of 40 selected pictures. For every basic movement category, activities were selected with variable degrees of rated harmfulness (see Fig.4.6 for a visual representation of PHODA-SeV). Using a computer monitor, patients are asked to 'Please observe each photograph carefully and try to imagine yourself performing the same movement. To what extent do you feel that this movement is harmful to your back?' They are then shown the photographs and requested to drag each photograph along a 'harmfulness thermometer' ranging from 0, not harmful to 100, extremely harmful. A mean total score ranging from 0–100 is calculated as the sum of each rating divided by 40.

This tool is highly standardised and data are automatically stored into an electronic database because of its electronic administration. The basic properties of the original PHODA are adhered to with the exception of the therapist not being present when the patient completes the task. Advantages of this PHODASeV over the original PHODA are its standardized administration, the fact that it is less time-consuming, and its automatic data storage. The PHODA-SeV measures a single factor and has a high internal consistency. The authors contend that the test-retest reliability of the PHODA-SeV over a 2-week time-interval is excellent (2007b). Leeuw et al (2007b) found that the construct validity of the PHODA-SeV is supported by consistent relationships with self-report measures of fear of movement/(re)injury, pain catastrophising, functional disability, and current pain intensity. After correction for the common variance between these constructs, it appeared that PHODA-SeV is specifically related to the degree of fear of

movement/(re)injury. Therefore, the higher the ratings of harm given, the higher the level of fear of movement/(re)injury.

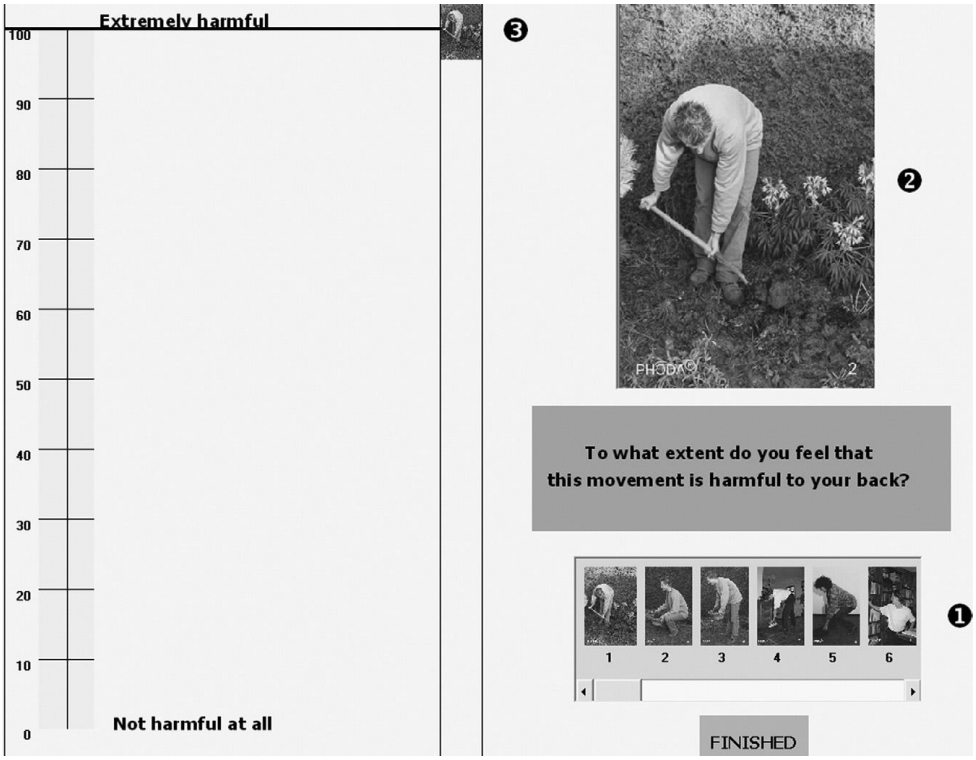


Fig.4.6 Visual representation of the PHODA-SeV.
❶ The photographs of the PHODA-SeV are presented in small format in a row. The patient can select each photograph by clicking on it.
❷ The small photograph that is selected by the patient emerges in large format.
❸ The selected photograph also appears in small format at this position, from which it can be dragged with the mouse to the corresponding value on the thermometer. By this means, all photographs remain visible along the thermometer.
The patient can reposition each photograph at any time, by selecting it with the mouse and dragging it somewhere else.

In further examining the construct validity of PHODA, Trost et al (2009) found that PHODA-SeV clearly distinguished between high and low fear participants. This study modified the original administration of the PHODA so that participants indicated the perceived pain of each physical activity, in addition to its perceived harmfulness. Trost et al (2009) therefore suggested that it may be useful to include assessment of perceived pain in PHODA administration as a greater insight may be gleaned regarding cognitions held by

high fear individuals which may support management decisions. This is supported by Leeuw et al (2007b), as a multiple linear regression found that PHODA-SeV may be specifically related to both TSK score and pain intensity. As a result, PHODA ratings may tap into pain as well as harm judgments.

The PHODA modification undertaken in Trost et al (2009) was based on prior clinical research and therefore, as acknowledged by the authors, does not comprise a formal clinical instrument. Therefore, Trost et al (2009) suggest that comparisons between the tool they modified and the original PHODA and PHODA-SeV are limited and should be interpreted with caution.

4.3.2 PHODA research

PHODA has emerged relatively recently as an assessment instrument in the context of chronic back pain and pain-related fear (Kugler et al. 1999) and has been used in a number of contexts, both clinically and in research. Although the thesis has not addressed management of pain-related attention, fear and catastrophising, to put PHODA in context, it is appropriate to highlight its use outside the confines of the thesis as its popularity has been in the measurement of the effectiveness of exposure in vivo in CLBP (Vlaeyen et al. 2001, 2002a; Vlaeyen et al. 2002b; Boersma et al. 2004; de Jong et al. 2005; Leeuw et al. 2007b; Leeuw et al. 2008).

These studies have used PHODA to establish individual fear hierarchies thereby facilitating the gradual confrontation of feared activities. A number of these studies have observed that PHODA-SeV scores are reduced by in vivo graded exposure intervention (Leeuw et al. 2007b; Leeuw et al. 2008).

4.3.3 PHODA pilot

Introduction

Several factors are thought to be involved in moderating the attentional demands of pain, the strongest and most consistent effects relate to fear, anxiety, and catastrophising (Eccleston and Crombez 1999). Pain-related fear and catastrophising are associated with increased attentional interference, awareness of pain, impaired disengagement from pain, and can moderate the effects of attentional coping attempts (Heyneman, Fremouw et al. 1990; Sullivan, Bishop et al. 1995; Asmundson, Kuperos et al. 1997; Crombez, Eccleston et al. 1999; Keogh, Ellery et al. 2001; Buck and Morley 2006; Van Damme, Crombez et al. 2008).

There are several cognitive behavioural models that try to explain the development and maintenance of pain-related disability in a CMSKP assigning a central role to the concept of pain-related fear (Asmundson et al. 1997b; Asmundson et al. 1999; Al-Obaidi et al. 2000; Boersma and Linton 2006; Leeuw et al. 2007a; Hasenbring and Verbunt 2010; Crombez et al. 2012a; Vlaeyen and Linton 2012). The TSK is a brief questionnaire that measures the extent to which patients with chronic pain experience fear of movement/(re)injury. Although psychometric studies have supported the reliability and validity of the TSK (Goubert et al. 2004c; Roelofs et al. 2004), a limitation is that it does not provide information about which specific movements or activities a patient fears or avoids. Therefore, PHODA may be more appropriate.

The PHODA is an instrument that includes photographs of various daily activities and patients with CLBP have to indicate to what extent they perceive the depicted activities to be harmful to their back. It is anticipated that this tool may be useful in future fMRI

research but will need to be modified to include photographs that have been judged salient to a CMSKP population as well as a CLBP population and also to change the emphasis from harm to perceived pain. It is recognised that while PHODA and the later modification PHODA-SeV are valid and reliable tools, modifications undertaken in this pilot may reduce the ability to compare with the existing research and does not equate to a new clinical tool until further research has been undertaken.

Aims

The aim was to identify the most salient PHODA and neutral photographs to use in a proposed fMRI pain-related fear study.

Participants

Following approval from Dyfed Powys Local Research Ethics Committee, twenty patients with diagnosed CNMP, awaiting treatment for their pain and twenty age and gender matched controls obtained from the School of Psychology volunteer panel were recruited. Ten patients had CLBP and ten CMSKP. Participants had to understand and be able to provide informed consent. Patients had to also have a diagnosis of chronic pain that was due to a musculoskeletal condition or mechanical low back pain and had an average pain score of 50 and above on a numerical rating scale of 0-100 ('No' – 'Worst Possible Pain') over the 3 months prior to enrolment. Exclusion criteria for all participants were: serious metabolic, rheumatoid, vascular or diagnosed psychiatric disorders; dyslexia or unable to read written English; inability to give informed consent.

Procedure

Participants were presented with the PHODA photographs without the original scoring in place and asked to imagine how much pain and anxiety they would feel if they were asked

to complete the activity represented in the photograph and rate both on a scale of 0 – 'no pain' to 3 'severe pain', 0 – 'no anxiety' to 3 'severe anxiety'. The activity photographs were taken from the PHODA library and the resting or neutral photographs were taken from pictures that were available from a number of free-photograph internet sites.

Outcome

We developed a set of appropriate activity photographs (pictures that caused the greatest anxiety and perceived pain in the patient group) and neutral or resting pictures (those that caused the least anxiety and pain in all participants) for use in the main studies presented in this thesis (Chapter 6 and 7): PHODA-MSK for those with CMSKP and PHODA-LBP for those with CLBP. Activity photographs were used if they scored 2-3 in the patient group and 0 in the control group and neutral of rest photographs were used if they scored 0 in both groups.

4.3.5 Summary

The PHODA-LBP and PHODA-MSK has resulted from the need to assess pain-related fear within neuroimaging research. It has evolved from a clinical instrument that is relatively new and not widely researched but has good construct validity. Chapter 6 and 7 will illustrate how it has been used to look at pain-related fear in CMSKP and CLBP patients and use of both modifications as suitable tools to examine pain-related fear be presented in the discussion chapter. A pilot prepared the pictures to be used attempting to improve the rigor of the study and to address the lack of salience in previous research.

4.4 USING IMAGINATION AND RECALL WITHIN RESEARCH

Pain is an unpleasant sensation but at the same time, it is subjective and emotional (Fields 1999). The experience of 'pain' is learned through previous injury or pain-related suffering and individuals are able to imagine pain from past and current experiences even without current or ongoing physical injury (Ogino et al. 2007) during the process of recall. It appears that perception and action are intimately related processes and not functionally distinguishable stages (Percher and Zwaan 2005).

A number of different approaches have been used in using imagery and recall within neuroimaging research. It has been used to elicit cognitive responses such as fear, pleasure, happiness and has also been used as a therapeutic modality in order to improve function and reduce pain. Recall and motor imagery can be used independently of each other or in combination but the choice of paradigm is critical in determining the results. Recall, for the purpose of this thesis is defined as passively viewing a scene in order to elicit an emotional response whereas motor imagery is defined as more active process of concentrating on mentally replicating the task seen or described either from a first or third person perspective, without physically moving (Ross et al. 2003). As PHODA needs to have some context, it appears reasonable to use an imagination task i.e. actively asking participants to imagine the activity shown and recall their feelings and perceptions about undertaking that task.

A number of brain regions have been identified in relation to using imagery within research. The imagery used within the thesis will use a global task in an attempt to elicit a emotional response (PHODA) (recall) , imagery was not used to facilitate a therapeutic response with the aim of improving function or reducing pain (motor imagery). However, a

short review of the common regions involved in imagery in both contexts will be presented for completion.

4.4.1 Motor imagery

Motor imagery is a dynamic state during which a subject simulates an action mentally without any body movement and is subdivided into different modalities including visual and kinaesthetic imagery (Guillot et al. 2008). Motor imagery emphasises mental rehersal of motor skills to improve function (Dickstein and Deutsch 2007). There is some evidence that supports the fact that motor imagery and motor performance share the same neural networks (Decety et al. 1994; Gerardin et al. 2000; Lafleur et al. 2002). However, these networks are not totally overlapping (Ruby and Decety 2001; Solodkin et al. 2004).

The benefits of motor imagery have been found to differ depending on the stages of the acquisition process, the subject's level of expertise and the ability to manipulate accurate and vivid mental images (Guillot et al. 2008). Therefore, it has been proposed that valid and reliable tools are required to evaluate the individual's ability when using motor imagery to maximise the benefit of this as a therapy (Butler et al. 2011). No evidence has been found to support the use of tools to test the ability of subjects when using recall in a research setting used to evoke emotional responses.

In a study examining good and poor imagers, it was found that during a motor imaging finger movement sequence task, both groups were found to recruit similar neural networks involving inferior and superior parietal lobules as well as motor-related regions including the lateral and medial premotor cortex, the cerebellum and putamen (Guillot et al. 2008). Inter-group comparisons showed that good imagers had greater activation in the parietal

and ventrolateral premotor regions; areas involved in mental image generation . Poor imagers recruited orbito-frontal, posterior cingulated cortices and the cerebellum. The authors proposed this reflected difficulties in eliciting vivid mental representation of sequential movements. Guillot et al (2008) concluded that this study had strong implications for motor learning and rehabilitation and that it is crucial to evaluate the individual motor imagery ability to determine optimal training conditions for learning how to use mental practice with motor imagery in neurological rehabilitation. Although this study is important in relation to motor imagery, its results cannot be generalised to the PHODA studies as they are not intended for neurological rehabilitation or research assessment of motor imagery used as a therapeutic tool. Therefore, it is not deemed necessary to test the participants ability to imagine.

The middle and caudal parts of the cerebellum have been seen to be activated bilaterally in subjects imagining playing tennis (Decety et al. 1990). However, Deiber et al (1998) showed that subjects did not activate the cerebellum when imagining simple finger tapping exercises.

Both studies are dated, but helps to explain why differences may occur; the former study involves a whole body activity and the latter, a discrete sequential movement. It may also reflect that the participants were more experienced or better imagers during the tennis imagery than those imagining a finger tapping exercise. Deiber et al (1998) proposed that executive processes, such as execution of a motor task, activate vermis and medial regions of the anterior lobe, whereas the lateral cerebellum plays a role in programming complex actions.

4.4.2 Recall

In a study on healthy volunteers imagining pain while viewing images showing painful events, the pain-rest contrast revealed several increased activations in the right upper bank of the Sylvian fissure corresponding to SII, right anterior insula, caudal portions of the bilateral ACC and the cerebellum (Ogino et al. 2007). When the pain condition was compared to the fear condition, they demonstrated activations in the bilateral SII regions with stronger activations on the right side compared to the left , right insula and cerebellum. Peaks of increased activation were also found in the bilateral lateral occipitotemporal cortices around the fusiform gyrus corresponding to an extrastriate region which is involved in the recognition of objects (Ogino et al. 2007).

Orgino et al (2007) also found increased activation in the rostral part of the posterior parietal cortex in both hemispheres when healthy participants viewed photographs inferring a painful event in the pain-rest condition and in the pain-fear condition. In this study, the posterior parietal cortex, in combination with SII was viewed as being relatively specific to the pain condition compared to the fear condition.

In a study of motor planning, expert golfers demonstrated that their brain activation during imagining their pre-shot routine to be radically different from novices (Milton et al. 2007). The posterior cingulate, the amygdala-forbrain complex and the basal ganglia were active only in novices, whereas experts had activation primarily in the superior parietal lobule, the dorsal lateral premotor area and the occipital area. The authors conclude that extensive practice over a long period of time leads experts to develop a focused and efficient organisation of task-related neural networks whereas novices have difficulty filtering out irrelevant information. An interested analogy could be made here with patients who suffer

chronic pain, could these be seen as ‘experts’? Patients are focused on their pain and may have a highly efficient organisation of task-related networks that respond to pain imagery or imagery that elicits perceived pain.

Fairhurst et al (2012) implemented a recall paradigm exploring and comparing nociceptive and centrally-driven pain experiences in healthy volunteers. Following a range of physical stimuli that included warm, low pain and high pain, subjects were then asked to recall and rate this experience. Recalling the sensory experience activated an extensive network of classical pain processing structures except the contralateral posterior insula cortex. The authors found that subjects could recall and create internally generated experiences of pain and perceived and rated the recalled imagined experience in terms of certain sensory qualities. They found that the quality of the pain event was strongly related to how well subjects could recall the pain event. Also, the recalled imagined pain activated core pain areas that are predominantly more active during physical events; physical events presumably being perceived as more painful. Therefore, in the PHODA imagination task recruiting patients with high pain scores and pain that increases with activity is required to enhance recall during the task. This may negate the need for assessing the ability to undertake imagination tasks.

4.4.3 Summary

On reading the literature surrounding motor imagery, there are some differences between the context the imagination task is going to be used in the studies in this thesis and its use in motore imagery:

- Motor imagery appears to be used as a therapeutic activity whereas PHODA task is used to generate fear, anxiety and catastrophising.

- Motor imagery tends to compares short duration of discrete activities while the PHODA task uses more global activities of daily living.
- The PHODA task involves a single event whereas motor imagery gains therapeutic improvements through repetition of imagined activities.

Motor imagery asks participants to imagine a physical movement, whereas the PHODA task asks participant to imagine how they would feel physically and mentally if asked to do the task.

Imagery appears to be a useful tool to use in neuroimaging research and there is evidence to suggest that imagery can be powerful enough to elicit similar neural networks as if undertaking the task imagined or recalled. If used for therapeutic benefit, or to assess the impact of imagery for therapeutic benefit it is essential that individuals are questioned about their ability to perform imagery. When used to recall an emotion or perception, it appears that it is less important to assess these abilities. However, the literature on motor imagery appears to be extremely useful in helping to explaining neuroimaging results.

4.5 RESEARCH APPROACH AND RESEARCH QUESTIONS

The literature review identified that there had been little research undertaken examining the role of fear, attention and catastrophising within a population of CNMP patients, specifically musculoskeletal and back pain. Therefore, the research approach taken for the studies presented in the thesis is exploratory. Exploratory research is conducted for areas or problems that have not been clearly defined. Exploratory research can support defining future research designs, data collection methods and selection of subjects. As a research method, interpretation of the data should be undertaken with caution and it should not be used to make definitive statements or change clinical practice.

The purpose of the research included in this thesis is to gain familiarity with fear, attention and catastrophising as applied to a CNMP population. The initial exploratory research will help gain familiarity with these concepts as related to pain in order to formulate more precise research problems and develop hypotheses in future research. At present, the research is too general to support the formation of hypotheses; exploratory research was perceived to be useful at this stage in order to support future hypotheses testing and more definitive research approaches.

Cognitive psychology and perception, including research within CNMP populations, has benefited greatly from fMRI studies, and it has been muted that these studies have revolutionised psychology (Ashby and Waldschmidt 2008). The majority of fMRI studies, within this field, has used fMRI as a tool for exploratory research (Ashby and Waldschmidt 2008). There appears to be untapped potential for fMRI as a tool for confirmatory research but a number of problems need overcoming before this can be realised. Ashby and Waldschmidt (2008) suggest these problems include:

- There are problems around predicting BOLD signal changes.
- It is difficult to predict changes in small sets of voxels in a region of interest.
- Problems lie in comparing the observed and predicted BOLD responses selected voxels, and to decide on the basis of this comparison if the model succeeds or fails at accounting for the results of the experiment.
- The boxcar model makes no predictions about which brain regions should show task-related activation.

Therefore, exploratory research has value but limitations need to be addressed. The research aims that are included in each research chapter is in keeping with this approach and when developing the research protocols to address the studies in Chapters 5, 6 and 7, the following research questions were identified:

- Stroop study:
    - Behavioural responses
        - Do patients with CMSK pain have greater response times for interference words compared to matched neutral words in all conditions?
        - How do patients and controls compare in their response to interference compared to control words?
        - How do patients compare to controls in error rates for interference words?
        - How to subjects error rates compare between interference and control words?
    - Brain responses

        - Are there differences in BOLD responses between patients and controls in the amygdala, dorsomedial and dorsolateral prefrontal cortices? This reflects the amount of emotional conflict that arises in the Stroop task.
        - Are there differences in BOLD responses between patients and controls in cortical areas involved in pain perception including ACC, insula, SI, SII and thalamus?

- PHODA and imagination task
    - Are there differences in BOLD responses between patients and controls in regions involved in fear conditioning?
    - Do patients differ from controls in BOLD signal changes in regions involved in the sensory discriminatory dimensions of pain - SI and SII, thalamus and insular cortex (Bornhovd et al. 2002)?
    - Do patients differ from controls in BOLD signal changes in regions involved in the affective-motivational dimensions of pain - insular cortex and rostral ventral ACC (Whalen et al. 1998)
    - Do patients differ from controls in BOLD signal changes in regions involved in cognitive evaluative dimensions of pain - parietal and prefrontal cortices and caudal ACC (Vogt et al. 1995).

CHAPTER 5: AN FMRI STROOP STUDY COMPARING PATIENTS WITH CMSKP AND HEALTHY CONTROLS

5.1. ABSTRACT

Chronic musculoskeletal pain (CMSKP) is attentionally demanding affecting how individuals function and behave. We used blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) to compare brain responses in patients with CMSKP (n=15) and healthy controls (n=14) to a pain-related counting (prcStroop) and a positive-emotional counting (pecStroop) Stroop task. We aimed to identify whether CMSKP patients had a different BOLD response in regions involved in pain perception and emotion. Bilaterally, there were significant differences in response to the pain words used between patients and controls in regions associated with pain and emotion, including the anterior cingulate cortex, insula and primary and secondary somatosensory cortex. In these areas BOLD differences were seen in patients compared to controls when viewing pain related words but not when viewing control or positive-emotional words. There was no difference in response times between patients and controls in either Stroop task. Patients made significantly more errors in word counting than controls but error rates were similar for pain and control words. The results suggest that the BOLD differences between patients and controls were due to the pain related words and not specifically related to a Stroop interference effect.

5.2 INTRODUCTION

Chronic musculoskeletal pain (CMSKP) poses a major clinical, social and economic problem (Woolf and Akesson 2001; Torrance et al. 2010) and can be complex to manage (Foster et al. 2003b). The impact of pain on daily life is more closely associated with cognitive, affective and behavioural factors than with identifiable objective pathology

(Loeser and Melzack 1999). Pain interrupts, distracts, and interferes with cognitive functioning (Eccleston 1994) because it grasps attention. Fear, anxiety and catastrophising are the strongest and most consistent moderators of pain-related attention (Eccleston and Crombez 1999; Main et al. 2010). Although attentional processes are clearly important in pain perception, the underlying mechanisms are not fully understood, particularly in the context of CMSKP.

Neuroimaging has improved our understanding of how cognition, emotion and context influence pain perception (Apkarian et al. 2004b; Tracey and Mantyh 2007; Baliki et al. 2008) and has important potential applications for clinical pain. However, it has not been exploited, especially within the CMSKP population, as this area of research is still in its infancy (Wartolowska and Tracey 2009). The majority of MRI work to date has focused on acute, experimentally induced pain in healthy volunteers, where the meaning of pain is different from CMSKP (Crombez et al. 1999a; Buck and Morley 2006) and the pain-related changes in brain structure and functioning (Apkarian et al. 2004b; Baliki et al. 2008) seen in chronic pain patients are not present in the healthy volunteers.

The Stroop paradigm focuses on the fact that cognitive interference occurs when the processing of one stimulus feature impedes the simultaneous processing of a second stimulus and is a well established paradigm for assessing attentional bias (Derbyshire et al. 1998; Crombez et al. 2000). It has been used in chronic pain populations to establish the degree to which patients attend to pain-related information (Crombez et al. 2000; Beck et al. 2001; Roelofs et al. 2002; Andersson and Haldrup 2003). However not all studies show an attentional bias to pain-related and negative interference words and the specificity of effects to chronic pain (versus healthy controls) has been debated (Asmundson et al.

1997a). Previous anxiety research has shown that positive words (describing a state that is desired but feared will never be achieved) provide as much interference as negative words (threatening words) and these interference effects are attributable to the extent to which the words used are related to the likely emotional concerns of patients (Mathews and Klug 1993). Therefore, positive words may be useful in CMSKP studies to address previous debates.

Areas of the brain activated in patients compared with controls during pain-related Stroop studies include pain and emotion-related centres such as the primary (SI) and secondary (SII) somatosensory cortices, prefrontal cortex, insula and anterior cingulate cortex (ACC) (Bantick et al. 2002; Seminowicz et al. 2004). Similar results have been seen in neuroimaging studies that have used pain-related words without the Stroop paradigm (Gu and Han 2007b; Richter et al. 2010).

The pain-related (prcStroop) and positive-emotional (pecStroop) tasks are variants of the emotional counting Stroop for neuroimaging studies (Bush et al. 2006; Whalen et al. 2006) and were considered appropriate tools to be used in CMSKP patients. This study aims to compare brain responses to prcStroop and pecStroop words between patients with CMSKP and pain-free controls using fMRI. Specifically we anticipate enhanced responses in CMSKP patients, compared to healthy controls, in pain (prcStroop) and emotion (prcStroop and pecStroop) related brain regions.

The second aim is to see if a behavioural attentional bias is present, signified by differences in motor response times (RTs) and accuracy of responses between patients and controls when viewing pain related and positive words.

5.3 METHODS

5.3.1 Participants

Following Dyfed Powys Research Ethics Committee and local Research and Development Committee approval, thirty participants provided informed written consent and were recruited for the study. Fifteen patients were recruited from a pain management programme and a multidisciplinary pain clinic in South Wales and 15 matched healthy (pain-free) controls were recruited from a volunteer panel. Patients had been assessed by a pain specialist because of the complex nature of their condition and as primary care management was ineffective and deemed suitable for specialist pain treatment and were awaiting this treatment. Criteria for patient inclusion in the study were: a physician-diagnosis of chronic non- malignant pain (International Association for the study of Pain) (Merskey and Bogduk 1994) and pain had to be of a non-inflammatory musculoskeletal origin. Patients had to have an average pain score of 50 and above on a numerical rating scale of 0-100 ('No' – 'Worst Possible Pain') over a three month prior to enrolment. Patients were only included if lying supine was a position that did not evoke pain and considered that they would be comfortable in the scanner. An additional criterion for all participants was English was the first language. Exclusion criteria for all participants were serious metabolic, rheumatoid, vascular or diagnosed psychiatric disorders, dyslexia or unable to read written English, inability to give informed consent, contraindications to MR scanning and claustrophobia. Regular analgesic regimens were not altered and patients continued to take their routine analgesia as prescribed.

5.3.2 Questionnaires and assessment

A least a month prior to scanning, participants were asked about their analgesic medication and intensity of pain. Patients rated their current pain on a numerical rating scale from 0

(no pain) to 100 (worse possible pain). Using the same scale, they also rated their worst pain, least pain and pain intensity over the last week and last 3 month period and the degree to which the pain interfered with activities of daily living over the previous week. The 101-point (i.e. 0–100) NRS of pain intensity is recommended as a core outcome measure in clinical trials of chronic pain (Dworkin et al. 2005). The Hospital Depression and Anxiety Scale (HADS) (Zigmond and Snaith 1983) was used to assess the level of anxiety and depression in both groups. HADS was originally developed by Zigmond and Snaith (1983) and is a fourteen item scale that generates ordinal data. Seven of the items relate to anxiety and seven relate to depression and it is a tool for the detection of anxiety and depression in people with physical health problems (see appendices for HADS).

5.3.3 PrcStroop and pecStroop development

The Stroop task is a well-established paradigm for assessing attentional bias (Derbyshire et al. 1998; Crombez et al. 2000). The prcStroop developed from the emotional counting Stroop (Beck et al. 2001; Bantick et al. 2002; Weissman-Fogel et al. 2011), is suitable for block-design fMRI studies and pain research (Bush et al. 2006; Whalen et al. 2006). Pain-related words (affective and sensory) from the McGill Pain Questionnaire (Melzack 1975) and a list of words that represented positive emotional states (e.g. ‘confident’, ‘motivated’, ‘able’) were rated for salience in a pilot study (see Section 4.2). The decision to use positive words rather than negative ones was taken because a previous study (Mathews and Klug 1993) found that positive emotional words caused as much interference with Stroop performance in anxious patients as negative words. Given the pain Stroop research to date has focused on negative words and has led to inconsistent findings, it was decided to examine positive words. The aim of this process was to maximise the differences in the

salience of the stimuli for CMSKP compared with controls (see Table 4.1, section 4.2 for final word list).

Positive, sensory pain-related and affective pain-related (collectively 'interference') words were then matched with neutral words (household objects) based on how often they were used in the English language, word length, and the number of orthographic neighbours (the number of words that are similar to the actual word used after changing a letter) using the English Lexical Project (Balota et al. 2007) database. Quality of matching was confirmed by statistical analysis (Mann Whitney U test) which demonstrated no statistically significant differences between the control and interference words. A few of the interference words had to be substituted with words that were placed below the top 16 ranked words where no lexically balanced household object words existed.

5.3.4 Imaging paradigm for prcStroop/pecStroop

The implemented protocol was based on the research by Whalen and colleagues (Whalen et al. 2006); who originally validated the emotional counting Stroop for fMRI investigations and led to the development of the prcStroop and pecStroop. On each trial, subjects viewed sets of one to four identical words on a screen and were instructed to report the number of words (see Fig.5.1).

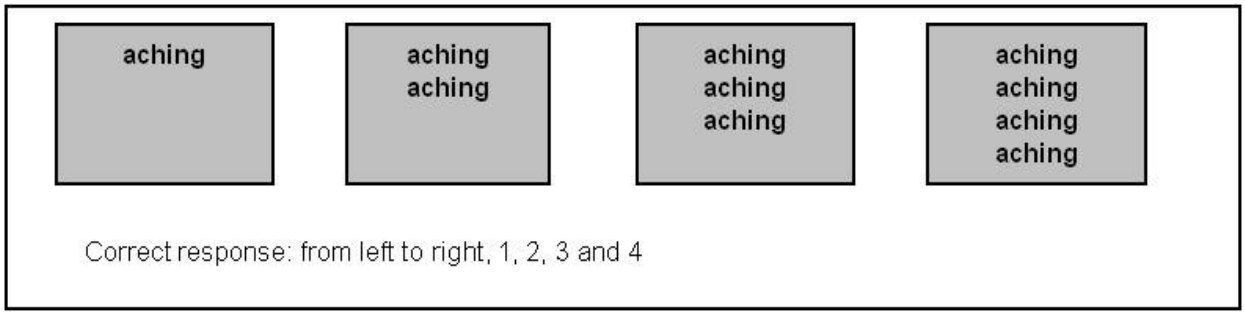
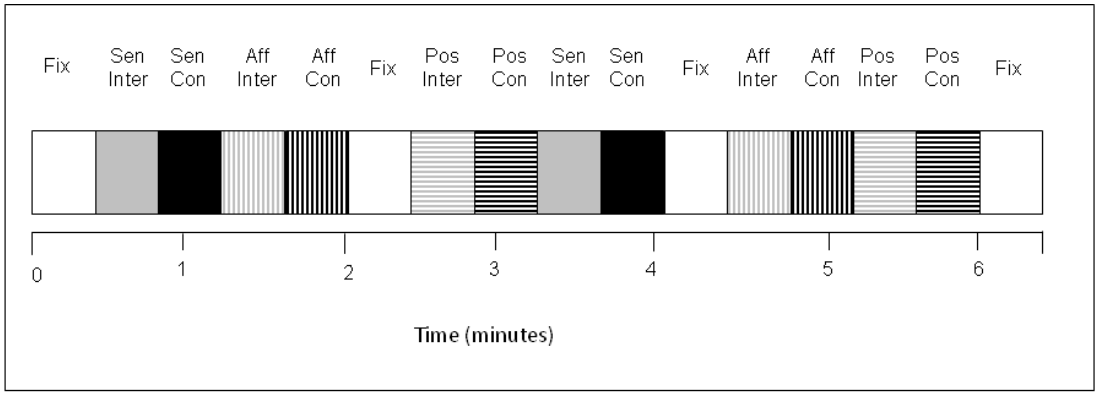


Fig.5.1. Example of individual stimuli

The correct answers were always 1, 2, 3, or 4. Subjects were instructed to 'work as quickly as possible, but not to sacrifice accuracy for speed, and do not blur vision in an attempt to make the task easier – keep the words in sharp focus'. Subjects made their response using two response boxes, one held in each hand. Subjects used their middle and index finger of their left hand when their response was 1 and 2, respectively, and the index and middle finger of their right hand when their response was 3 and 4, respectively. Each trial lasted 1.5 s and there were 16 trials in a 24 s block. Each run included 16 blocks, consisting of 2 blocks for each word-type, 2 blocks for each corresponding control word set and four fixation-cross (rest) blocks (24s duration) presented on the screen at the beginning and end of both runs and twice within a run (Fig. 5.2). A block consisted of one word type and the word type and appearance was randomised and counterbalanced across subjects, within runs and across runs and subjects. Subjects completed two runs of the combined prcStroop/pecStroop during MR imaging. Each run lasted 414 s so the whole session could be administered in less than 15 minutes, with a short break between the two runs.



Key
Fix = Fixation Cross
Sen Inter = Sensory Interference Words
Sen Con = Sensory Control Words
Aff Inter = Affective Interference Words
Aff Cont = Affective Control Words
Pos Inter = Positive Interference Words
Pos Cont = Positive Control Words

Fig.5.2. Block design for prcStroop and pecStroop task

5.3.5 Behavioural data analysis

Questionnaire data, pain and HADS scores, are analysed with Mann-Whitney tests because of the non-parametric nature of the data obtained and the median and inter-quartile range will be used to describe the central tendency and spread of non-parametric data. To test for differences in Stroop RTs, a repeated-measures analysis of variance (RM-ANOVA) was used. HADS for each subject was included as a covariate as suggested in a previous Stroop study (Pincus et al. 1998) since depression and anxiety can result in an attentional delay to pain words. The dependent variable was the RT and the fixed factor was the study group. Run 1 and run 2 were analysed separately to test for habituation and to inform the imaging analysis.

The number of accurate responses was compared between groups using Student's t-test. Participants were judged to be responding accurately if the number pressed on the button box equated to the number of words presented on the screen. Trials without a response were excluded from the RT analysis. Significance was set at P-value of less than 0.05. Statistical analysis was performed using SPSS software version 16.0 for Windows (SPSS, Chicago, Illinois, USA).

5.3.6 Participant training

Prior to scanning, subjects completed a 96 s practice version of the task within a realistic mock scanner. This was to familiarise subjects with the tasks and to reduce anxiety and fear for those that had not been in a scanner previously. All words used in the practice session were different to those presented in the scanning session. Responses from the training session were reviewed to ensure that the subject understood the task.

5.3.7 Imaging

Imaging was performed on a 3-T MRI system (HDx, General Electric Healthcare, Waukesha, Wisconsin, USA) using an 8-channel receive-only head coil. Functional MRI data were acquired with a gradient-echo, echo-planar imaging sequence, scanning parameters were: repetition time (TR)/echo time (TE) = 3000 ms/35 ms, 20.5 cm field of view, acquired on a 64 x 64 matrix with 53 contiguous 3.2 mm slices. Each run consisted of 138 repetitions. For anatomic localization, a T1-weighted, three-dimensional fast-spoiled gradient echo acquisition was performed, with a voxel resolution 1x1x1 mm^3 (scanning parameters included: TR/TE = 7.8/3 ms, 450 ms inversion time, 256 x 128 acquisition matrix) for each participant.

5.3.8 Image analysis

Analysis of BOLD fMRI data was performed using FEATv5.98 (FMRI Expert Analysis Tool), part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Registration to each subject's high resolution structural image was performed using FLIRT (Jenkinson and Smith 2001; Jenkinson et al. 2002) and registration to standard space was then performed using FNIRT nonlinear registration (Andersson et al. 2007). The functional data for each subject was motion corrected (MCFLIRT (Jenkinson et al. 2002)) and fieldmaps were processed using PRELUDE+FUGUE (Jenkinson 2003, 2004) to correct for field distortions in the functional data. Data was smoothed spatially with a Gaussian kernel with a FWHM of 5mm and filtered with a highpass temporal filter (cut off of 100 s) and the data was demeaned on a voxel-by-voxel basis across the time course. At the voxel level, the signal was linearly modelled (FILM-FMRIB's Improved Linear Model) with autocorrelation correction (Woolrich et al. 2001).

Data were initially analyzed at the individual subject level in each run, modelling data as the convolution of the word blocks and a haemodynamic response function (a gamma-variate). A second-level, fixed effects analysis was performed to combine the two runs for each subject. A third level, mixed effects analysis, including HADS score as a covariate, was performed to indicate differences between patients and control groups.

Each interference word group (sensory pain, affective pain and positive emotional) was compared with the corresponding control word group. The affective and sensory interference words were also examined when combined together to reflect the way the McGill Questionnaire is used clinically as the word groups are not separated to provide a final score (Melzack 1975). Combining of scores has been undertaken in previous Stroop research (Snider et al. 2000; Pincus and Morley 2001).

For all analyses, statistic images were thresholded using clusters determined by a Z>2.3 and cluster corrected at a significance threshold of p=0.05 (Worsley 2001). FLAME (Woolrich et al. 2004) was used for the higher level analysis and examined affect and sensory words which formed the prcStroop and positive words which formed the pecStroop.

FSL was used to view the statistical parametric maps and the areas of BOLD signal differences were identified by using the Harvard-Oxford cortical and subcortical atlases. Functional regions of interest were identified as the intersection of the anatomical mask from the Harvard-Oxford atlas and the thresholded z-statistic image and the average signal change for each region for each group was plotted for illustrative purposes. No further statistical tests were used for or applied to these results.

5.4.1 Demographic data and questionnaires

Twenty nine participants were scanned (9 male, 20 female), age range 25 to 83 years old, including 15 patients with pain and 14 age-matched controls. One patient did not have a control as the control was unable to tolerate the scanner and withdrew from the study. The groups were similar in respect to marital status, work status, years in school and dependents.

Pain scores and HADS were compared between groups with a Mann-Whitney test. As expected, patients and controls differed in pain scores and patients median current numerical rating score was 60 (range 40 – 70) (0 – 'no pain', 100 'worst possible pain') (scale counted in units of 10). The HADS score illustrated that patients were more depressed and anxious compared to controls (see Table 5.1).

Patients' clinical characteristics are described in Table 5.2. Of those scanned, 2 patients and 1 control were left handed. All patients but two had previously undergone a diagnostic MRI scan and 9 volunteers had previously been scanned as participants in previous studies or for non-pain related clinical reasons. All reported being comfortable in the scanner.

Table 5.1: Pain Scores and HADS

	Patient Median values (25th, 75th percentiles)	Control Median values (25th, 75th percentiles)	*p*= Value Mann-Whitney test
Current pain 0 (no pain) – 100 (worst possible pain) NRS	60 (40-70)	0 (0-0)	<0.001
Worst pain (past week) 0 (no pain) – 100 (worst possible pain) NRS	90 (70-95)	0 (0-0)	<0.001
Least pain (past week) 0 (no pain) – 100 (worst possible pain) NRS	35 (25-54)	0 (0-0)	<0.001
Pain intensity (past week) 0 (no pain) – 100 (worst possible pain) NRS	64 (50-70)	0 (0-0)	<0.001
Pain intensity (average 3months), 0 (no pain) – 100 (worst possible pain) NRS	64 (50-70)	0 (0-0)	<0.001
Pain disturbance (past week) 0 (no pain) – 100 (worst possible pain) NRS	61 (50-85)	0 (0-0)	<0.001
HADS Total score < 7 normal, 8-10 borderline abnormal, >11 abnormal	19 (13-23)	5 (1.5-9.75)	<0.001
HADS Anxiety scores	10 (6-13)	2.50 (0.75-6.75)	<0.001
HADS Depression scores	7(4-11)	1.50 (0-3.25)	<0.001

Table 5.2: Description of the patient group

Patient	Age	Pain sites	Duration of pain in years	Current medication
1	29	Knees	2	Weak opioids, NSAIDS, antidepressant pain adjuvant
2	59	Back, neck	1	Weak opioids
3	65	Shoulders, hips	3	Strong opioids, antiepileptic pain adjuvant
4	25	Knees, hips	1	Strong opioids, NSAIDS, paracetamol, antiepileptic and antidepressant pain adjuvants, lidocaine patch
5	60	Back, knees	3	Weak opioids, paracetamol, antiepileptic pain adjuvant, lidocaine patch
6	61	Back, feet	4	Weak opioids, NSAIDS, antiepileptic pain adjuvant
7	83	Major joints	20	Weak opioids, NSAIDS, antiepileptic pain adjuvant, lidocaine patch
8	76	Major joints	5	Weak opioids
9	65	Major joints	25	Weak opioids
10	71	Back, shoulders	25	Weak opioids, NSAIDS antidepressant pain adjuvant
11	62	Back, shoulders	1	Weak opioids
12	38	Back, neck	10	Weak opioids, lidocaine patch
13	64	Major joints	10	Strong opioids, antiepileptic pain adjuvant
14	56	Back and neck	5	Weak opioids
15	55	Back, neck	15	Weak opioids

5. 4.2 Behavioural responses to Stroop

There were no statistically significant RT differences for any word group (i.e., sensory, affective or positive word types, control or interference condition) between patients and controls in individual runs or combined runs. There were no differences between run 1 and run 2. Comparison of the accuracy of responses showed significant differences between patients and controls (run 1, p= 0.001; run 2, p= 0.006). Patients were more likely to press a number on the button box that did not agree with the number of words presented on the

screen and they were equally inaccurate in the responses to the interference words as they were to the control words. There were no patterns to the inaccuracies in that they were not specific to any word block.

5.4.3 fMRI results

The HADS was used in the imaging data analysis to ensure that the study was primarily focussed on pain by accounting for co-variation with anxiety and depression. There were no behavioural differences between the two runs of the Stroop task and imaging analysis and results were pooled across runs (Bush et al. 2006). Whole brain analysis revealed that the interference affective pain words compared to control words or positive emotional words compared to control words showed no differences between the patients and controls. The sensory pain interference words compared to control words showed increased BOLD signal change in patients relative to controls in the right insular cortex (peak voxel at x 32, y16, z -6, z-stat 2.78), right frontal operculum (peak voxel at x 44, y 18, z 6, z-stat 3.09) and right central operculum (peak voxel at x 40, y-8, z 16, z-stat 2.84) (Fig.5.3) in the third level analysis.

The affective and sensory MPQ words (prcStroop) were combined in the second level analysis and in the third level analysis, positive BOLD responses were observed in centres involved in pain, emotion and attention for pain words compared to control words in patients compared to controls (see Table 5.3, Figure 5.4.a,b,c and d).

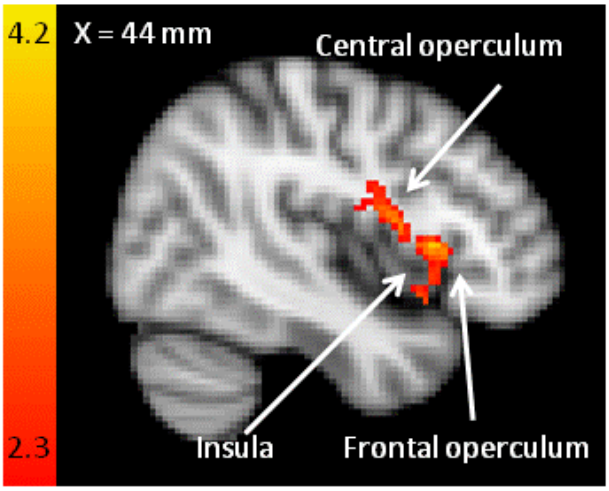
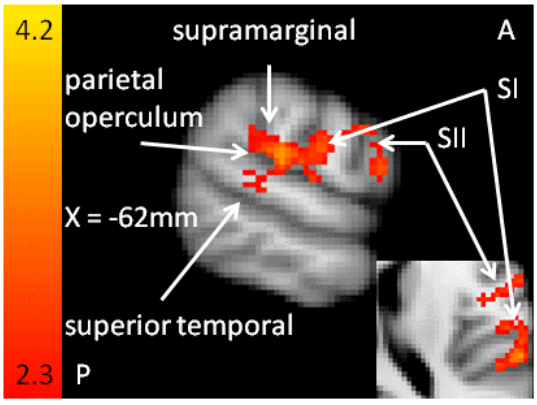


Fig.5.3 Sensory word BOLD responses
Map comparing activation during prcStroop task with control task between the patient and control groups. Patients with CMSKP have significantly different BOLD activation when sensory words are used in a prcStroop task. Each z-statistic map represents these group differences in a whole brain analysis. The colour bar shows the scale of the Z-statistic (2.3 – 4.2).

Fig.5.4 Statistical parametric maps comparing activation during prcStroop task
Comparing prcStroop task with control task between the patient and control groups. Patient with CMSKP have significantly different BOLD signal changes in sensory-discriminatory pain related regions when undergoing a prcStroop task using sensory and affective pain words compared to the control words. Each z-statistic map represents these group differences in a whole brain analysis. The graphs show the percentage signal change (interference words – control words) with the error bars representing standard deviations across subjects. The images are a combination of anatomical and functional data and the graphs represent the direction and magnitude of the signal change within the region and were therefore not tested for statistical significance. This avoids distorted descriptive statistics and invalid statistical inference.The colour bar shows the scale of the z-statistic (2.3 – 4.2).

Fig 5.4a



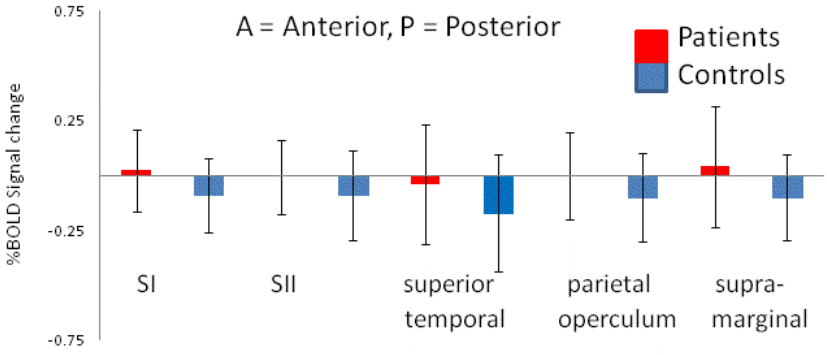
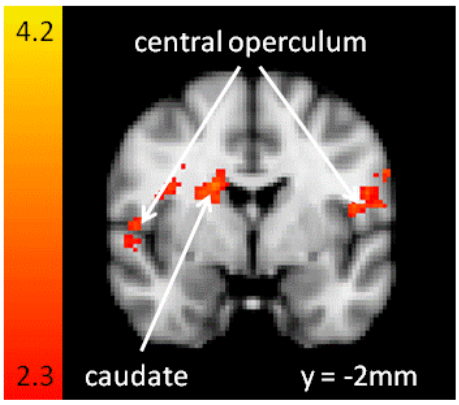


Fig 5.4b



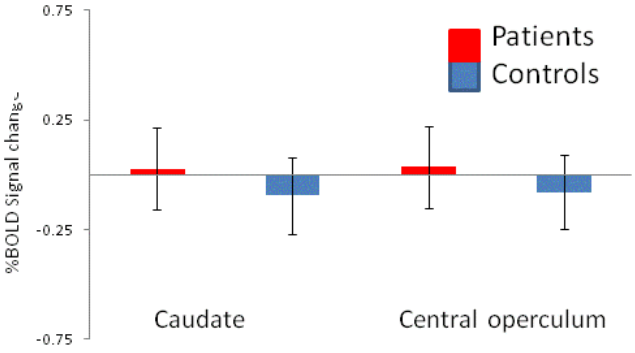
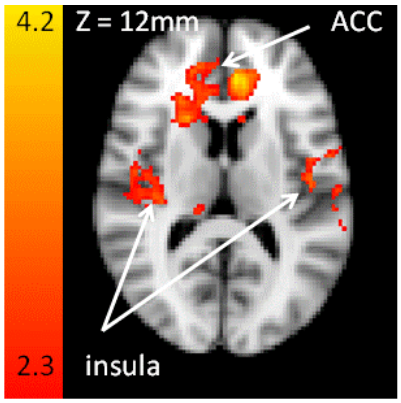


Fig 5.4d



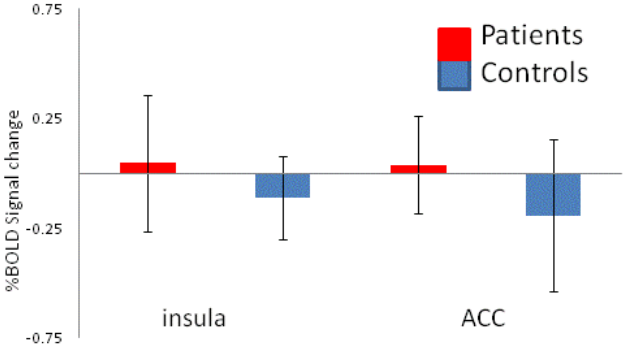
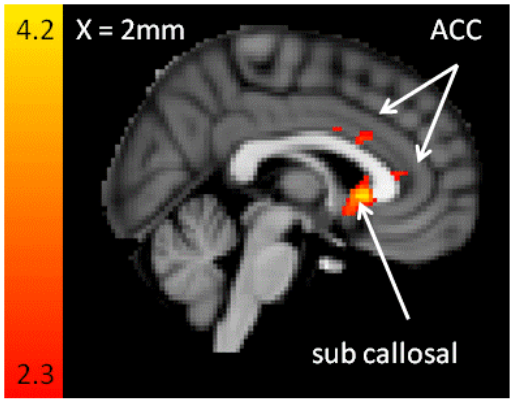
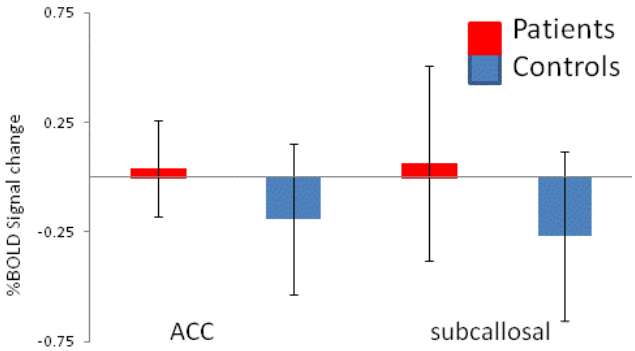


Fig 5.4c





Some of these centres responded bilaterally, others were lateralised to one hemisphere. Bilaterally, BOLD signal response differences were seen in the patient group (interference compared to control words) compared to controls in the ACC, insula, Heschl's gyrus, parietal operculum, central operculum, SI, SII, planum temporale, anterior supramarginal gyrus, subcallosal cingulate cortex and paracingulate cortex. In the right hemisphere, there was an increased BOLD response in the caudate, posterior supramarginal gyrus, superior temporal gyrus, left hemisphere, and in the frontal pole in the patients relative to the controls. [There were no differences in BOLD responses between patients and controls to positive interference words or control words (i.e. in the pecStroop task).]

Appendix 6 contains the statistical parametric maps for the within group differences and descriptive text.

Table 5.3: Group differences for the affective and sensory words vs. control words. Anatomical locations and peak activation co-ordinates (in MNI 152 TI 2mm brain) extracted from brain regions that were found to be significantly different between patients and controls (patients > controls) at Z>2.3 and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
BOLD responses patients > controls				
ACC (L)	-6	36	10	3.34
ACC (R)	8	44	10	2.70
Caudate (R)	18	-2	22	3.15
Central operculum (L)	-48	-14	2	2.83
Central operculum (R)	48	-8	12	2.84
Frontal pole (L)	-20	54	-2	3.36
Heschl's gyrus (L)	-44	-14	2	2.91
Heschl's gyrus (R)	38	-22	12	2.91
Insula cortex (L)	-42	-14	8	2.66
Insula cortex (R)	38	-12	12	2.61
Paracingulate cortex (L)	-10	42	12	3.60
Paracingulate cortex (R)	14	46	12	3.29
Parietal operculum (L)	-58	-28	18	3.02
Parietal operculum (R)	52	-26	20	2.72
Planum temporale (L)	-60	-34	22	2.72
Planum temporale (R)	54	-30	20	2.71
SI(L)	-62	-16	18	2.65
SI(R)	54	-16	32	2.86
SII (L)	-62	4	18	2.81
SII (R)	44	-16	38	2.42
Subcallosal cortex (L)	-2	16	-2	2.99
Subcallosal cortex (R)	2	14	-2	3.23
Superior temporal gyrus, posterior division (R)	66	-34	20	2.68
Supramarginal gyrus, anterior division (L)	-62	-24	18	2.59
Supramarginal gyrus, anterior division (R)	54	-18	28	2.68
Supramarginal gyrus, posterior division (R)	66	-38	20	2.72

5.5. DISCUSSION

To our knowledge, this is the first study that demonstrates pain words used in a prcStroop task result in BOLD signal differences between CMSKP patients and controls in pain processing centres which commonly are seen when a physical pain stimulus in used.

BOLD signal differences were seen bilaterally in the patient group compared to the control group in pain-related regions including the ACC, insula, parietal operculum and SI, SII. No differences in BOLD signal were seen between the patients and controls in the positive interference words. Response time differences were not found between patients and controls for interference words which we interpret as the imaging results highlighted specific differences in the processing of pain-related information that were not observable in the behavioural Stroop data.

Whalen et al (2006) proposed that in an emotional counting Stroop, the patient group should demonstrate RTs that are greater for interference trials than for neutral trials and RTs should not be greater for interference trials than for neutral trials for healthy control subjects. They proposed that the ACC would coincide with greater response latencies and healthy participants would show a typical 'deactivation' in the pregenual/subgenual ventral ACC, PCC and hippocampus.

In terms of the behavioural data, there were no differences in the RTs between patients and controls for all words or when comparing the interference words and control words in each group, but response accuracy was lower for patients. In a typical 'Stroop effect', impaired response times and/or accuracy would be expected for words that are attentionally demanding. The findings of previous studies using pain-related versions of Stroop have been equivocal; some have not demonstrated differences in response times (Duckworth et al. 1997; Pincus et al. 1998; Weissman-Fogel et al. 2011) while others have found attentional bias for pain words in patients but not controls (Crombez et al. 2000; Roelofs et al. 2002).

The fact that patients were equally poor in accurately responding to both interference and control words suggests a more general impairment rather than one specific to pain, and therefore does not indicate a 'Stroop effect' per se. The cognitive effects of analgesics such as opioids, antidepressants and anticonvulsants in the pain group cannot be ruled out.

In addition, the neuroimaging results did not concur with the emotional Stroop study of Whalen et al (2006). Patients did have different BOLD responses in the ACC to the prcStroop but not the pecStroop and this response was not linked to increased RT latencies. It may be that the Stroop paradigm was not sensitive enough to detect behavioural effects hence the lack of Stroop effect. The results may also indicate a degree of neural compensation in patients during the behavioural task in order to perform adequately. However, the BOLD responses to pain words did produce neural differences in patients compared with controls, which may illustrate that patients were attending to pain-related information.

Pain has multiple dimensions, including the sensory-discriminative (lateral pain pathway), affective-motivational (medial pain pathway) and cognitive-evaluative components. The sensory-discriminative component involves the lateral pain pathway and the cortical areas SI and SII (Seminowicz et al. 2004). These two regions showed different BOLD response in patients compared to controls. SI is considered important for attentional aspects of pain processing (Worthen et al. 2011) and sensory localization and intensity discrimination (Bushnell et al. 1999). SII has been shown to be activated in rating pain intensity of actions depicted as words (Gu and Han 2007a), and in combination with the insula, may have a role in pain discrimination (Brooks et al. 2002) and the memory of pain (Albanese et al. 2007). These combined results support our findings that somatosensory activity can be

modulated by processing pain words and that noxious stimuli are not necessary to activate some of the major regions that process the sensory-discriminatory component of pain. The right caudate is engaged during evaluation of spatial locations of noxious stimuli (Oshiro et al. 2007), and showed increased activation in the patient group compared to the controls during the presentation of the pain interference condition. This may illustrate that sensory features of pain extend beyond the somatosensory cortices in patients with CMSKP.

The insula receives its major input from the lateral system but projects to the limbic system (Treede et al. 1999). The anterior insula (Peyron et al. 2000; Porro et al. 2002) and the ACC (Peyron et al. 2000; Bantick et al. 2002; Rainville 2002) are associated with the evaluative-cognitive and affective-motivational aspects of pain. The insula is activated during painful compared to non painful touch (Price 2000; Apkarian et al. 2005), in anticipation of pain (Ploghaus et al. 1999), pain empathy (Singer and Frith 2005) and stimulation of the insula evokes painful experiences (Ostrowsky et al. 2002). The ACC, is an area involved in pain, pain affect and with the evaluation of emotional stimuli (Phillips et al. 2003). Therefore, it is unsurprising that these regions showed different BOLD signal changes in patients compared with controls given that pain words were used in the present study. Our data suggest that pain-related words, in the absence of induced noxious stimulation, can activate the areas of the brain associated with affective-motivational aspects of pain in CMSKP patients.

Accompanying the above key regions, the parietal operculum and inferior parietal lobe were also seen to have BOLD signal differences between patients and controls. The parietal operculum is activated when visual pain stimuli are used (Jackson et al. 2006b; Ogino et al. 2007; Benuzzi et al. 2008) and has a substantial role in the cortical

representation of pain (Treede et al. 2000). Combined with the inferior partietal lobe (supramarginal gyrus) it is likely to play a significant role in attention to noxious stimuli (Duncan and Albanese 2003). We suggest that these regions showed BOLD response differences in patients compared to controls because patients were assessing the unpleasantness of their pain triggered by the pain words.

The cognitive-evaluative component of pain involves evaluation and interpretation of the meaning of pain and emotional distress. BOLD signal differences were seen in patients compared to controls in the central operculum bilaterally and in the left frontal pole. The central operculum and frontal pole (Bonda et al. 1996) are involved in memory processing and the paracingulate is involved in reality monitoring in relation to memory processing (Buda et al. 2011). We propose the differences in these regions are related to the salience of the pain words for patients but not controls. The subcallosal cingulate cortex (and caudate) is implicated in late-life depression (Kenny et al. 2010) and BOLD signal differences occurred in the patient group compared to the controls during the presentation of the pain interference condition. As anxiety and depression were adjusted for in the statistical analysis, we suggest this result was due to the patients evaluating their pain, as the subcallosal cingulate cortex has a role in fear (Dunsmoor et al. 2011). Given that attending to pain is motivated by fear, the BOLD signal differences in patients but not controls in this region would be expected.

The difference between the neuroimaging and behavioural Stroop data in the present study highlights the importance of neuroimaging in revealing information about differences underlying cognitive and affective processes in patients with CMSKP that are not always observable using behavioural data. Differences between behavioural and neural results

implies that reaction times and accuracy may be imperfect measures of cognition (Wilkinson and Halligan 2004). In imaging studies of pain words using alternative paradigms to Stroop (Gu and Han 2007b) changes in centres involved in pain perception have been observed, although direct comparison with our data is difficult due to use of a healthy subjects and different tasks. Nonetheless, it is clear that emotion as well as cognition is important in processing pain-related information and the use of pain words may be useful in future neuroimaging chronic pain research.

There are a number of limitations. The BOLD signal changes provides only an indirect measure of neural activation (Ogawa and Lee 1990; Ogawa et al. 1990) and the BOLD signal lags behind the neural activation that is assumed to drive the BOLD response. Button box response could also have had an impact on the BOLD responses seen, although this is unlikely as responses were balanced between the 2 button boxes. The use of a positive word task appeared to be innovative but in order to assess validity, a negative, non pain word task should also have been included to disassociate the effects of true interference from negative and pain words compared to positive words. Patients undertaking this study were not asked to stop their opioids and therefore, the behavioural responses seen may have resulted from opioid use and may have an impact on the results.

Our study has shown that patients with CMSKP attend to pain-related information differently from matched controls, involving BOLD signal changes in regions known to process pain. These regions are involved in pain, emotion and attention to pain and have been demonstrated to have behavioural consequences and contribute to pain chronicity (Wang et al. 2009; Henschke et al. 2010). Behavioural measures used in Stroop may be testing different attentional processes than those revealed by the neuroimaging (this has

been discussed within the Stroop literature review, see 2.1.2). Performance of the task maybe similar, but the way the brain is dealing with the information may be different. Therefore, neuroimaging may be beneficial in identifying which behavioural tasks more accurately reflect neural processing and could in the future support the development of more robust clinical assessment tools. The use of a pain word task is non-invasive, does not require pain induction, and is suitable for use in FMRI studies.

The population in this study also participated in the next study (Chapter 6) as we wanted to establish if images produced different BOLD responses than words in attending to pain related information and in attempting to identify the neurocorrelates of fear and catastrophising. It has been mooted in the review that the TSK lack sensitivity because it uses words rather than images and hence why the study discussed in the next chapter was undertaken.

CHAPTER 6: PHODA AND CHRONIC MUSCULOSKELETAL PAIN

6.1 ABSTRACT

Pain related fear refers to an excessive and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to pain. Research examining fear of movement is controversial; findings are inconsistent and commonly used tools lack sensitivity in its measurement. Further research is required to address some of these controversies and explore the concept of 'fear'. Blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) was used to compare brain responses in patients with chronic musculoskeletal pain (CMSKP) (n=15) and healthy controls (n=15) to a picture and imagination task. The aim was to identify differences in BOLD responses between the two groups, when asked to view an activity of daily living and to imagine how they would feel mentally and physically if asked to perform the activity. The study demonstrated that the task resulted in BOLD differences in a network of brain regions associated with fear conditioning, emotional and sensory pain processing, including anterior cingulate cortex (ACC), insula, primary sensory cortex (SI) and thalamus. Increased BOLD responses were also seen in patients and not controls in areas that are deemed to be part of the default mode network (DMN) activity; posterior cingulate cortex, precuneus, angular gyrus and middle frontal cortex when completing the picture activity, supporting the contention that the DMN is abnormal in patients with CMSKP. This study illustrates the importance of anticipated fear and catastrophising in patients with CMSKP through the use of a photograph and imagination task.

6.2. INTRODUCTION

Chronic musculoskeletal pain (CMSKP) poses a major health and socioeconomic burden (Sprangers et al. 2000; Belsey 2002; Torrance et al. 2010) and can be a complex condition to manage (Foster et al. 2003a; Foster et al. 2003b). The physical manifestation of chronic pain is modified by the way in which the individual attends to the pain, adding to the complexity (Eccleston and Crombez 1999; Buck and Morley 2006), the meaning that the pain has for the individual (Richardson et al. 2006; Foster et al. 2010; Main et al. 2010) and the pain-related behaviours that ensue (Newton-John and Williams 2006; Henschke et al. 2010).

Several factors are thought to be involved in moderating the attentional demands of pain, the strongest and most consistent effects relate to fear, anxiety, and catastrophising (Eccleston and Crombez 1999). Pain related fear refers to an excessive and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to pain (Keefe et al. 1991). Fear-anxiety-avoidance models posit pain-related anxiety and anxiety sensitivity as important contributing variables in the development and maintenance of CMSKP (Asmundson and Nicholas Carleton 2005). Catastrophising in the context of pain, is central to the fear-anxiety- avoidance model (Vlaeyen and Linton 2000), and can be defined as an individual's tendency to exaggerate, ruminate, focus on how threatening pain is, and negatively evaluate their ability to cope with it (Sullivan 1995).

Experimental studies have shown the impact of fear avoidance on pain behaviour in laboratory settings (Vlaeyen et al. 1995; Vlaeyen and Crombez 1999; Trost et al. 2011). Other studies have used a range of physical capacity tasks that have demonstrated no or limited influence of fear on behaviour (Lacker et al. 1996; Geisser et al. 2000; Reneman et

al. 2003; Smeets et al. 2007). However, there are several methodological limitations that account for these findings including the lack of sensitivity in fear avoidance scales. Patients may harbour undisclosed fears for a set of movements not defined in behavioural questionnaires and/or the physical capacity task chosen may be unsuitable to tap into individual's fear (Pincus et al. 2010). Pincus et al (2010) suggest that future pain fear-related research should obtain individual information about feared movements and relate this specifically to the individuals involved in the research.

A potentially useful measure for establishing fear of movement is through the Photograph Series of Daily Activities (PHODA) (Kugler et al. 1999; Leeuw et al. 2007b). It asks participants to rate the perceived harmfulness of a number of activities and is an instrument that has been developed to assess patients with chronic low back pain (CLBP) (Kugler et al. 1999). Reporting increased perceived harm correlates well with increasing fear avoidance scores, as measured by Tampa Scale of Kinesiophobia (Leeuw et al. 2007b), supporting its use in assessing pain-related fear. Leeuw et al (2007b) proposed that PHODA has good psychometric properties, however it has not been extensively researched. Future research using the PHODA needs to focus on disentangling responses to the photographs in terms of fear, attribution of pain and avoidance (Pincus et al. 2010).

Past experiences influencing pain-related fear are reliant on memory and recall (Johnson 1973; Fordyce et al. 1984) and a number of studies have investigated this by asking healthy volunteers to imagine pain in the absence of noxious stimuli (Derbyshire et al. 2004; Kelly et al. 2007; Ogino et al. 2007). The results suggest that a number of common brain regions are activated including ACC, thalamus, insula, prefrontal and parietal cortices. However, there is evidence to suggest that naturally occurring pain differs greatly

from experimentally induced pain in relation to fear avoidance (George and Hirsh 2009) and such studies need to be undertaken in chronic pain populations.

Neuroimaging has provided some insights into understanding aspects of CMSKP (Buffington et al. 2005; Baliki et al. 2006; Sitges et al. 2007). Further research is needed however, as while behavioural studies have shown that people who are fearful and catastrophise attach more threat or harm to non-painful stimuli (Peters et al. 2000; Crombez et al. 2002a), results are not conclusive and the neural correlates of this are not clear. Comparing behavioural study outcomes with neuroimaging results may provide better insights into how cognitions such as fear and catastrophising result in and maintain pain related disability. Therefore there is a need to develop methods to allow for the investigation of naturally occurring changes in pain and responses to pain cues that are suitable for use with clinical populations in the scanning environment. The aim of this fMRI study is to investigate whether using pictorial images and imaging activity tasks will cause blood oxygenation level dependent (BOLD) changes in brain regions involved in fear and phobic responses, as well as pain-processing, in patients with chronic musculoskeletal pain compared to healthy, pain-free controls. Regions expected to demonstrate fear-related BOLD differences in patients compared to controls include the amygdala, orbitofrontal cortex, substantia nigra/ventral tegmental, putamen, insula, thalamus, globus pallidum, inferior parietal and mid cingulated (Etkin and Wager 2007). Regions shown to be involved in phobic responses are also anticipated to demonstrate BOLD changes in patients compared with controls and these include amygdala, fusiform gyrus, substantia nigra, insula and mid cingulated (Etkin and Wager 2007). A secondary aim is to investigate whether commonly used scales of catastrophising and pain-related fear reflect the neural responses observed using fMRI.

6.3.1 Participants

Following Dyfed Powys Research Ethics Committee and local Research and Development Committee approval, participants provided informed written consent and were recruited for the study. Fifteen patients were recruited from a pain management programme and a multidisciplinary pain clinic in South Wales and 15 age and sex matched healthy (pain-free) controls were recruited from the Cardiff University School of Psychology's volunteer panel. Criteria for patient inclusion in the study were: a physician-diagnosis of chronic non- malignant pain (International Association for the Study of Pain; (Merskey and Bogduk 1994); non-inflammatory musculoskeletal pain; a pain score of 50 or above on a numerical rating scale (NRS) of 0-100 ('No Pain' – 'Worst Possible Pain') as an average pain experienced over the month prior to enrolment; that lying down would not provoke pain and participants perceived that they would be comfortable in the scanner. Exclusion criteria for all participants were serious metabolic, rheumatoid, vascular or diagnosed psychiatric disorders; the inability to give informed consent, and contraindications to MR scanning. Regular Analgesic regimens were not altered and patients continued to take their routine analgesia as prescribed but asked not to commence new ones.

6.3.2 Questionnaires and assessment

In an interview, conducted at least two weeks prior to scanning, patients were asked about their current medication and intensity of pain. They were asked which movement (exercise, twisting, bending, pull/push, carrying, and lifting) made their pain worse and caused them the greatest anxiety and how they liked to relax or distract themselves from their pain. This information provided the bespoke pictures (see section 6.3.4). Using a numerical rating scale (where 0 = no pain and 100 = the worst possible pain), patients

were asked to indicate the number that best described the worst pain, least pain and pain intensity over the previous week, average pain intensity over the previous 3 months and the degree to which the pain interfered with activities of daily living. The NRS measure of pain intensity is recommended as a core outcome measure in clinical trials of chronic pain (Dworkin et al. 2005).

Depressed mood was assessed using Beck Depression Inventory (BDI) (Beck et al. 1961). The BDI comprises 21 questions where each item ranges from 0 to 3 points, maximum score 63 points; with scores indicating: <10 no depression, 10-18.7 mild depression, 18.7-25.4 moderate depression, and > 35.4 severe depression (Beck et al. 1961). The Tampa Scale of Kinesiophobia (TSK) (Kori et al. 1990; Roelofs et al. 2004) was used to evaluate fear of movement. The TSK questionnaire comprises 17 items assessing the subjective rating of kinesiophobia. Each item has a 4-point Likert scale with scoring alternatives ranging from 'strongly disagree' to 'strongly agree'. A total score is calculated that varies between 17 and 68. A high TSK value indicates a high degree of kinesiophobia. Vlaeyen et al. (1995) defined a cut-off >37 as a high degree of kinesiophobia. Catastrophising was assessed using the catastrophising subscale from the Coping Strategies Questionnaire (CSQ) (Rosenstiel and Keefe 1983). The CSQ assesses the frequency of patients' use of pain coping strategies. Using 7-point scales (six cognitive strategies: diverting attention, reinterpreting pain sensations, ignoring pain sensations, coping self-statements, praying or hoping, and catastrophising and one behavioural strategy: increasing activity level). Subjects use this 7-point scale to rate how often they use each strategy to cope with pain. Subjects are also asked to make two ratings of their appraisal of the overall effectiveness of coping strategies (how much control they have over pain and how much they are able to

decrease pain). A clinically relevant catastrophising score is defined as one of 11 and above (Jellema et al. 2005). (See appendices for the above questionnaires).

6.3.3 PHODA-MSK development

As described in Chapter 4, the Photograph Series of Daily Activities (PHODA, (Kugler et al. 1999) has been validated as a tool to assess kinesiophobia (Leeuw et al. 2007b). Subjects are asked 'To what extent do you think this is harmful to your back' and rated the perceived harm on a numerical rating score from 0 (not harmful at all) to 10 (extremely harmful) when viewing PHODA. PHODA was developed for studies of back pain and for clinical assessment, however, our intention was to use it for musculoskeletal pain and perception of pain-related anxiety rather than perceived harm. Therefore, prior to the use of PHODA, a pilot study was performed in 20 CMSKP patients aged and gender matched with 20 pain-free controls. Participants were asked to imagine how much pain and anxiety they would feel if they were asked to complete the activity represented in the photograph and rate both on a scale of 0 – 'no pain' to 3 'severe pain', 0 – 'no anxiety' to 3 'severe anxiety'. The activity photographs were taken from the PHODA library and the resting or neutral photographs were taken from pictures that were available from a number of free-photograph internet sites (Google images). We therefore developed a set of appropriate activity photographs (pictures that caused the greatest anxiety and perceived pain in the patient group) and neutral or resting pictures (those that caused the least anxiety and pain in all participants) for use in the present study resulting in PHODA-MSK.

6.3.4 Imaging paradigm for PHODA-MSK

The PHODA-MSK task was chosen for our event-related design fMRI study with chronic musculoskeletal pain patients. Subjects were presented with individual photographs of

daily activities (e.g. a person lifting a shopping bag, bending to pick something off the floor) and asked to imagine carrying out the activity. Subjects were shown a series of photographs with these instructions 'A photograph will be presented for 3 seconds. Study the photograph carefully and imagine that after scanning we will ask you to attempt this activity. Think about how this would make you feel. Imagine how you would feel both mentally and physically during your attempt.' Participants were required to rate their anxiety using two 4-button response boxes, one held in each hand. Subjects used their middle and index finger of their left hand for no anxiety and mild anxiety, respectively, and the index and middle finger of their right hand for moderate and severe anxiety, respectively.

Seven categories of PHODA-MSK activities were viewed by the participants and these included exercise, twisting, bending, pull/push, carrying, lifting and neutral (please see appendices for examples). Of 40 activity-related photographs, 30 were common to all subjects and consisted of 5 photographs from each group. The additional 10 photographs were specific to the category that caused each patient the most anxiety or pain, based on the interview conducted at least 2 weeks prior to scanning. Participants also viewed 20 neutral or relaxing photographs of which 10 were common to all and 10 were bespoke to the individual. Each patient had an age and gender matched control who viewed the same photographs as the patient. Each trial (see Fig.6.1) lasted between 7s and 15s and consisted of a photograph presented on screen for a fixed duration of 3s, a fixation cross for a random number of seconds between 1s and 5s (mean 3s), a response period ('RATE NOW') whereby the subject had a fixed 2s to rate their anxiety, and finally another fixation cross for between 1s and 5s (mean 3s) before the commencement of the next trial.

The durations of both fixations were in a random fixed order and counterbalanced across the 60 photographs which lasted 11 minutes.

Following the scanning session, participants were shown the photographs that they had previously seen and were asked to rate their perceived pain if asked to undertake the activity shown. A similar scale to that used on the button box was used with 0 = 'no pain', 1 = 'mild pain', 2 = 'moderate pain' and 3 = 'severe pain'.

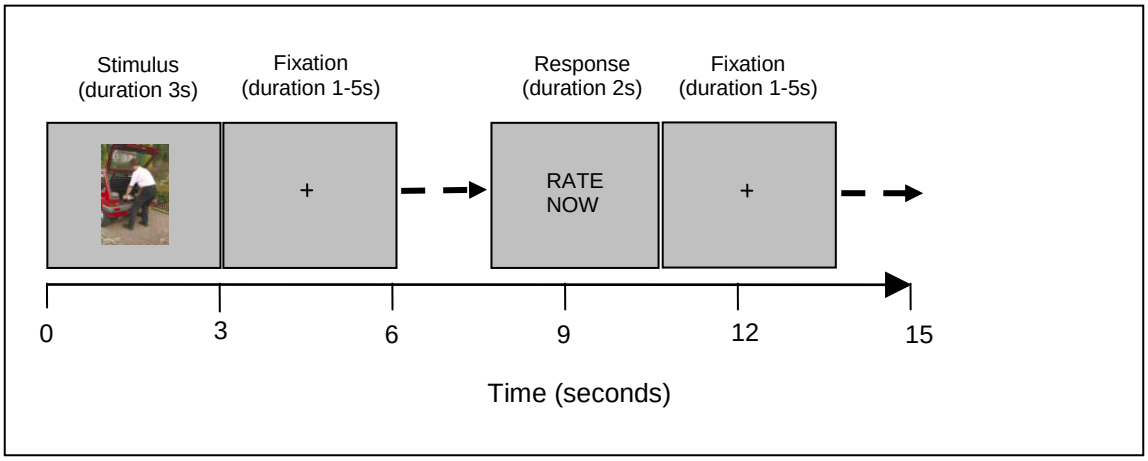


Fig.6.1. Trial timing.
Each trial in the task lasted 7-15 s and was composed of 4 different screens; a picture from either PHODA or a neutral activity, a fixation cross, a screen to indicate the subject should respond and ended with a second fixation cross.

6.3.5 Participant training

Prior to scanning, subjects completed a practice version of the task in a mock scanner lasting approximately 90s and consisting of 10 trials. All photographs used in the practice session were different to those presented in the scanning session. Thus, subjects practised the task components of button pressing but were not exposed to the photographs used in the scanner. Responses were reviewed to ensure that the subject understood the task.

6.3.6 Imaging

Imaging was performed on a 3 T MRI system (HDx, General Electric Healthcare, Waukesha, Wisconsin, USA) using an 8-channel receive-only head coil. Functional MRI data were acquired with a gradient-echo, echo-planar imaging sequence, scanning parameters were: repetition time (TR)/echo time (TE) = 3000 ms/35 ms, 20.5 cm field of view, acquired on a 64 x 64 matrix with 53 contiguous 3.2 mm slices. Subjects completed one run and each of these runs consisted of 236 repetitions. For anatomic localisation, a T1-weighted, three-dimensional fast-spoiled gradient echo acquisition was performed, with a voxel resolution 1x1x1 mm^3 (scanning parameters included: TR/TE = 7.8/3 ms, 450 ms inversion time, 256 x 128 acquisition matrix) for each participant.

6.3.7 Image analysis

Analysis of BOLD fMRI data was performed using FEATv5.98 (FMRI Expert Analysis Tool), part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Registration to each subject's high resolution structural scan was performed using FLIRT (Jenkinson and Smith 2001; Jenkinson et al. 2002) and registration to standard space was then performed using FLIRT followed by FNIRT nonlinear registration (Andersson et al. 2007). The functional data for each subject was motion corrected (MCFLIRT (Jenkinson et al. 2002)) and fieldmaps were processed using PRELUDE+FUGUE (Jenkinson 2003, 2004) to correct for field distortions in the functional data. Data was smoothed spatially with a Gaussian kernel with a FWHM of 5mm and filtered with a highpass temporal filter (cut off of 100 s) and the data was demeaned on a voxel-by-voxel basis across the time course. At the voxel level, the signal was linearly modelled (FILM-FMRIB's Improved Linear Model) with autocorrelation correction (Woolrich et al. 2001).

Data were initially analysed at the individual subject level (first level analysis) in response to PHODA. The anxiety scores rated during the scanning session were modelled into the first level analysis as the convolution of 'picture' and 'rate now' events and a gamma variate hemodynamic response function. A second level mixed effects analysis was performed comparing the patient group and control group responses to the PHODA and 'rate now' anxiety responses. An average of the anxiety score responses rated during the picture viewing task and an average of the catastrophising and TSK scores for patients and controls were regressed into a covariate Feat analysis in another second level analysis. This second level analysis compared BOLD activity across all participants using de-meaned behavioural scores. Anxiety scores were recorded by button box during the viewing task and catastrophising and TSK scores were obtained via questionnaires. These regressions were 'picure + anxiety scores', 'picture + TSK scores' and 'picture and catastrophising scores' looking for a correlation between high scores and areas of BOLD activity. Catastrophising is strongly associated with depression and both augment pain perception through increased attention to the pain and heightened emotional responses (Gracely et al. 2004). Therefore, all second level analyses were undertaken with de-meaned Beck Depression Scores included in the model as a covariate to adjust for the effects of depression. Statistical images were thresholded using clusters determined by a $z>2.3$ followed by cluster correction at a significance threshold of $p=0.05$ (Woolrich et al. 2001). FLAME (Woolrich et al. 2004) was used for the higher level analysis.

FSL was used to view the statistical parametric maps and the areas of BOLD signal differences were identified by using the Harvard-Oxford cortical and subcortical atlases. Functional regions of interest were identified as the intersection of the anatomical mask from the Harvard-Oxford atlas and the thresholded *z*-statistic image and the average signal

change for each region for each group was plotted for illustrative purposes. No further statistical tests were used for or applied to these results.

6.4. RESULTS

6.4.1 Demographics and questionnaires

Thirty participants were scanned (5 male, 10 female for patients and the same for controls), age range 25 to 83 years old, including 15 patients with pain and 15 age-matched controls. No differences were found in marital status, years in school or dependents. Thirteen patients had previously undergone a diagnostic MRI scan and 9 volunteers had previously been scanned as participants in previous studies or for non-pain related clinical reasons. Pain scores, demographic data and psychological variables were compared between groups. Patients' clinical characteristics are described in Table 6.1.

Patients and controls differed in pain scores and psychological variables (Table 6.2). All patients had received a course of physiotherapy, 9 had received education on self management but no patient had attended a pain management programme or an expert patient programme. Two patients and 1 control were left handed. The anxiety ratings performed on the button box provided statistically significant differences between patients and controls (Table 6.3) illustrating that the activity pictures caused medium to high anxiety in patients but not in controls. Similarly the perceived pain ratings, rated after the scanning session, provided statistically significant differences between patients and controls illustrating that patients perceived that the activities would result in moderate to severe pain if undertaken.

Table 6.1: Clinical characteristics

Patient	Age	Pain sites	Duration of pain in years	Current medication
1	29	Knees	2	Weak opioids, NSAIDS, antidepressant pain adjuvant
2	59	Back, neck	1	Weak opioids
3	65	Shoulders, hips	3	Strong opioids, antiepileptic pain adjuvant
4	25	Knees, hips	1	Strong opioids, NSAIDS, paracetamol, antiepileptic and antidepressant pain adjuvants, lidocaine patch
5	60	Back, knees	3	Weak opioids, paracetamol, antiepileptic pain adjuvant, lidocaine patch
6	61	Back, feet	4	Weak opioids, NSAIDS, antiepileptic pain adjuvant
7	83	Major joints	20	Weak opioids, NSAIDS, antiepileptic pain adjuvant, lidocaine patch
8	76	Major joints	5	Weak opioids
9	65	Major joints	25	Weak opioids
10	71	Back, shoulders	25	Weak opioids, NSAIDS antidepressant pain adjuvant
11	62	Back, shoulders	1	Weak opioids
12	38	Back, neck	10	Weak opioids, lidocaine patch
13	64	Major joints	10	Strong opioids, antiepileptic pain adjuvant
14	56	Back and neck	5	Weak opioids
15	55	Back, neck	15	Weak opioids

Table 6.2: Psychological variables and pain scores

Median pain score or psychological variable is presented (interquartile range shown in parentheses). Differences between groups were tested using Mann-Whitney tests.

Variable	Patient	Control	*p* value*
Beck Depression Inventory <10 no depression, 10-18.7 mild, 18.7-25.4 moderate, > 35.4 severe depression	23 (12-34)	3 (0-5)	< 0.001
CSQ Catastrophise 0 = Never catastrophise, 36 = Always catastrophise about pain	14 (3-23)	2 (0-3)	< 0.001
Tampa Scale of Kinesiophobia The total score ranges between 17 and 68. A high value on the TSK indicates a high degree of kinesiophobia, a score of 37 differentiates between high and low scores	23 (17-32)	9 (4-14)	< 0.001
Current pain (present pain) (NRS 0-100)	49 (12-65)	6 (0-0)	< 0.001
Worst pain (worst pain imaginable during week) (NRS 0-100)	74 (55-94)	7 (0-0)	< 0.001
Least pain (during week) (NRS 0-100)	34 (20-50)	5 (0-0)	< 0.001
Pain intensity (during week) (NRS 0-100)	56 (45-70)	5 (0-0)	< 0.001
Pain distress (during week) (NRS 0-100)	64 (60-80)	2 (0-0)	< 0.001
Disturbance (during week) (NRS 0-100)	63 (50-80)	3 (0-0)	< 0.001

Table 6.3: Anxiety ratings undertaken on the button box during scanning and perceived pain ratings undertaken post scanning

Function	Anxiety ratings during scanning session 0 = no anxiety – 3 severe anxiety		Perceived pain ratings post scanning session 0 = no pain – 3 severe pain	
	Median (25^{th}, 75^{th} quartiles)	*p* value (Mann-Whitney)	Median (25^{th}, 75^{th} quartiles)	*p* value (Mann-Whitney)
Bending	Patients 2 (1, 3) Controls 0 (0, 0)	< .001	Patients 2 (1.6, 2.8) Controls 0 (0, 0)	< .001
Twisting	Patients 2 (1.4, 2.4) Controls 0 (0, 0)	< .001	Patients 2 (1.4, 2.4) Controls 0 (0, 0)	< .001
Carrying	Patients 2 (1.8, 3) Controls 0 (0, 0)	< .001	Patients 2 (2, 3) Controls 0 (0, 0)	< .001
Exercise	Patients 3 (2.2, 2.8) Controls 0 (0, 0)	< .001	Patients 2 (2.2, 2.8) Controls 0 (0, 0.6)	< .001
Push/pull	Patients 2 (2, 2.8) Controls 0 (0, 0)	< .001	Patients 2 (2, 2.8) Controls 0 (0, 0.2)	< .001
Lifting	Patients 2 (2, 2.8) Controls 0 (0, 0)	< .001	Patients 2 (2, 2.8) Controls 0 (0, 0)	< .001
Bespoke	Patients 2 (1.8, 2.6) Controls 0 (0, 0)	< .001	Patients 2 (2, 2.6) Controls 0 (0, 0.1)	< .001
Neutral	Patients 1 (0, 1) Controls 0 (0, 0)	< .001	Patients 1 (0.4, 1.2) Controls 0 (0, 0)	< .001

6.4.2 Imaging

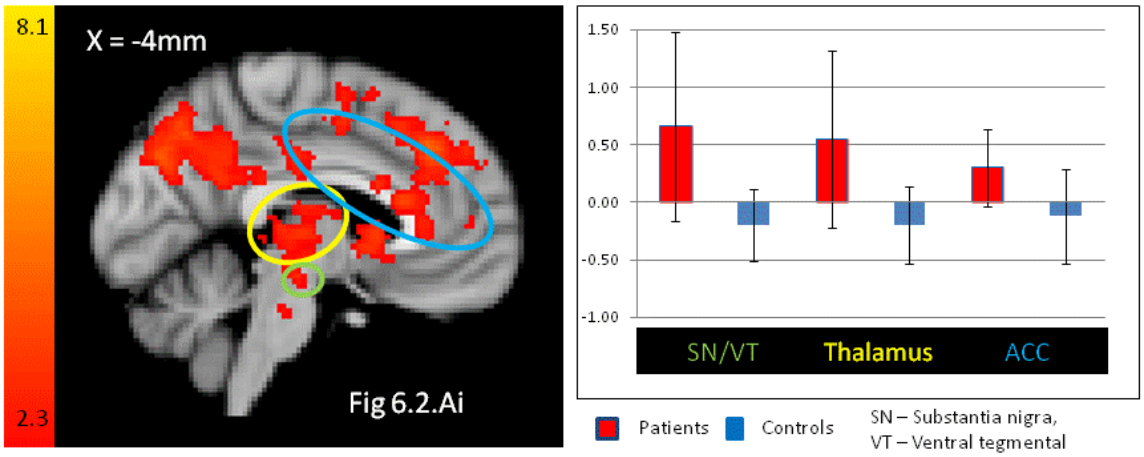
Pictures

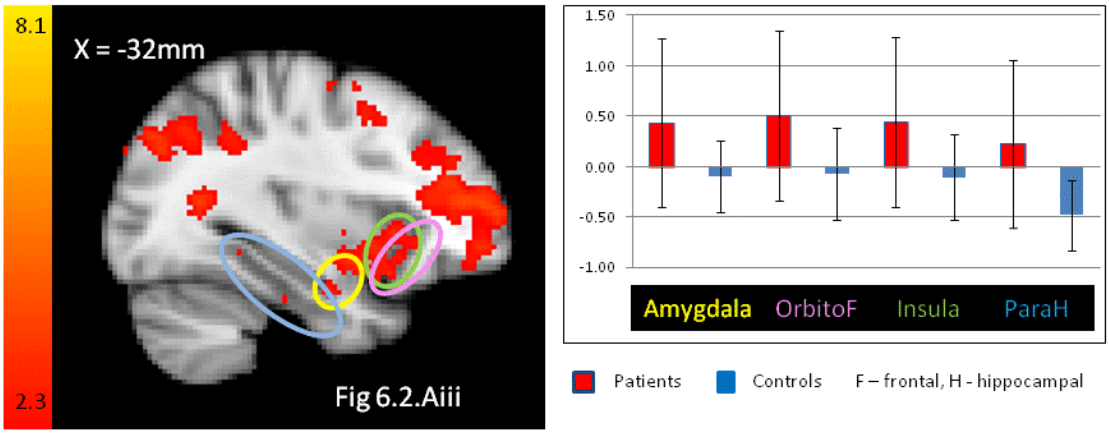
Bilaterally, positive BOLD responses were seen in patients compared to controls when viewing the photographs and imagining the activity in the following cortical regions: SI, cuneus, supramarginal gyrus posterior and anterior divisions, ACC, insula, orbitofrontal cortex, superior frontal gyrus, superior occipital gyrus, paracingulate cortex, precuneus, middle frontal gyrus, angular gyrus, PCC, middle temporal gyrus (posterior division).

Left-sided increased BOLD responses were seen in patients compared to controls during the task in superior temporal gyrus (posterior division), supplementary motor cortex, superior parietal cortex, parahippocampal (posterior division), parietal operculum and frontal pole. Right-sided increased BOLD responses were seen in patients compared with controls during the task including the inferior temporal gyrus (posterior and temporo-occipital divisions), superior temporal gyrus, anterior division, parahippocampal, posterior division and inferior frontal cortex. Sub-cortical regions with increased BOLD responses in patients compared with controls during the task: bilateral putamen, caudate, thalamus, brain stem and right accumbens. Anatomical locations and peak activation co-ordinates can be seen in Table 6.4. Figures 6.2-6.4 present the BOLD region activations. Appendix 7 contains the within group statistical parametric maps and the accompanying descriptive tables.

Fig.6.2.A. Statistical parametric maps illustrating regions known to be involved in phobia and fear conditioning

Comparing activation during the PHODA-MSK task between patients and controls. Patients with CMSKP have significantly different BOLD activation in regions known to be involved in phobia and fear conditioning. Each z-statistic map represents these group differences in a whole brain analysis. The graphs show the percentage signal change with the error bars representing standard deviations across subjects. The images are a combination of anatomical and functional data and the graphs represent the direction and magnitude of the signal change within the region and were therefore not tested for statistical significance. The colour bar shows the scale of the *z*-statistic (2.3 – 8.1). The circles represent the anatomical location of the corresponding coloured region in the graph.





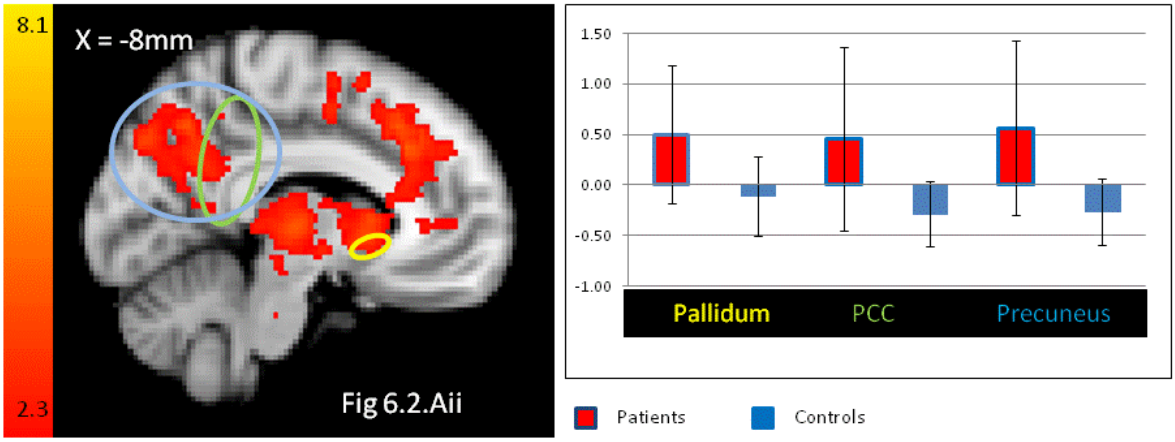
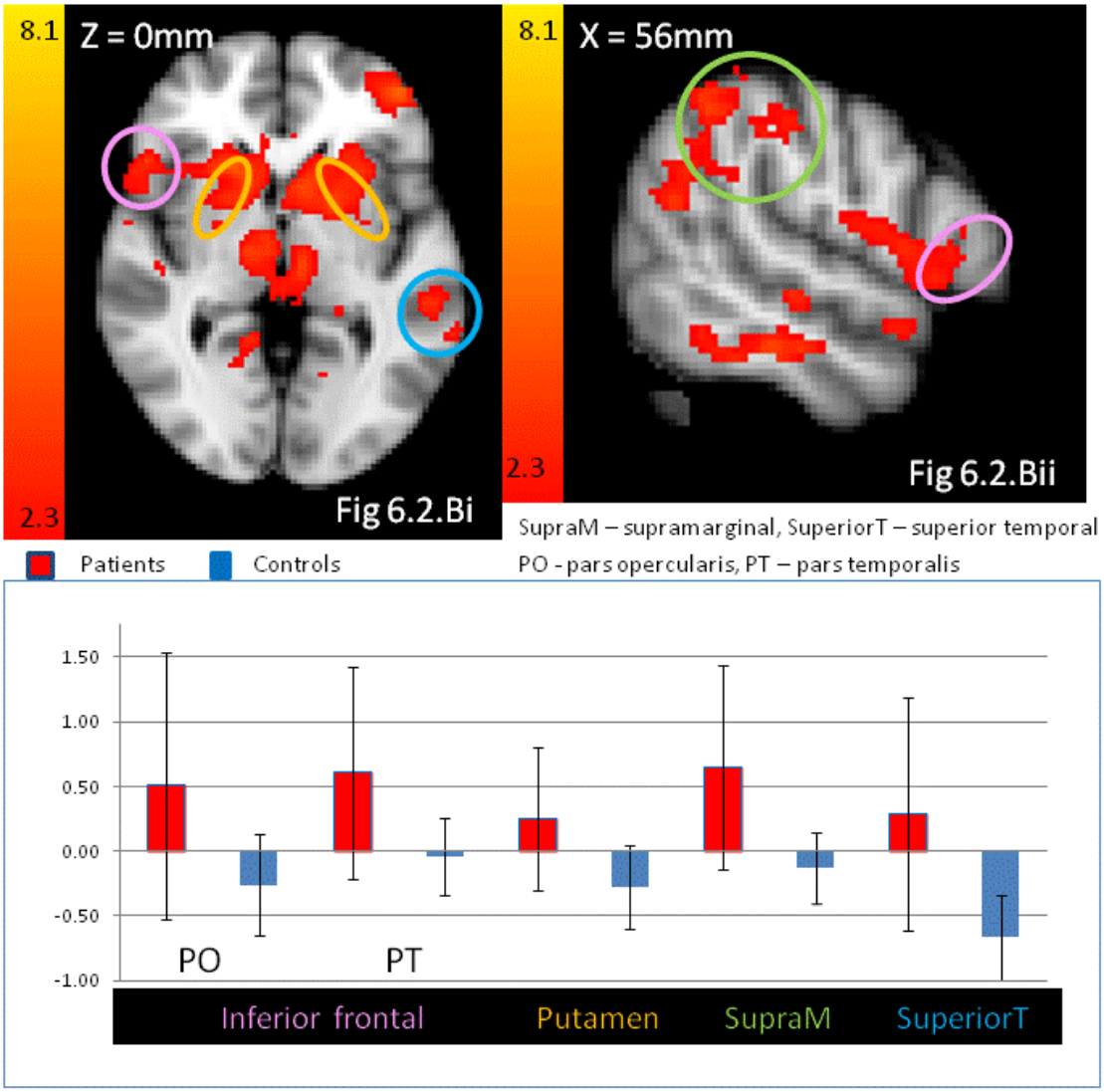


Fig.6.2.B. Statistical parametric maps illustrating regions known to be involved in phobia and fear conditioning

Comparing activation during the PHODA-MSK task between the patient and control groups when viewing the pictures and imagining undertaking the task depicted. Patient with CMSKP have significantly different BOLD activation in regions known to be involved in phobia and fear conditioning. Each z-statistic map represents these group differences in a whole brain analysis. The graphs show the percentage signal change with the error bars representing standard deviations across subjects. The images are a combination of anatomical and functional data and the graphs represent the direction and magnitude of the signal change within the region and were therefore not tested for statistical significance. The colour bar shows the scale of the Z-statistic (2.3 – 8.1). The circles represent the anatomical location of the corresponding coloured region in the graph.



Rate now

Positive BOLD responses were seen in patients compared to controls when viewing the pictures but not when rating the anxiety associated with the picture activities.

Picture + anxiety scores

BOLD responses were positively correlated with high anxiety scores in the lingual gyrus, precuneus and cuneal cortex; right-sided in the occipital pole, intracalcarine cortex and lateral occipital cortex, superior division, and on the left, occipital fusiform and temporal occipital fusiform cortex. Anatomical locations and peak activation co-ordinates can be seen in Table 6.5.

Picture + CSQ catastrophising sub-scale scores

BOLD responses responses correlating with high catastrophising scores were all lateralised to the right, with the exception of the cerebellum and brain stem activity. Cortical areas were lateral occipital cortex, precuneus, lingual gyrus, middle and inferior temporal gyrus, temporal occipital fusiform. The only sub-cortical area was the brain stem where BOLD signal changes could be seen in the pons. Cerebellum regions included right V, VIIb, VIIIb, Crus II and left IX, VIIIa and b, crus II and X. Anatomical locations and peak activation co-ordinates can be seen in Table 6.5.

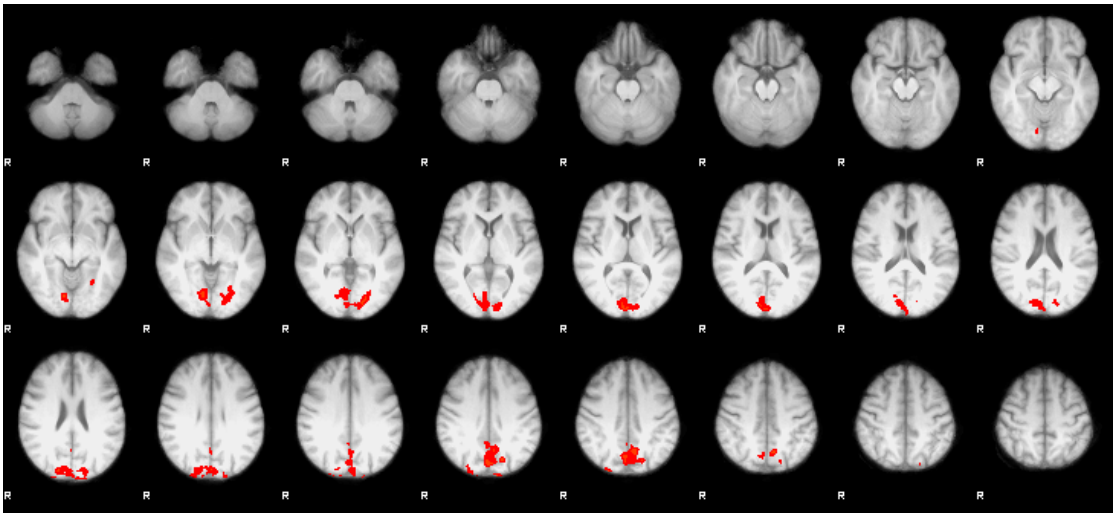
Picture + TSK

This analysis did not show any BOLD response correlations with TSK.

Fig.6.3 Maps illustrating BOLD responses to high anxiety (A) and catastrophising (B)

De-meaned anxiety and catastrophising scores were regressed into a covariate statistical model in which the FEAT analysis was run independently for each. Each z statistic map represents these group differences in a whole brain analysis. The scale of the Z-statistic (2.3 – 7.0).

A. Anxiety scores



B. Catastrophising scores

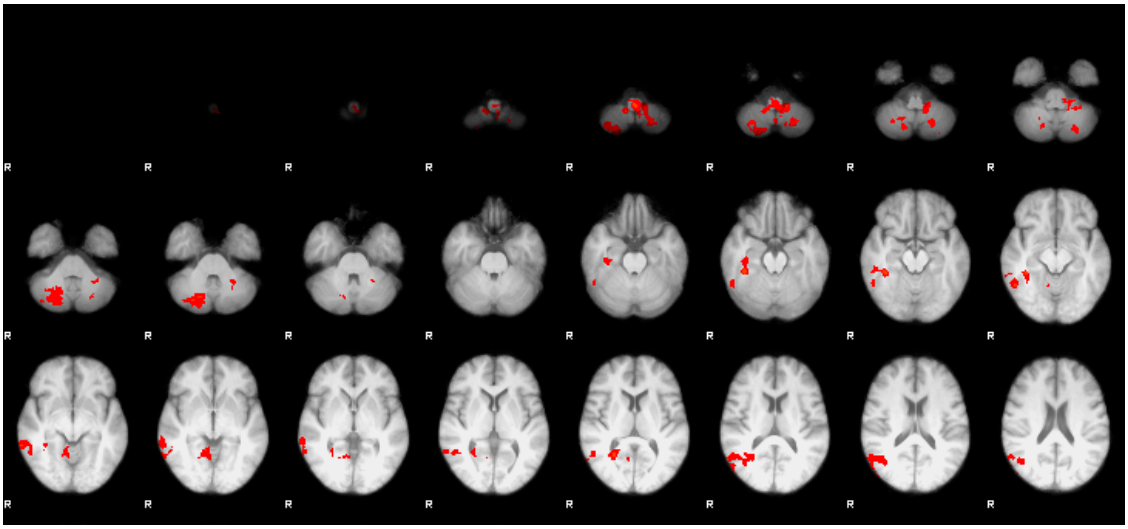


Table 6.4: Group differences for PHODA-MSK task

Group differences for PHODA-MSK task obtained during second level analysis. Anatomical locations and peak activation co-ordinates (in MNI 152 space) extracted from brain regions that were found to be significantly different between patients and controls (patients > controls) at Z>2.3 and cluster corrected $p<0.05$.

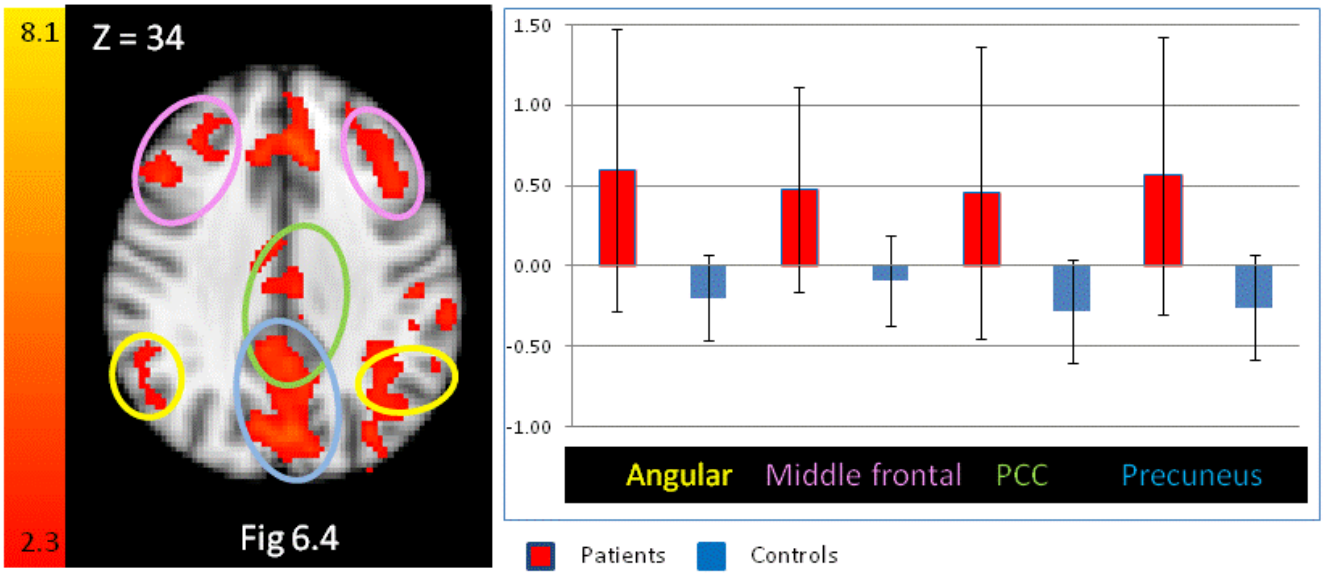
	Co-ordinates			z-stat
	x	y	z	
ACC (L)	-8	30	22	3.09
ACC (R)	12	36	16	2.70
Accumbens (R)	10	12	-8	2.83
Amygdala (L)	-32	-6	-24	2.76
Angular gyrus (L)	-44	-56	50	4.53
Angular gyrus (R)	48	-50	50	3.19
Caudate (L)	-10	14	0	3.78
Caudate (R)	14	16	0	3.86
Cuneus (L)	-8	-80	34	3.36
Cuneus (R)	8	-78	34	2.91
Frontal orbital cortex (L)	-28	20	-12	2.46
Frontal orbital cortex (R)	40	20	-8	2.79
Frontal pole (L)	-30	58	14	3.39
Inferior frontal pars opercularis (R)	56	18	0	3.04
Inferior frontal pars temporalis (R)	52	24	2	3.45
Insula cortex (L)	-30	20	-4	2.76
Insula cortex (R)	36	18	-2	2.56
Middle frontal gyrus (L)	-44	18	38	3.67
Middle frontal gyrus (R)	48	20	40	2.46
Pallidum (L)	-12	4	2	3.27
Paracingulate cortex (L)	-4	32	34	4.02
Paracingulate cortex (R)	4	32	34	2.88
Parahippocampus anterior (R)	24	-18	-28	2.68
Parahippocampus posterior (L)	-22	-24	-28	2.57
Parietal operculum (L)	-60	-30	20	2.96
PCC (L)	-4	-50	32	3.33
PCC (R)	6	-46	32	3.51
Precuneus (L)	-4	-74	42	3.43
Precuneus (R)	2	-74	42	3.88
Putamen (L)	-24	6	-2	3.13
Putamen (R)	22	10	-2	3.17
SI(L)	-58	-22	26	3.13
SI(R)	44	-34	48	3.28
Substantia nigra/ventral tegmental (L)	-4	-20	-14	3.19
Superior frontal gyrus (L)	-2	32	46	2.93
Superior frontal gyrus (R)	22	22	46	3.27
Superior parietal cortex (L)	-40	-48	50	4.09
Superior temporal gyrus posterior (L)	-58	-32	0	3.04
Supplementary motor cortex (L)	-4	0	50	3.09
Supramarginal gyrus, anterior division (L)	-52	-32	42	3.66
Supramarginal gyrus, anterior division (R)	46	-42	50	4.25
Supramarginal gyrus, posterior division (L)	-52	-48	42	4.17
Supramarginal gyrus, posterior division (R)	48	-38	48	3.57
Thalamus (L)	12	-12	6	3.37
Thalamus (R)	-12	-20	6	4.00

Table 6.5: BOLD regions correlating to higher anxiety and catastrophising scores

BOLD regions responding to higher anxiety and catastrophising scores (FEAT analyses were run independently), found in the covariate analysis during observation of the photographs and imagining undertaking the task depicted. Anatomical locations and peak activation co-ordinates (from MNI atlas) extracted from brain regions that were found to be significantly different between patients and controls (patients > controls) at Z>2.3 and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
Regions corresponding to higher anxiety scores				
Cuneal cortex (L)	-6	-88	30	3.41
Cuneal cortex (R)	10	-84	24	2.66
Intracalcarine (R)	6	-78	4	2.48
Lateral occipital cortex (R)	28	-84	36	2.50
Lingual gyrus (L)	-16	-78	-2	2.84
Lingual gyrus (R)	8	-70	-2	3.11
Occipital fusiform (L)	-20	-80	-2	3.44
Occipital pole (R)	6	-94	6	3.04
Precuneus (L)	-6	-53	36	3.26
Precuneus (R)	6	-74	38	3.08
Temporal occipital fusiform (L)	-26	-58	-8	2.80
Regions corresponding to higher catastrophising scores				
Inferior temporal gyrus (R)	54	-52	-14	2.87
Lateral occipital cortex (R)	50	-62	18	2.53
Lingual gyrus (R)	8	-58	-4	2.46
Middle temporal gyrus (R)	66	-42	-8	3.17
Precuneus (R)	30	-58	10	2.89
Temporal occipital fusiform (R)	38	-42	-14	2.88
Cerebellum:				
Crus II (R)	22	-76	-38	2.68
V (R)	8	-54	-6	2.95
V IIb(R)	30	-68	-54	2.50
VIIIb (R)	12	-48	-58	3.35
Crus II (L)	-24	-74	-44	2.41
IX (L)	-12	-48	-50	2.99
VIIIa (L)	-22	-60	-54	2.90
VIIIb (L)	-14	-42	-52	3.33
X (L)	-18	-38	-44	2.47
Brain stem	-2	-44	-56	3.19

Fig.6.4. Statistical parametric map showing DMN BOLD regions
Map comparing activation during the PHODA-MSK task between the patient and control groups during viewing the picture and imagining undertaking the task depicted. Patient with CMSKP have significantly different BOLD activation in regions associated with the default mode network when undergoing the task when imagining undertaking the activity depicted in the photograph. Each z-statistic map represents these group differences in a whole brain analysis. The graphs show the percentage signal change with the error bars representing standard deviations across subjects. The images are a combination of anatomical and functional data and the graphs represent the direction and magnitude of the signal change within the region and were therefore not tested for statistical significance. The colour bar shows the scale of the Z-statistic (2.3 – 6.8). The circles represent the anatomical location of said region.



6.5. DISCUSSION

This study illustrates that people with CMSKP, but not controls, engage brain regions, which are known to process pain, fear and phobia related information, when undertaking the PHODA-MSK task. Patients respond differently to PHODA and the imagination task than their matched controls and we propose that this is due to pain related catastrophising, fear and associated anxiety.

6.5.1 Regions involved in phobic responses and fear conditioning

This study found a number of regions that are seen in studies of emotional responses to fear (Etkin and Wager 2007) (Table 4); specifically, studies that involved fear conditioning (Etkin and Wager 2007). These common regions are the amygdala, orbitofrontal cortex, substantia nigra/ventral tegmentum, putamen, insula, thalamus, pallidum, inferior parietal (supramarginal and angular gyrus) and cingulate (ACC and PCC).

Interestingly, our patients were rated as low kinesiophobics on the TSK as they scored well below the cut-off point between low and high kinesiophobics at a score of 37 (Vlaeyen et al. 1995) and yet the neural responses suggested that patients were fearful, or at least anxious of the movements depicted in PHODA and this was confirmed by the high anxiety rating undertaken on the button box in response to imagining the activity. Furthermore, when the TSK scores were regressed into the statistical model, no differences were found between patients and controls and this tends to support the literature suggesting that TSK may lack sensitivity and may account for, in part, the contradictory findings in fear-avoidance studies (Pincus et al. 2010). We identified a network of regions that were almost identical to the fear conditioning regions found in the systematic review by Etkin and Wager (2007). This could imply that the suggested cut-off score is too high, TSK lacks sensitivity and/or the regions are not closely related to fear of movement/(re)injury.

6.5.2 Anxiety and catastrophising

Higher anxiety ratings and catastrophising scores correlated to BOLD activation in the lateral occipital cortex, precuneus, lingual gyrus and temporal occipital fusiform gyrus. Anxiety ratings also showed increased BOLD activation in the occipital pole, intracalcarine cortex, and cuneal cortex and higher catastrophising scores in the inferior

and middle temporal gyrus, multiple regions in the cerebellum and brain stem. Patients' anxiety and catastrophising scores were significantly greater than controls, therefore, these finding are most pertinent to the patient group.

Since both catastrophising and diffuse inhibitory noxious control are involved in pain processing, they may be associated with each other. Evidence does exist to support this based on connectivity between brain areas associated with catastrophising (Gracely et al. 2004; Seminowicz and Davis 2006) and the brain stem (Villanueva et al. 1998; Desbois et al. 1999; Desbois and Villanueva 2001; Monconduit and Villanueva 2005) associated with the diffuse noxious inhibitory control effect (Weissman-Fogel et al. 2008). Catastrophising may be affecting the sensitivity to pain through indirectly acting via the inhibitory pathways.

The catastrophising cortical regions were all lateralised to the right, consistent with previous research in anxious arousal (Heller et al. 1995; Heller et al. 1997; Nitschke et al. 2000). Anxious arousal is characteristic of high-stress situations that are impending rather than in the distant future (Nitschke et al. 2000). Therefore, anxious arousal may explain the lateralisation of the catastrophising regions.

The middle temporal cortex (in addition to medial prefrontal cortex) plays a role in the extinction of fear through inhibition of amygdala function (Jarrell et al 1987; Romanski and LeDoux 1993). Increased BOLD responses in this region in the present study may indicate that this region is working to reduce the fear. It may also be that the medial prefrontal cortex is not responding as it does in healthy individuals, patients with CMSKP have been shown to have cortical loss in the medial prefrontal cortex (Apkarian et al.

2004b) and hence the middle temporal cortex may be compensating for reduced activity in the prefrontal cortex.

The occipital and calcarine regions of the visual cortex can be modulated by emotional visual stimuli (Taylor et al. 2000; Pizzagalli et al. 2002) with increased fusiform activation (2000; Pizzagalli et al. 2002) and increased amygdala activation (Taylor et al. 2000) facilitated by the saliency of the images shown. The cuneus, also involved in visual processing has also shown increased activation for affective stimuli (Carretie et al. 2004). The lingual gyrus has been implicated in visual memory (Kapur et al. 1995). It has been postulated that the mechanisms for increased activation in these regions is that projections from the limbic circuitry enhance activation in the ventral stream when viewing emotional content and affective salience of a stimulus and memory directly influences visual activity (Duncan and Barrett 2007). Similarly occipital poles are modulated by salient, emotional visual stimuli (Kober et al. 2008) possibly via back projections from the amygdala (Sabatinelli et al. 2009).

The association between increased anxiety and BOLD signal changes in visual areas of the brain have been shown to be predictive of treatment outcome in people with social anxiety disorder when treated with cognitive behavioural therapy (Doehrmann et al. 2012). Those with higher activation to viewing angry compared to neutral photographs responded much better to CBT than those who had low activity. The authors proposed that their findings suggested that attentional mechanisms related to visual perception of social stimuli may be mediated, in part, by activation of occipitotemporal regions and that the status of these mechanisms prior to treatment is important in determining whether CBT is an effective management option. This may be key in future pain studies in looking at pre-screening for

treatment options; those patients with high activity in occipitotemporal regions may be more responsive to CBT than those with low activity.

In the second level analysis, comparison of patients and controls when undertaking the task, a number of regions saw an increase in BOLD activity in patients compared to controls in areas that are involved in memory processing such as the frontal pole (Bonda et al. 1996), paracingulate (reality monitoring in relation to memory processing) (Buda et al. 2011) and the supplementary motor cortex (important for tasks that demand retrieval of motor memory and for motor planning) (Tanji 1994). We proposed that PHODA was salient to patients given the BOLD responses in the memory centres and in the supplementary cortex which may indicate that patients were imagining the movement in the task.

The BOLD signal changes in these regions, when undertaking the task, suggests the ecological impact of PHODA, in those with higher anxiety and catastrophising scores (i.e. patient group) and appeared to tap into the affective-motivational aspects of pain. This is further supported by the responses seen in the precuneus which has been shown, in combination with the cuneal cortex, to have a role in attentional biases (Mercado et al. 2009). The precuneus also has a role in attentional orientation (Cavanna and Trimble 2006) and enhancing attention for the processing of threatening events (Small et al. 2003).

Cerebellar activation has been consistently shown in studies on emotion and while this may be related to increased demands on motor planning during affective and emotional states, there is accumulating evidence for a more direct role for the cerebellum in emotion-related processing (Kober et al. 2008). The majority of regions in our study reflected

sensory motor areas (IV-V, VIII). Accompanying this was the increased BOLD responses within the brain stem which is also involved with sensory motor processing (Stoodley et al. 2012). Combined, this may suggest that patients were attending to the impact of the task on physical performance. This could also reflect sympathetic drive engaged by the 'flight or fight' mechanisms due to the anxiety induced by PHODA.

The lateral occipital cortex has been associated with object perception (Grill-Spector et al. 2001) and emotional scene processing (Bradley et al. 2003; Sabatinelli et al. 2004; Sabatinelli et al. 2007). The latter role may lend further credibility to the fact that the patients perceive the pictures of activities as being emotive; the stimuli for emotional scene processing in previous studies have shown increased activation to threat related images compared to family and neutral images (Bradley et al. 2003; Sabatinelli et al. 2004; Sabatinelli et al. 2007).

6.5.3. Regions involved in pain processing

Pain has been described in a number of dimensions: the sensory-discriminative dimension involving SI and SII, thalamus and insular cortex (Bornhovd et al. 2002); the affective-motivational one, including the insular cortex and rostral ventral ACC (Whalen et al. 1998) and the cognitive evaluative involving the parietal and prefrontal cortices and caudal ACC (Vogt et al. 1995). A number of regions showing increased BOLD responses in patients compared to controls when viewing pictures and imagining the task activity involved the sensory-discriminative dimensions of pain. Areas included those that have been shown to be involved with attentional aspects (SI, inferior and superior parietal cortices, thalamus) (Duncan and Albanese 2003; Kulkarni et al. 2005; Ralston 2005; Worthen et al. 2011), sensory localisation (SI, putamen, ACC, thalamus, caudate) (Bushnell et al. 1999; Oshiro

et al. 2007; Worthen et al. 2011), intensity discrimination (SI, superior frontal gyrus, thalamus, ACC, insula, parietal operculum, accumbens, substantia nigra/ventral tegmental) (Bushnell et al. 1999; Buchel et al. 2002; Dunckley et al. 2005; Koyama et al. 2005; Aharon et al. 2006; Rodriguez-Raecke et al. 2010) and integration with other stimuli and cognitive processes (cuneus, putamen, parietal operculum, thalamus) (Price 2000; Treede et al. 2000; Ralston 2005; Starr et al. 2011). Although there was no sensory pain input, our findings suggest that patients with CMSKP, when viewing images, are concentrating on the sensory aspects of the pain they are physically likely to feel and these are thus represented as BOLD changes in these sensory-discriminatory regions.

The affective-motivational regions that had increased BOLD responses in patients compared to controls during the task included insula, ACC, orbitofrontal, amygdala and frontal pole. These areas are involved in the unpleasantness of pain (ACC, insula, orbitofrontal, amygdala, frontal pole, parahippocampal gyrus) (Ploghaus et al. 1999; Phillips et al. 2003; Kulkarni et al. 2005; Roy et al. 2009; Lamm et al. 2011) and future implications such as the need to escape (insula, ACC) (Price 2000). The PHODA is not designed to evoke unpleasantness; the participants in the pictures demonstrate neutral faces and do not exhibit pain behaviour. Our results suggest that the thought of undertaking the activities seen by the patients cause unpleasantness as brain regions involved in the affective-motivational domain of pain are implicated.

Regions involved in the cognitive-evaluative dimension include the parietal and prefrontal cortices and the ACC (Devinsky et al. 1995; Vogt et al. 1996; Kelly et al. 2007) and our data show increased BOLD activity in patients but not controls, when viewing the pictures and imagining undertaking the activity depicted, in ACC, superior and inferior parietal

cortices and in superior, inferior frontal and orbitofrontal regions. It has been shown that when individuals view pictures of body parts in painful situations, regions such as the inferior parietal cortex (supramarginal gyrus, intraparietal sulcus) and ventral premotor areas (inferior frontaly gyrus, pars opervularis) are activated (Lamm et al. 2011). The joint activation of inferior parietal and inferior frontal cortex appears to be a key feature of action observation (Van Overwalle and Baetens 2009) and action understanding is the core function of this network (Rizzolatti et al. 2006).

The recruitment of the above network relates to predicting and understanding the outcome of the shown situation and we propose that patients process the pictures differently than controls because of differing perceptions of the outcome. This is particularly relevant given that participants were explicitly instructed to imagine undertaking the task seen and hence patients but not controls are likely to consider pain as the outcome of undertaking the tasks in PHODA. This is reinforced by the pain ratings provided by participants following the scanning session to the pictures shown in the scanning session. Patients but not controls perceived that the activity pictures would result in moderate to severe pain should the activity presented be undertaken.

6.5.4 Default Mode Network

Regions such as the precuneus, PCC and medial frontal cortex are a part of the DMN which is the network that decreases its activation during a task compared to the average brain activity at rest (Baliki et al. 2008; Mantini et al. 2009; Kong et al. 2010). Recently, the angular gyrus has also been implicated in the DMN (Qiu et al. 2011). In the present study, regions in the DMN including the angular gyrus, remain active or are less deactivated during the task in patients with CMSKP compared to healthy controls. This is

consistent with a number of studies (Gusnard et al. 2001; Baliki et al. 2008; Mantini et al. 2009) where it appears that enduring pain for a long time affects brain function; the brain is never truly at rest because it is constantly processing pain. This abnormality in chronic pain populations (Baliki et al. 2008) may be related to their ongoing symptoms of depression, anxiety, sleep disturbances and decision making abnormalities (Apkarian et al. 2004a).

6.5.5 Strengths and limitations

We used pictures and an imagination task that were specifically designed for a CMSKP population where pain is naturally occurring and in whom neuroimaging research is relatively sparse. Through the use of our paradigm we were able to demonstrate differences in BOLD responses between those with CMSKP and controls. While, some of the BOLD differences between patients and controls within the affective-motivational and anxiety regions may have been due to the anxiety of being scanned, all participants had to be comfortable in the scanner to be enrolled in the study and had an opportunity to familiarise themselves within the environment in the mock scanner. If all participants demonstrated scanner-induced anxiety, this would not explain the differences between patients and pain-free controls. Patients did continue with their routine medications and no new drugs were commenced within the study period. We are not able to rule out that medication affected the BOLD responses seen in patients and not controls. However, it would seem reasonable to expect that analgesics would reduce the extent to which pain is processed; this is not the case. This could be important in explaining the lack of efficacy of analgesics for many chronic pain patients. This important issue is beyond the scope of the current study but requires further investigation.

6.5.6 Conclusion

This study has illustrated that viewing photographs of people engaging in activities that the patients with CMSKP would find painful produces BOLD differences between patients and controls in established areas associated with emotional and sensory aspects of pain that would be expected when individuals actually experience pain. Although the TSK scores illustrated that patients had low levels of kinesiophobia, the neuroimaging results would suggest otherwise. This may suggest that when patients with CMSKP see others engaging in activities, their pain could potentially be exacerbated and perpetuated through fear and anxiety. Therefore, it may be important to assess the social context of the pain i.e. how patients with CMSKP relate to or interpret the activities of others as well as how they experience their own pain.

Our study findings support the need for further research into mapping fear and catastrophising neural responses to develop more bespoke approaches to assessing and managing individuals with CMSKP. In terms of the DMN, these findings support previous research and illustrates as Baliki et al (2008) eloquently stated, that the brain of someone with chronic pain 'is not simply a healthy brain processing pain information, but rather is altered by the persistent pain in a manner reminiscent of other neurological conditions associated with cognitive impairment' (pg 1402).

Fear and catastrophising in patients with CMSKP does have a number of neural correlates and neuroimaging research may be useful in refining questionnaires and to assist the production of cut-off points to uncover aspects of daily living that impact on pain-related fear, anxiety and catastrophising. For example, a range of fear avoidance and catastrophising questionnaires could be administered to subjects prior to scanning and then

subjects stratified into low and high responders. Using fMRI, the neural correlates of high and low responders could be mapped and compared with questionnaire responses, those that compare well to the fMRI data may be a more robust method to assess fear and catastrophising. Further research could then compare treatment outcomes between these groups attempting to identify predictors of good and poor treatment outcomes.

The study in Chapter 5 was aiming to examine the role of pain-related attention rather than specifically looking at fear, anxiety and catastrophising but it can be seen in the behavioural literature review (Chapter 2) that these are closely linked with and facilitated by pain-related attention. Again, in Chapter 2, one of the issues that emerged is that TSK is limited by the fact that it uses words rather than images and the study here and the Stroop study in Chapter 5, in the same group of patients with CMSKP tentatively support the fact that images of activities are probably more salient than pain words in this group of patients.

The PHODA modifications undertaken for the study have not been through a full validation process but the neuroimaging results in the CMSKP group appear promising. Therefore, it was deemed important to use a similar methodology in a group in which PHODA was originally designed, i.e. chronic low back pain. Also to examine the modified PHODA in a more discrete group of patients and in a large sample size to reduce the impact of different pain sites and improve the power of the study. Lastly, we intended to omit the bespoke pictures as the behavioural anxiety scores were no different between bespoke pictures and standardised pictures but did increase the time spent in the scanner.

CHAPTER 7: PHODA AND CHRONIC LOW BACK PAIN

7.1 ABSTRACT

Chronic low back pain (CLBP) and the accompanying disability represent a large socioeconomic problem, involving great individual suffering and health care expense. The Fear Avoidance Model of pain addresses how catastrophising and fear of movement (kinesiophobia) influence disability. Research examining fear of movement is controversial and further research is required to address some of these controversies. We used blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) to compare brain responses in patients with chronic low back pain (CLBP) (n=20) and healthy controls (n=20) to a picture and imagination task. We asked participants to view pictures of daily activities and imagine how they would feel mentally and physically during the task with the aim of comparing BOLD responses in CLBP patients with age and gender matched controls. The task results in BOLD differences in brain regions associated with fear conditioning, emotional and sensory pain processing, including anterior cingulate cortex (ACC), insula, primary sensory cortex (SI) and thalamus. Higher kinesiophobia and catastrophising scores resulted in BOLD differences in regions associated with fear and negative emotion processing. Increased BOLD responses were also seen in patients and not controls in areas that are deemed to be part of the default mode network activity; posterior cingulate cortex, precuneus, angular gyrus and middle frontal cortex when completing the picture activity. Resting BOLD and VBM were undertaken in a sub-group of the total population. There were no differences between patients and controls in grey matter density (voxel based morphometry analysis), but there were differences in resting state connectivity (dual regression and seed region analyses). This study illustrates the importance of anticipated fear and catastrophising in patients with CLBP through the use of a photograph and imagination task and illustrates some dysfunctional aspects of brain

processing in the CLBP population. It also illustrates that resting BOLD may be a useful technique but some of our findings do not concur with the current, sparse literature in chronic pain populations.

7.2 INTRODUCTION

Despite an increased understanding of the factors contributing to the maintenance of pain and disability through behavioural research in chronic low back pain (CLBP), there has been only a moderate improvement in treatment outcomes (Croft 2000; van der Windt et al. 2008) and the prevalence has remained relatively constant over the past two decades (Palmer et al. 2000; Maetzel and Li 2001). CLBP and the accompanying disability continues to be a major socioeconomic problem involving great individual suffering and health care expense (Taylor et al. 2000; Benuzzi et al. 2008) and interventions have shown at best, only moderate effects in reducing pain and disability (Chou and Huffman 2007). This suggests that while knowledge has increased, there is much still to understand about assessment, screening and management of CLBP.

The development of chronicity in patients with low back pain has been increasingly accepted as resulting from the Fear Avoidance (FA) Model, and it is in this group that the majority of fear-avoidance research has been undertaken (Vlaeyen and Crombez 1999; Leeuw et al. 2007c). The FA model proposes that in the acute phase, a fear of movement or 'kinesiophobia' is acquired (Kori et al. 1990) leading to avoidance of physical activity. Eventually physical deconditioning results with the cognitive sequelae associated with CLBP such as depression and anxiety (Waddell et al. 1993; Vlaeyen and Crombez 1999; Leeuw et al. 2007a). Typically, catastrophising, fear and avoidance of movement, hypervigilance and pain sensitisation are components of chronicity (Lundberg et al. 2011).

Studies in CLBP have shown that high fear-avoidance behaviour leads to reduced performance in movement tasks (Vlaeyen et al. 1995; Crombez et al. 1999b; Geisser et al. 2004), the expectation of more movement-related pain (Trost et al. 2009) and the prediction of self-reported disability (Vlaeyen et al. 1995; Crombez et al. 1999b; Peters et al. 2005). However, research surrounding fear of movement and (re)injury is not conclusive with observational studies showing contradictory results and interventions based on the model not providing convincing results (Pincus et al. 2010). Pincus et al (2010) proposed that the FA model needs to be conceptually expanded and further tested to provide adequate and appropriate clinical utility. While fear of movement appears to play a prominent part in explaining chronicity in CLBP, it is clear further investigation is required especially given that little is known about the neural correlates of fear in patients with CLBP who are highly kinesiophobic.

Neuroimaging has allowed for an improved understanding of how variables such as cognition, emotion and context can influence pain perception (Tracey and Mantyh 2007). For chronic pain patients, it is possible to use a number of paradigms such as asking people to imagine, recall, or view images of stimuli that they may associate with (Shimo et al. 2011). Pain-relevant stimuli appear to activate similar regions of the brain in chronic pain patients as those activated by noxious stimulation (Shimo et al. 2011), and therefore this method can provide an opportunity to investigate neural responses without the need to induce pain and moving away from our current over-reliance on self-report measures. While this method has significant potential, studies in chronic pain patients are still relatively rare, which is important as both neural structure and function can be different in this group to healthy controls (Giesecke et al. 2004; Buffington et al. 2005; Baliki et al. 2006; Baliki et al. 2010). Furthermore, naturally occurring pain can differ greatly from

experimentally induced pain in relation to fear avoidance (George and Hirsh 2009). Pincus et al (2010) suggest that future pain fear-related research should use more individualised designs to increase sensitivity by obtaining information about specific feared movements/situations.

The previous chapter presented a study which examined the use of PHODA in trying to determine the neural correlates of fear, anxiety and catastrophising in patients with CMSKP who were low kinesiophic. A modified PHODA was used and BOLD differences were found in patients compared to controls when undertaking the PHODA task in regions closely aligned to fear- and phobia-related regions reported in a recent systematic review (Etkin and Wager 2007). These regions are also of interest in this study. Therefore, given that PHODA was developed to assess fear-avoidance in patients with CLBP, further investigation has been suggested in this group of patients and as the modified PHODA has only been tested in one group of patients, further research is warranted. We also investigate whether patient group responses are different to the BOLD signals observed in pain-free controls.

Of note, was the activity of the DMN in the patient group in Chapter 6. In this group, we had not collected resting BOLD data but did so in this study. Therefore, the analysis of the resting BOLD data may help to further explain any DMN abnormalities seen in the CLBP patients if indeed they are present. Recent neuroimaging studies have focused on identifying neural correlates of chronic pain (Baliki et al. 2006; Tracey 2008)but it has been difficult to elicit chronic pain in a controlled manner as it can arise spontaneously and can fluctuate in magnitude. Resting BOLD connectivity examines intrinsic connectivity which is defined as ongoing neural and metabolic activity that occurs in the resting basal

state (Napadow et al. 2010). The role of intrinsic brain connectivity has not been definitively resolved to date but it may be important for the maintenance of synaptic connectivity and for information transfer between disparate brain regions comprising known primary sensory, executive and associative networks (Fox and Raichle 2007).

Voxel based morpometry has been used previously to examine structural changes that occur in the brain in association with long-term pain (Apkarian et al. 2004b; Schmidt-Wilcke et al. 2006a; Kuchinad et al. 2007; Lutz et al. 2008; Hsu et al. 2009; Gerstner et al. 2011). The majority of studies have shown grey matter loss with a number of chronic pain conditions. Given that, in Chapter 6, some assumptions were made about BOLD signal differences occurring in patients compared to controls which may be accounted for by structural changes, it was decided to include VBM in this population to ascertain if structural loss was present.

7.3 METHODS

Given the fact that the study is being replicated in a more discrete group of patients (i.e. CLBP) than in the study presented in Chapter 6, the methods section is very similar to that used in the previous chapter.

7.3.1 Participants

A total of 40 participants were enrolled in this study and included 20 patients with CLBP and 20 age and gender matched control subjects. Patients were referred from the local teaching hospital's chronic pain clinic where they had been diagnosed with chronic non-malignant pain due to mechanical low back pain. Control participants were recruited from either the School of Psychology' volunteer panel or through local advertisement within

Cardiff University. Dyfed Powys Research Ethics Committee and local Research and Development Committee approval was obtained prior to commencement of the study.

Criteria for patient inclusion in the study were: an average pain score of 50 and above on a numerical rating scale of 0-100 ('No Pain' – 'Worst Possible Pain') over the 3 months prior to enrolment and for all participants that lying down did not provoke pain and they were comfortable being in the scanner. Exclusion criteria for all participants were: serious metabolic, rheumatoid, vascular or diagnosed psychiatric disorders; dyslexia or unable to read written English; inability to give informed consent, and; contraindications to MR scanning. Regular analgesic regimens were not altered and patients were asked not to commence new analgesics.

7.3.2 Questionnaires and assessment

Participants were interviewed at least two weeks prior to scanning to commence the informed consent process, to obtain information regarding pain and current medication and to complete the behavioural questionnaires. Participants rated their current pain on a numerical rating scale (NRS) from 0 (no pain) to 100 (worse possible pain). Using the same scale, they also rated their worst pain, least pain, pain intensity and the degree to which the pain interfered with activities of daily living over the previous week. The 101-point (i.e. 0–100) NRS measure of pain intensity is recommended as a core outcome measure in clinical trials of chronic pain (Dworkin et al. 2005).

Depressed mood was assessed using Beck Depression Inventory (BDI) (Beck et al. 1961). The BDI comprises 21 questions where each item ranges from 0 to 3 points, giving a maximum score of 63 points; <10 no depression, 10-18.7 mild depression, 18.7-25.4

moderate depression, and > 35.4 severe depression (Beck et al. 1961). The Tampa Scale of Kinesiophobia (TSK) (Kori et al. 1990; Roelofs et al. 2004) was used to evaluate fear of movement; it comprises 17 items assessing the subjective rating of kinesiophobia. Each item has a 4-point Likert scale with scoring alternatives ranging from 'strongly disagree' to 'strongly agree'. The total score lies between 17 and 68 and a cut-off >37 has been defined as a high degree of kinesiophobia. Catastrophising was assessed using the catastrophising subscale from the Coping Strategies Questionnaire (Rosenstiel and Keefe 1983). The Coping Strategies Questionnaire assesses the frequency of patients' use of pain coping strategies using a 7-point scale to rate how often they use each strategy to cope with pain. Clinically relevant catastrophising is defined as scores of 11 and above (Jellema et al. 2005). Data were analysed using a Mann-Whitney test because of their non-parametric nature.

7.3.3 PHODA-LBP development

As discussed in section 4.3, we previously validated PHODA-LBP in a pilot study to ensure that the series of photographs used was specifically tailored to the patient group and given that the context and question posed would be different from the original cited above. The modified tool, PHODA-LBP, consisted of 30 pain-related photographs belonging to one of six categories: exercise, twisting, bending, pull/push, carrying, and lifting (5 images in each category, and 10 photographs which were neutral or relaxing photographs.).

We decided to omit the 'bespoke' category from this study as it increased scanning time, limiting its future use in patients who may not be able to tolerate long periods in a scanner and given that it appeared to have little impact on the study results.

7.3.4 Imaging paradigm for PHODA-LBP

The event-related design fMRI study used PHODA-LBP to study CLBP patients. When the pictures were presented, participants were asked to imagine undertaking the depicted activity (e.g. a person pushing a sweeping brush, twisting to move an object). At the start of the scanning session, subjects were presented with the following on a screen: 'The task is about to begin. For each trial you will be presented with a photograph depicting a daily activity. Imagine that after scanning we will ask you to attempt this activity. Imagine how you would feel both mentally and physically during your attempt'. After the photograph was shown, participants were required to rate their anxiety using a 4-button response box held in their right hand. When processing the data post-collection the responses were scored as follows: 0 = no anxiety; 1 = mild anxiety; 2 = moderate anxiety; and 3 = severe anxiety. The participants viewed 40 photographs consisting of 30 pain-related activities (PHODA-LBP) and 10 neutral or relaxing activities. Relaxation pictures were required to provide contrasts in the experiment. It transpired however, that patients rated these relaxation photographs also. FMRI needs contrasting stimuli within a scan run. FMRI needs contrasting stimuli within a scan run. Participants viewed five photographs for each of the 6 activity categories; pull/push, lifting, twisting, bending, carrying and exercise. Each trial (see Fig.7.1) lasted between 7s and 15s and consisted of a photograph presented on screen for a fixed duration of 3s, a fixation cross for a random number of seconds between 1s and 5s (mean 3s), a response mode ('RATE NOW') whereby the subject has a fixed 2s to rate their anxiety, and finally another fixation cross for between 1s and 5s (mean 3s). The durations of both fixations were randomised and the 40 photographs were counterbalanced. The stimuli were presented in fixed random order: i.e. every subject viewed the pain-related and neutral trials in the same random order, with the same random order of fixation durations.

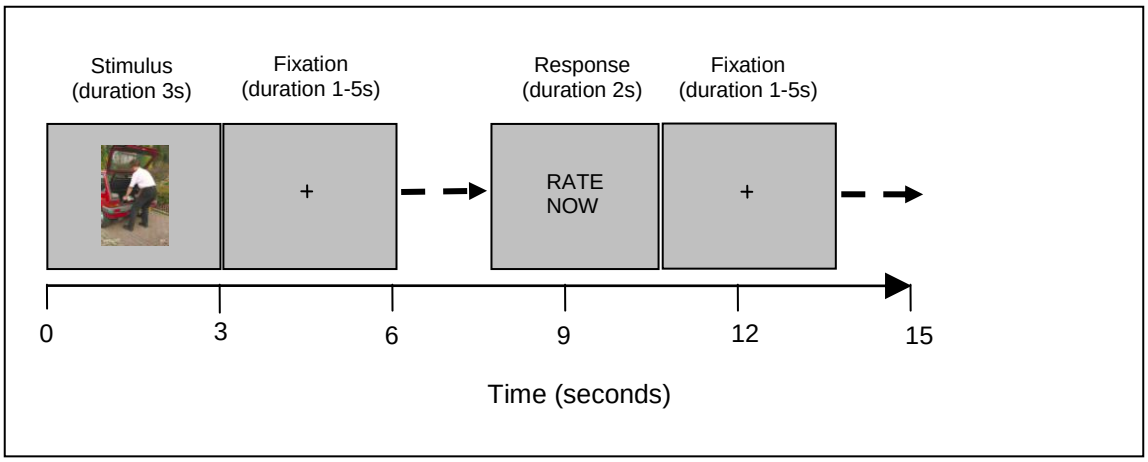


Fig.7.1. Trial-to-trial timing

7.3.5 Participant training

Subjects completed a practice version of the task in the mock scanner lasting approximately 90s and consisting of 10 trials prior to scanning. The categories of photographs presented in the mock scanner were the same as the ones to be used in the scanning session but the actual pictures were unique to the mock session. Therefore participants practiced the task components of button pressing but were not exposed to the photographs used in the scanner. Participants were asked if they understood the task and were comfortable with it and the mock data was scanned to ensure that the participants were correctly responding.

7.3.6 Imaging

Imaging was performed on a 3-T MRI system (HDx, General Electric Healthcare, Waukesha, Wisconsin, USA) using an 8-channel receive-only head coil. Functional MRI data were acquired with a gradient-echo, echo-planar imaging sequence, scanning parameters were: repetition time (TR)/echo time (TE) = 3000 ms/35 ms, 20.5 cm field of view, acquired on a 64 x 64 matrix with 53 contiguous 3.2 mm slices. Each run consisted of 236 repetitions. For anatomic localisation, a T1-weighted, three-dimensional fast-

spoiled gradient echo acquisition was performed, with a voxel resolution 1x1x1 mm^3 (scanning parameters included: TR/TE = 7.8/3 ms, 450 ms inversion time, 256 x 128 acquisition matrix) for each participant. Six minutes and 5 seconds of resting-state BOLD data was collected (130 volumes and 53 slices). Patients were asked not to think about anything and fixate on a crosshair displayed on the computer screen. Physiological data were collected during the scanning session as cardiorespiratory fluctuations are known to influence estimations of intrinsic connectivity within several brain networks (Birn et al. 2006; Chang and Glover 2009). Cardiac data were acquired using an infrared pulse oximeter attached to the left middle finger and respiratory volume data were acquired using an MR-compatible belt which was placed around the subject's rib cage.

7.3.7 Image analysis

FEATv5.98 (FMRI Expert Analysis Tool), part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl), was used to analyse the BOLD fMRI data. The functional data for each subject was motion corrected (MCFLIRT (Jenkinson et al. 2002)) and fieldmaps were processed using PRELUDE+FUGUE (Jenkinson 2003, 2004) to correct for field distortions in the functional data. A Gaussian kernel with a FWHM of 5mm was used to spatially smooth the data and then data was filtered with a highpass temporal filter (cut off of 100 s). Data were demeaned on a voxel-by-voxel basis across the time course. At the voxel level, the signal was linearly modelled (FILM-FMRIB's Improved Linear Model) with autocorrelation correction (Woolrich et al. 2001).

FLIRT was used to register each participant's high resolution structural data and FLIRT followed by FNIRT nonlinear registration registered this data to standard space (Andersson et al. 2007).

A first level analysis was performed on the data which used the individual subject level data (see page 167) as the convolution of 'picture' and 'rate now' events with the haemodynamic response function (a gamma-variate). A second-level, mixed effects analysis was performed comparing the varience between the patient group and the control group during picture viewing and rating the anxiety score. Anxiety scores rated on a button box during the picture viewing task were regressed into the FEAT analysis along with the catastrophising and TSK self-rating scores. The regressions were 'pictures and anxiety scores rated in the scanner', 'pictures and TSK scores' and 'picture and catastrophising scores' looking for a correlation between higher scores and areas of BOLD activity.

For all analysis, statistic images were thresholded using clusters determined by a $z>2.3$. For the second level analysis, patient compared to controls and cluster corrected at a significance threshold of $p=0.05$ (Worsley 2001). FLAME (Woolrich et al. 2004) was used for the higher level analysis. Beck Depression Scores were de-meaned and regressed into all of the higher level analysis to adjust for the possible effects of depression (Gracely et al. 2004).

FSL was used to view the statistical parametric maps and the areas of BOLD signal differences were identified by using the Harvard-Oxford cortical and subcortical atlases and for identification of primary and secondary somatosensory regions, Juelich Histological Atlas was used as Harvard-Oxford does not identify these regions. Functional regions of interest were identified as the intersection of the anatomical mask from the Harvard-Oxford and Juelich atlases and the thresholded *z*-statistic image and the average

signal change for each region for each group was plotted for illustrative purposes. No further statistical tests were used for or applied to these results.

VBM analysis

A structural analysis was performed using FSL's VBM tool (Smith et al. 2004; Douaud et al. 2007) that is based on the analysis pipeline of Good et al (2001) T1-weighted anatomical images were brain extracted using BET and segmented for grey matter (FSL, FAST) before being registered to standard space using non-linear registration (FNIRT). These images were averaged and mirrored to create a right-left symmetric image. From this, a study specific grey matter template was defined to which all grey matter was non-linearly registered while correcting for local expansions and contractions due to the non-linear spatial transformations. An isotropic Gaussian smoothing kernel of sigma = 3 mm was then applied to the segmented images. Then a voxel-wise GLM was applied using permutation-based non-parametric testing, correcting for multiple comparisons, as is standard with VBM in FSL.

Resting BOLD analysis

The resting BOLD analysis followed methods previously described in the literature that were deemed to be robust (Filippini et al. 2009; Napadow et al. 2010). Data was analysed using FSL (available from the FMRIB Software Library at www.fmrib.ox.ac.uk/fsl). Noise correction was first achieved using a previously described component based noise correction method (CompCor) (Behzadi et al. 2007) as not all subjects had corroborative physiological data. Data were corrected for motion artifact, compensating for any head movements using an FSL linear (affine) transformation (FSL-MCFLIRT) procedure. Extraction of functional data was performed using FSL-BET. Data were smoothed using a

Gaussian kernel of 5-mm and high-pass temporal filtering (f = 0.003 Hz) was also performed to remove very low frequency scanner-drift artifacts.

Analyses of the within- and between-subject resting state BOLD data were performed using FSL's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (FSL-MELODIC) tool and a previously validated dual-regression approach (Beckmann et al. 2005). This approach allows for voxel-wise comparisons of resting-state functional connectivity; firstly by temporally concatenating resting state BOLD data from all subjects and then by back-reconstructing the group intrinsic connectivity networks for individual subjects. Previous research has shown this approach to have moderate to high test-retest reliability (Zuo et al. 2010).

Co-registration of functional data was undertaken using FLIRT after it was projected to standard Montreal Neurological Institute space and nonlinear co-registration was undertaken using FNIRT. These BOLD functional data (130 volumes for each subject) were then concatenated in time across all subjects, creating a single 4-dimensional (4-D) data set. Probabilistic ICA using MELODIC was performed to identify global, distinct (independent) patterns of functional connectivity in the entire subject population. The number of independent components was limited to 25 as had been described (Filippini et al. 2009; Napadow et al. 2010). The spatial IC maps, identified from the total population data, were used in a GLM of the subject's resting state BOLD data as a spatial regressor. This model was used to find the subject-specific temporal dynamics within the 25 IC networks defined above. The time series for each component was variance normalised by subtracting the mean and dividing by the SD and used as a temporal regressor in the GLM of the subject's resting state BOLD data. Group analyses were performed to evaluate

differences in intrinsic brain connectivity between the 2 groups and to establish how the intrinsic connectivity covaries with spontaneous pain intensity in the patient group. Group main-effects maps for both groups, as well as between-group difference maps (calculated using unpaired *t*-tests for patients versus healthy controls) were determined for each of the IC networks using permutation-based non parametric testing (FSL randomise) (Nichols and Holmes 2002; Hayasaka and Nichols 2003). The results were subject to threshold-free cluster enhancement (Smith and Nichols 2009) and family-wise error (FWE) corrected for multiple comparisons by permutation testing using a significance level of $p<0.05$.

Following the dual regression analysis, as recommended by Napadow et al (2010), covariation between intrinsic connectivity and current pain scores was undertaken, as this analysis had been proposed to more closely link intrinsic pain connectivity to the chronic pain state (Napadow et al. 2010). Regions that were deemed of interest, the ACC, insula, DMN network and PCC, were identified as seed regions using data from the PHODA analysis. The DMN seed regions were defined using a template downloaded from the Beckmann et al (2005) and the ACC and insula were defined anatomically using the MNI atlases and all were restricted using data from the PHODA analysis (Fig 7.3 and 7.5). Time courses were extracted from individual subjects and used as regressors in the first level analysis and the second level analysis was performed comparing patients and controls, covarying current pain scores into this analysis. Current pain scores were demeaned.

7.4 RESULTS

7.4.1 Demographics and questionnaires

Forty participants were recruited to the study and scanned (20 male, 20 female), age range 21 to 70 years old (mean age 47.5 years), including 20 patients with chronic low back pain

and 20 age-matched controls. All patients had previously undergone a diagnostic MRI, as had 4 of the pain-free volunteers for non-pain associated clinical reasons. The average duration of pain suffered in the patients was 149.2 months (range 24 months – 408 months). No differences were found in marital status, years in school, or number of dependents between patients and volunteers. Pain scores, anxiety scores rated in the scanner, demographics and psychological variables were compared between groups and patients and controls differed in pain scores and psychological variables (Table 7.1, 7.2).

Table 7.1: Psychological variables and pain scores

Variable	Patient	Control	*p* value*
Beck Depression Inventory <10 no depression, 10-18.7 mild, 18.7-25.4 moderate, > 35.4 severe depression	23 (11, 35)	2 (0, 3)	< 0.001
CSQ Catastrophise 0 = Never catastrophise, 36 = Always catastrophise about pain	18 (6, 28)	0 (0, 0)	< 0.001
Tampa Scale of Kinesiophobia The total score ranges between 17 and 68. A high value on the TSK indicates a high degree of kinesiophobia, a score of 37 differentiates between high and low scores	41 (33, 48)	21 (17, 22)	< 0.001
Current pain (present pain) (NRS 0-100)	62 (64, 80)	0 (0, 0)	< 0.001
Worst pain (worst pain imaginable during week) (NRS 0-100)	82 (75, 90)	4 (0, 0)	< 0.001
Least pain (during week) (NRS 0-100)	44(30, 59)	0 (0, 0)	< 0.001
Pain intensity (during week) (NRS 0-100)	66 (50, 84)	1 (0, 0)	< 0.001
Pain distress (during week) (NRS 0-100)	66 (47, 84)	0 (0, 0)	< 0.001
Disturbance (during week) (NRS 0-100)	70 (54, 90)	0 (0, 0)	< 0.001

Table 7.2 Anxiety ratings undertaken on the button box during scanning

Function 0 = no anxiety – 3 severe anxiety	Median (25^{th}, 75^{th} quartiles)	*p* value (Mann-Whitney)
Bending	Patients 2 (1, 2) Controls 0 (0, 0)	< 0.001
Twisting	Patients 2 (1, 2) Controls 0 (0, 0)	< 0.001
Carrying	Patients 2 (1, 3) Controls 0 (0, 0)	< 0.001
Exercise	Patients 2 (2, 3) Controls 0 (0, 0)	< 0.001
Push/pull	Patients 2 (1, 3) Controls 0 (0, 0)	< 0.001
Lifting	Patients 3 (2, 3) Controls 0 (0, 0)	< 0.001
Neutral	Patients 1 (1, 2) Controls 0 (0, 0)	< 0.001

All patients had chronic back pain as their primary diagnosis, 6 patients were taking strong opioids, 12 weak opioids, 7 non-steriodal anti-inflammatory drugs, 9 paracetamol, 10 adjuvant analgesia, 4 had a lidocaine patch and 1 was on a topical preparation for pain management. All had received at least one course of physiotherapy, none had attended self-management programmes or self-management training. Of those scanned, 4 controls and 2 patients were left handed.

7.4.2 Imaging

Pictures

Patients had increased BOLD responses compared with controls when viewing pictures and imagining how they would feel. When viewing the pictures, bilateral BOLD signal increases were seen in patients and not controls in paracingulate gyrus, anterior cingulate cortex (ACC), supplementary motor cortex, precuneus cortex, posterior cingulate cortex (PCC), frontal pole, middle frontal gyrus, putamen, caudate, thalamus, insula, primary

somatosensory cortex (SI), secondary somatosensory cortex (SII), superior frontal gyrus, superior partietal cortex, supramarginal gyrus posterior division, angular gyrus, intercalcarine, cuneus, frontal orbital cortex, lingual gyrus, temporal fusiform cortex, posterior division, parietal operculum, supracalcarine, pallidum, accumbens and within the cerebellum. Appendix 8 contains statistical parametric maps and tables illustrating within group differences.

Lateralised to the left, positive BOLD responses were seen in patients compared with controls in the inferior frontal gyrus (pars opecularis and pars triangularis), inferior temporal cortex (temporoccipital and posterior divisions), supramarginal gyrus anterior division, lateral occipital gyrus, superior division, parahippocampal cortex, posterior division and Heschl's gyrus (Table 7.3,7.4, Figures 7.2-7.4).

No BOLD differences were seen between patients and controls when rating the anxiety scores and there was no correlation between anxiety scores and BOLD responses. Lateralised to the right was a discrete region that represented increased BOLD responses associated with higher CSQ catastrophising sub-scale scores during picture viewing. This region included superior and middle temporal gyri, orbitofrontal cortex, putamen, insula, temporal pole and amygdala (Table 7.5, Fig 7.5). A distinct area was also found that reflected increased BOLD responses while viewing pictures associated with TSK scores, and this included occipital fusiform, parahippocampal gyrus, temporal occipital fusiform and lingual gyrus (Table 7.5, Fig 7.6).

Table 7.3: Group differences for PHODA-LBP and imagination task

Group differences for PHODA-LBP and imagination task in regions involved in pain processing. Anatomical locations and peak activation co-ordinates (in MNI 152 TI 2mm brain) extracted from brain regions that were found to be significantly different between patients and controls (patients > controls) at $z>2.3$ and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
ACC (L)	-4	-4	44	3.48
ACC (R)	4	-2	44	2.96
Accumbens (L)	-14	14	-8	3.30
Accumbens (R)	12	16	-8	3.11
Caudate (L)	-12	10	8	3.76
Caudate (R)	12	10	8	3.17
Cerebellum:				
Crus I (L)	-32	-72	-34	3.26
Crus I (R)	34	-56	-32	3.26
I-IV (L)	-2	-52	-18	2.78
V (R)	14	-56	-18	2.59
Vermis VI	-6	-68	-22	2.93
Vermis VIIIb	4	-68	-30	2.64
VI (L)	-14	-68	-22	2.42
VI (R)	30	-50	-34	2.93
Cuneal cortex (L)	-12	-74	24	2.72
Cuneal cortex (R)	14	-68	24	4.62
Inferior frontal pars triangularis (L)	-48	24	8	2.73
Inferior frontal, pars opecularis (L)	-48	14	14	2.70
Insula cortex (L)	-32	22	4	3.33
Insula cortex (R)	32	18	-6	3.14
Orbitofrontal cortex (L)	-32	28	-2	3.00
Orbitofrontal cortex (R)	30	30	-2	2.60
Parahippocampal gyrus, posterior division (L)	-18	-36	-14	2.60
Parietal operculum (L)	-50	-36	30	3.31
Parietal operculum (R)	52	-28	28	2.43
Putamen (L)	-22	8	-4	4.20
Putamen (R)	22	14	-4	3.54
SI(L)	-50	-26	54	3.36
SI(R)	42	-30	54	2.49
SII(L)	-52	-30	42	4.21
SII(R)	42	-26	54	2.57
Superior frontal gyrus (L)	-22	16	48	2.98
Superior frontal gyrus (R)	24	14	48	3.34
Superior parietal lobule (L)	-36	-48	48	3.09
Superior parietal lobule (R)	36	-40	48	3.10
Supramarginal gyrus, anterior division (L)	-52	-34	48	3.30
Supramarginal gyrus, posterior division (L)	-50	-48	48	3.18
Supramarginal gyrus, posterior division (R)	54	-40	48	2.72
Thalamus (L)	-14	-20	6	3.11
Thalamus (R)	16	-14	6	2.80

Table 7.4: Group differences for memory, motor and DMN BOLD regions

Group differences for PHODA-LBP and imagination task in regions involved in memory and DMN. Other regions found have been included for completeness. Anatomical locations and peak activation co-ordinates (in MNI 152 TI 2mm brain) extracted from brain regions that were found to be significantly different between patients and controls (patients > controls) at $z>2.3$ and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
Memory and motor regions				
Frontal pole (L)	-24	62	-4	2.89
Frontal pole (R)	22	56	2	3.77
Inferior frontal gyrus pars triangularis (L)	-48	24	8	2.73
Inferior frontal gyrus, pars opecularis (L)	-48	14	14	2.70
Inferior temporal lobe (temporooccipital part) /fusiform gyrus (L)	-52	-48	-22	2.87
Paracingulate cortex (L)	-4	22	42	3.50
Paracingulate cortex (R)	4	22	42	3.59
Supplementary motor cortex (L)	-4	0	50	2.83
Supplementary motor cortex (R)	8	2	50	3.11
Default Mode Network				
Angular gyrus (R)	50	-50	48	2.47
Angular gyrus (L)	-48	-54	48	2.66
Middle frontal gyrus (R)	26	14	48	3.66
Middle frontal gyrus (L)	-42	30	36	3.39
Precuneus (R)	2	-72	46	3.60
Precuneus (L)	-2	-72	46	3.38
PCC (R)	4	-46	18	2.58
PCC (L)	-4	-36	38	2.76

Fig.7.2. Regions implicated in the sensory-discriminative dimensions of pain

Statistical parametric maps comparing activation during the PHODA-LBP task between the patient and control groups. Patient with CLBP have significantly different BOLD activation in main sensory discriminative pain regions (ACC and Insula are presented in Fig 7.3) when undergoing the task and imagining undertaking the activity depicted in the photograph. Each z-statistic map represents these group differences in a whole brain analysis. The colour bar shows the scale of the *z*-statistic (2.3 – 8.7). The images are a combination of anatomical and functional data and the graphs represent the direction and magnitude of the signal change within the region and were therefore not tested for statistical significance. The graphs show the percentage BOLD signal change with the error bars representing standard deviations across subjects.

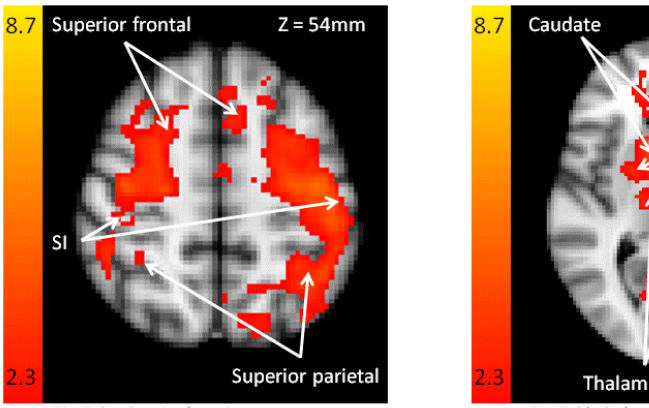


Fig 7.2a Cortical regions

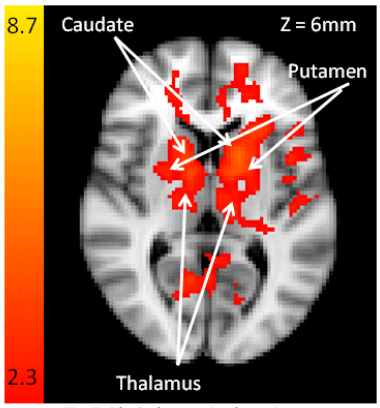
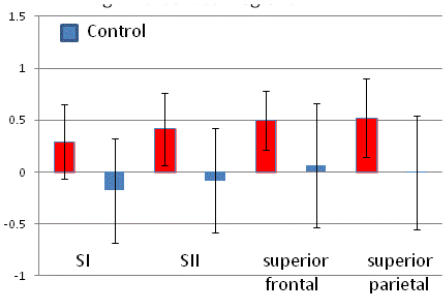
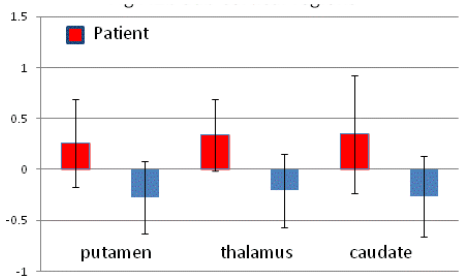


Fig 7.2b Sub-cortical regions





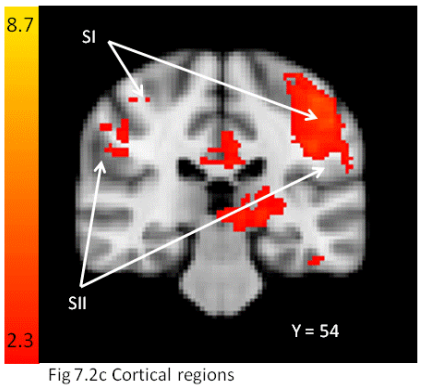


Fig 7.2c Cortical regions

Fig.7.3. Regions involved in the affective-motivational dimensions of pain
Statistical parametric maps comparing activation during the PHODA-LBP task between the patient and control groups. Patient with CLBP have significantly different BOLD activation in main affective-motivational pain regions when undergoing the task and imagining undertaking the activity depicted in the photograph. Each z-statistic map represents these group differences in a whole brain analysis. The colour bar shows the scale of the *z*-statistic (2.3 – 8.7). The images are a combination of anatomical and functional data and the graphs represent the direction and magnitude of the signal change within the region and were therefore not tested for statistical significance. The graphs show the percentage BOLD signal change with the error bars representing standard deviations across subjects.

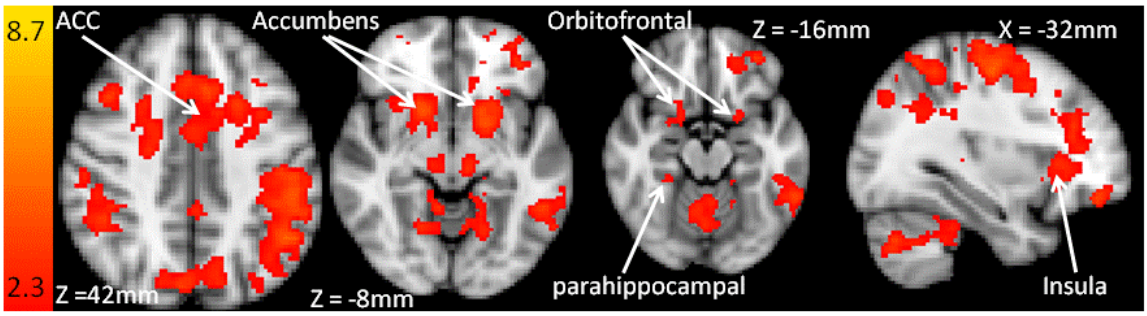


Fig 7.3

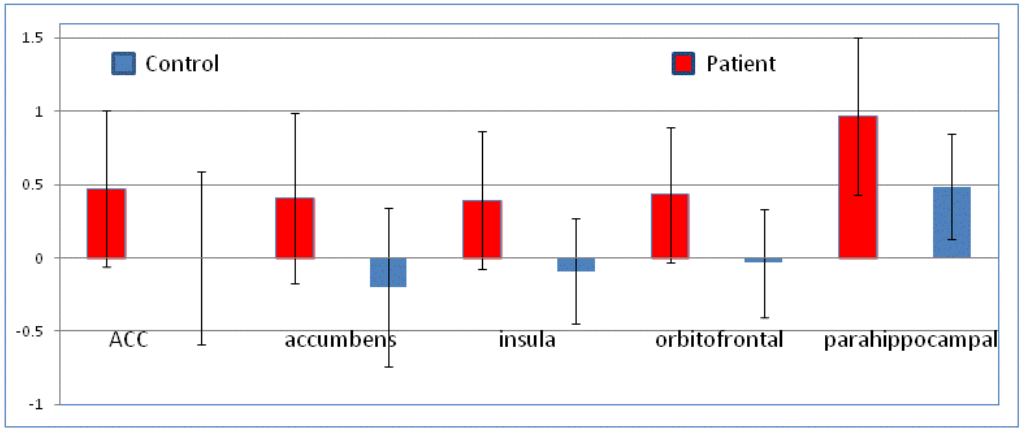
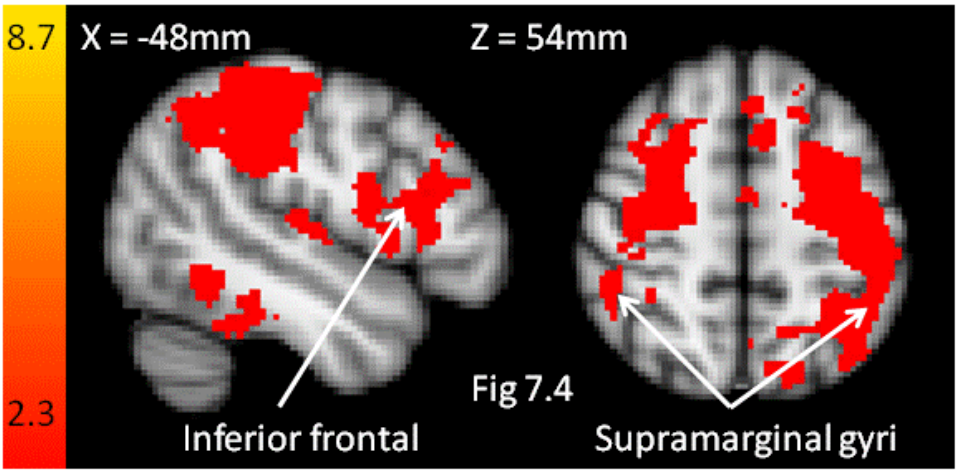


Fig.7.4. Regions involved in the cognitive-evaluative dimensions of pain
Statistical parametric maps comparing activation during the PHODA-LBP task between the patient and control groups. Patient with CLBP have significantly different BOLD activation in main cognitive-evaluative pain regions when undergoing the task and imagining undertaking the activity depicted in the photograph. Each z-statistic map represents these group differences in a whole brain analysis. The colour bar shows the scale of the *z*-statistic (2.3 – 8.7). The images are a combination of anatomical and functional data and the graphs represent the direction and magnitude of the signal change within the region and were therefore not tested for statistical significance. The graphs show the percentage signal change with the error bars representing standard deviations across subjects.



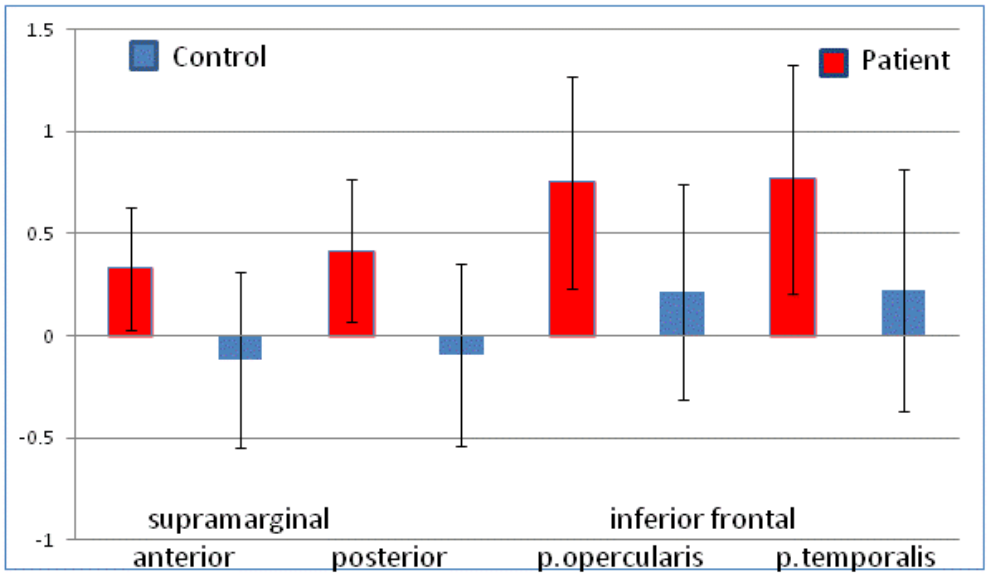


Fig.7.5. DMN Regions

Statistical parametric maps comparing activation during the PHODA-LBP task between the patient and control groups. Patient with CLBP have significantly different BOLD activation in regions known to be involved in DMN when undergoing the task and imagining undertaking the activity depicted in the photograph. Each z-statistic map represents these group differences in a whole brain analysis. The colour bar shows the scale of the *z*-statistic (2.3 – 8.7). The images are a combination of anatomical and functional data and the graphs represent the direction and magnitude of the signal change within the region and were therefore not tested for statistical significance. The graphs show the percentage signal change with the error bars representing standard deviations across subjects.

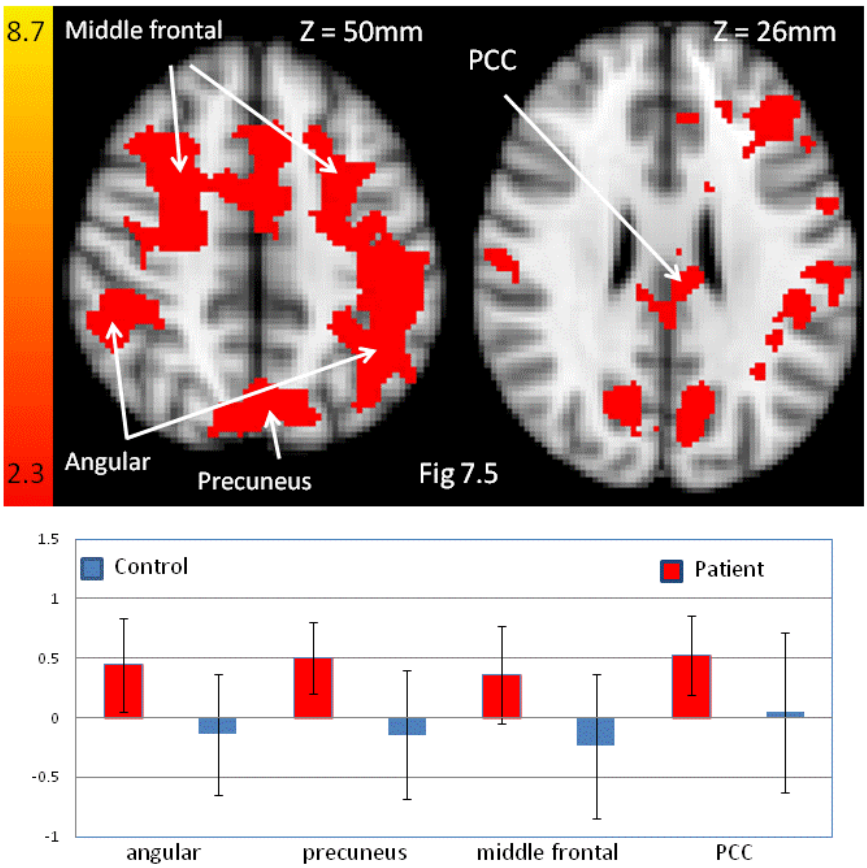
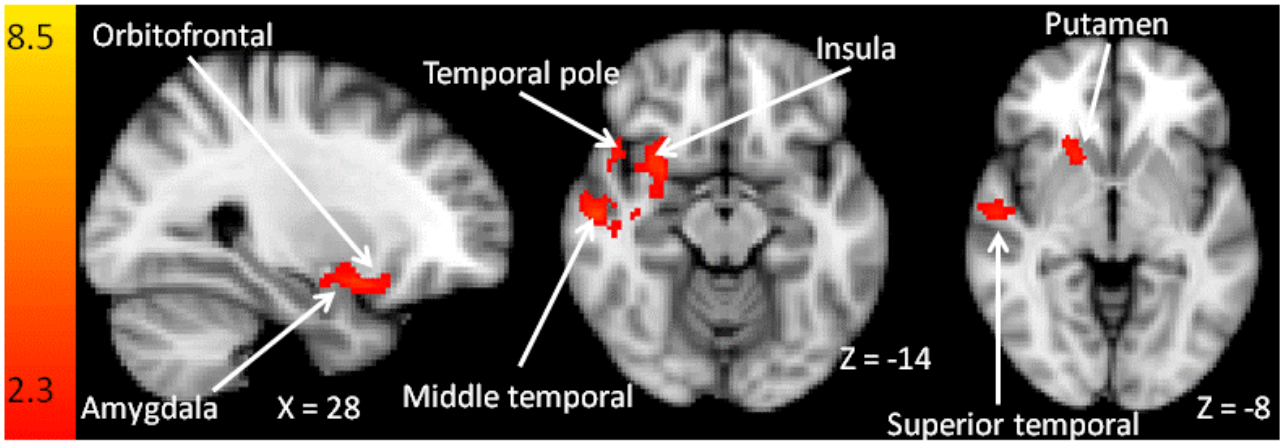


Fig.7.6. Statistical parametric maps illustrating BOLD signal changes with higher catastrophising and TSK scores

Maps illustrating activation during the PHODA-LBP task in regions associated with higher catastrophising (A) and TSK (B) scores. Each z-statistic map represents these group differences in a whole brain analysis. The colour bar shows the scale of the *z*-statistic (2.3 – 8.7) and the slice co-ordinate is stated.

A. Catastrophising scores



B. TSK scores

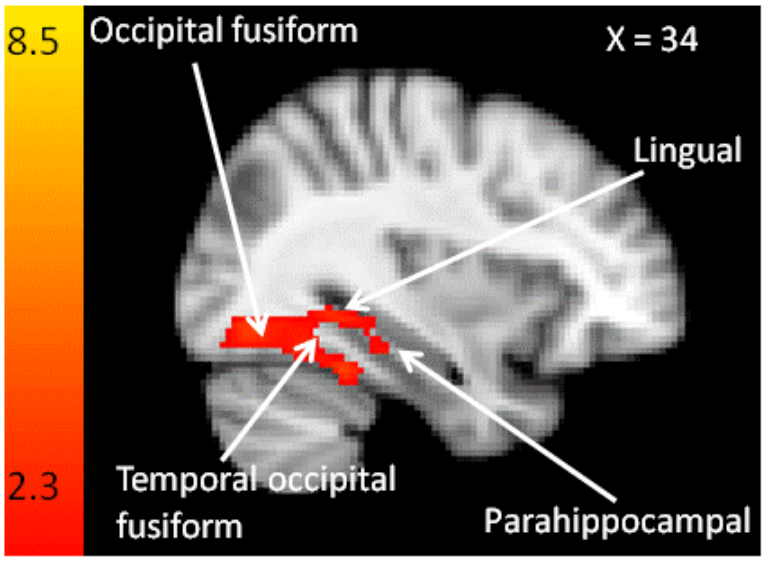


Table 7.5: BOLD signal changes with higher TSK and catastrophising scores

BOLD regions responding to higher TSK and catastrophising scores (FEAT analyses were run together), found in the covariate analysis during observation of the photographs and imagining undertaking the task depicted. Anatomical locations and peak activation co-ordinates (from MNI atlas) extracted from brain regions that were found to be significantly different between patients and controls (patients > controls) at $z>2.3$ and cluster corrected $p<0.05$.

	Co-ordinates x	y	z	z-stat
Regions corresponding to higher TSK scores (lateralised to the right)				
Lingual gyrus	14	-74	-6	2.47
Occipital fusiform	36	-72	-14	3.21
Parahippocampal gyrus (posterior)	24	-34	-16	3.05
Temporal occipital fusiform	34	-56	-14	3.09
Regions corresponding to higher catastrophising scores (lateralised to the right)				
Amygdala	30	-2	-14	2.52
Insula	40	-6	-10	2.73
Middle temporal gyrus (posterior)	56	-16	-14	3.46
Orbitofrontal cortex	44	22	-10	3.32
Putamen	18	14	-4	3.11
Superior temporal gyrus (posterior)	50	-14	-10	2.44
Temporal pole	46	12	-14	2.80

7.4.3 Resting BOLD and VBM

Voxel based morphometry was performed on 16 patients and 19 controls, these were the only subjects that had suitable structural scans for the analysis. The analysis did not detect differences in grey matter density between patients and controls.

Resting BOLD analysis was also undertaken on 16 patients and 19 controls as again, these were the only subjects with suitable scans. Given the exploratory nature of the resting BOLD analysis, it was decided to use all 25 components in the dual regression analysis to evaluate differences between patients and controls.

The resting BOLD analysis showed no differences between groups in any of the 25 components. However, correlation with current pain scores across the group revealed a positive association with component 2.

The dual regression analysis showed positive association between intrinsic connectivity component 2 and current pain scores (Table 7.6 and Figure 7.7) and included regions in the cerebellum, cortical and sub cortical areas of the brain.

In the seed-based functional connectivity analysis, only the ACC and insula seed regions showed greater connectivity in controls than patients in a large number of regions that can be seen in Table 7.7 and Figure 7.8 with no evidence of regions having greater connectivity in patients than controls. However, in the DMN and PCC seed regions there was a positive correlation with current pain scores in the subgenual ACC and medial frontal cortex bilaterally and in the PCC region also, the orbitofrontal cortex (Table 7.8 and Figure 7.9).

Fig.7.7. Positive association between intrinsic connectivity in independent component 2 and current pain scores

Statistical parametric maps illustrating the positive association between intrinsic connectivity in independent component 2 and current pain scores. Each statistical map represents these associations and the colour bar represents the *p* value.

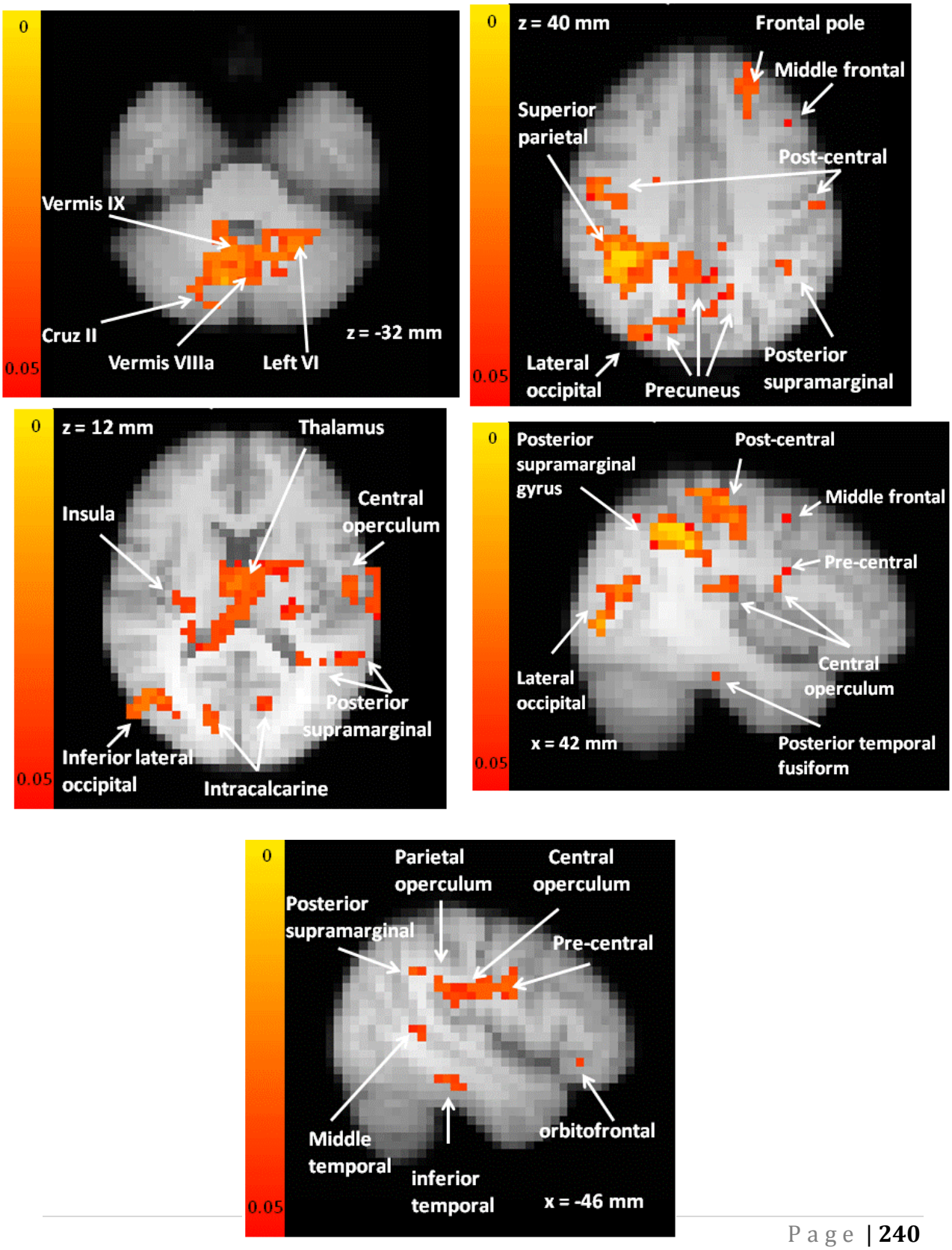


Table 7.6: Resting bold results - anatomical locations and peak activations

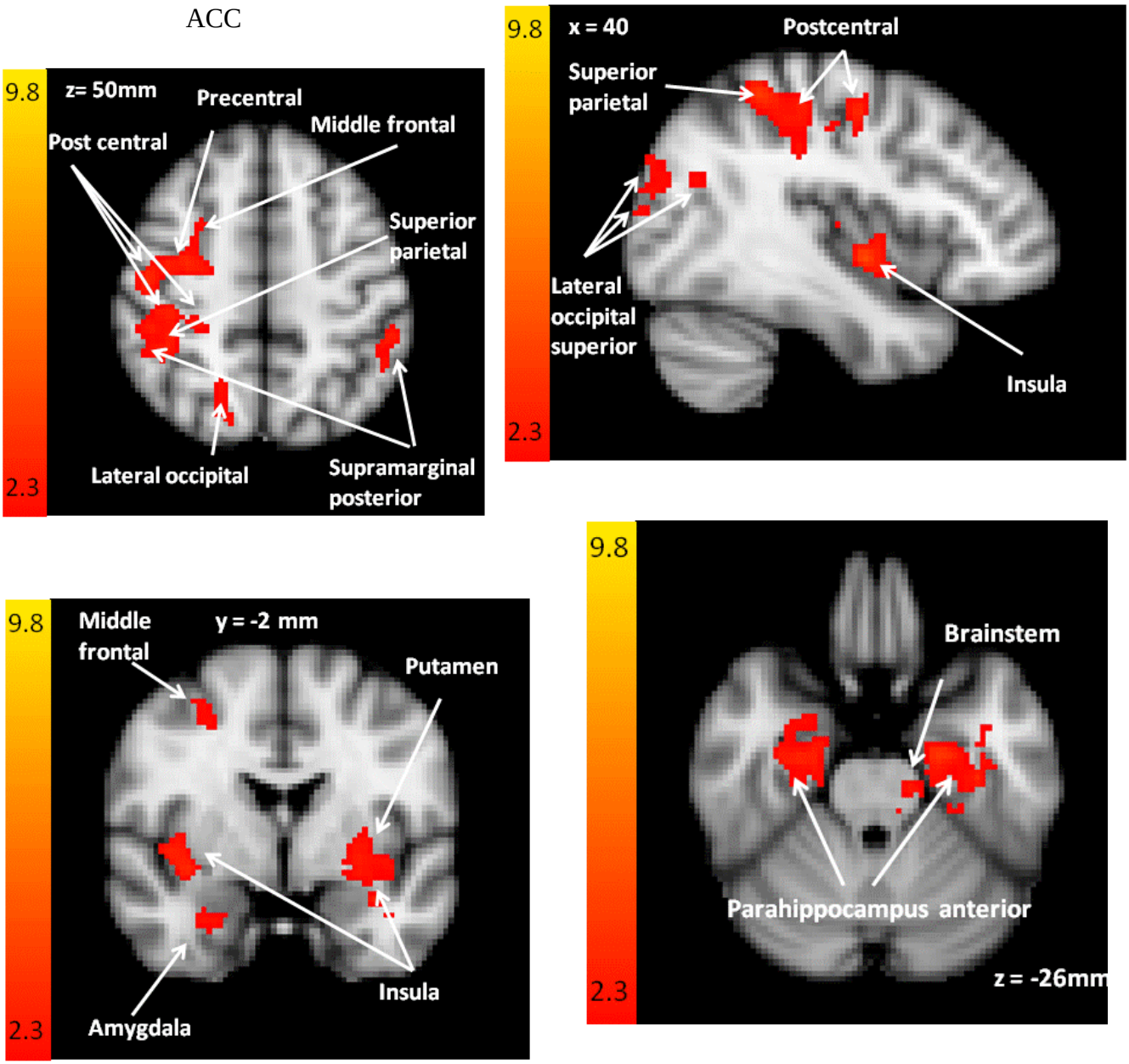
Table illustrating anatomical locations and peak activation co-ordinates (from MNI atlas) of regions showing a positive association between intrinsic connectivity in independent component 2 and current pain scores.

	Co-ordinates			1-*p* values
	x	y	z	
Central operculum (L)	-14	10	12	0.968
Central operculum (R)	42	-18	20	0.962
Cerebellum				
Vermis IX (R)	2	-54	-32	0.972
VI (L)	-34	-46	-32	0.968
Crus II (R)	14	-82	-32	0.968
Vermis IIIa (R)	2	-66	-32	0.974
Frontal pole (L)	-22	42	40	0.964
Insula (R)	34	-18	12	0.962
Intracalcarine cortex (L)	-14	-70	12	0.96
Intracalcarine cortex (R)	14	-78	12	0.964
Middle frontal gyrus	-42	22	40	0.952
Middle frontal gyrus	-42	22	40	0.952
Pre-central gyrus (L)	-46	-2	28	0.968
Post-central gyrus (L)	-58	-18	40	0.952
Post-central gyrus (R)	38	-18	40	0.962
Precuneus (L)	-6	-70	40	0.962
Precuneus (R)	-14	-74	40	0.962
Superior lateral occipital (R)	30	-82	40	0.968
Superior parietal lobule (R)	34	-46	40	0.968
Superior supramarginal gyrus (L)	-54	-50	12	0.964
Thalamus (L)	-10	-10	12	0.968
Thalamus (R)	6	-10	12	0.974
Inferior lateral occipital gyrus (R)	42	-74	4	0.968
Posterior temporal fusiform gyrus (R)	43	-26	-24	0.962
Middle temporal gyrus (L)	-46	-46	8	0.968
Parietal operculum (L)	-46	-30	20	0.962
Inferior temporal gyrus (L)	-46	-34	-20	0.948
Lingual gyrus (L)	22	-46	-12	0.992

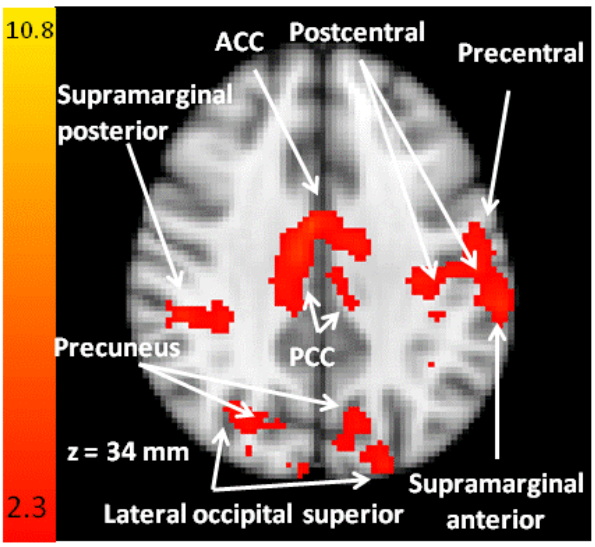
Fig 7.8 ACC and Insula seed analyses

Statistical parametric maps illustrating the differences between patients and controls in resting BOLD ACC and insula seed connectivity analyses. Each z-statistic map shows greater connectivity in controls in a voxel wide whole brain analysis compared to the seed regions. The colour bar shows the scale of the *z*-statistic (2.3- 9.8 for ACC and 2.3 – 10.8 for insula).

ACC



Insula


10.8
ACC
Postcentral
Precentral
Supramarginal posterior
Precuneus
PCC
z = 34 mm
2.3
Lateral occipital superior
Supramarginal anterior

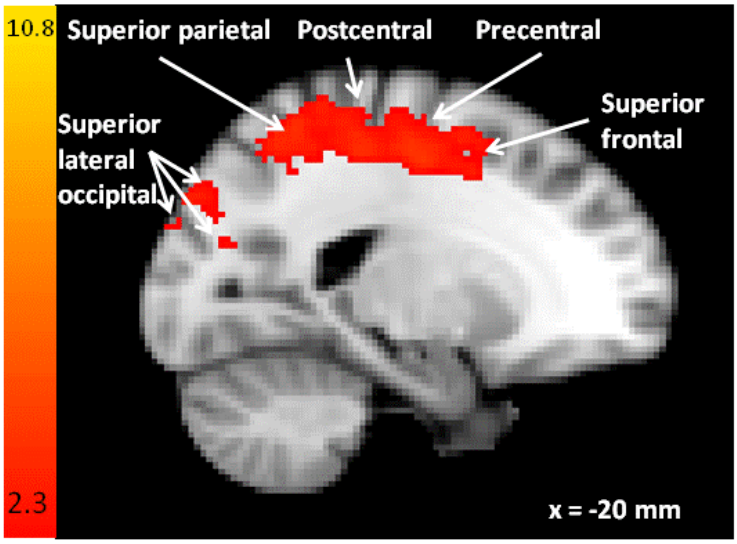
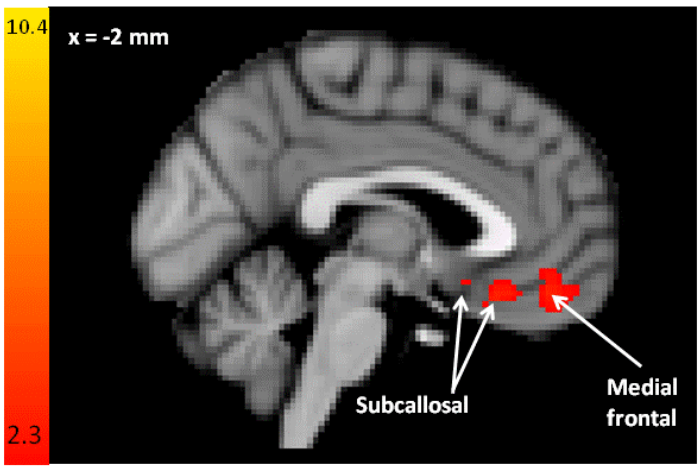

10.8
Superior parietal
Postcentral
Precentral
Superior frontal
Superior lateral occipital
2.3
x = -20 mm

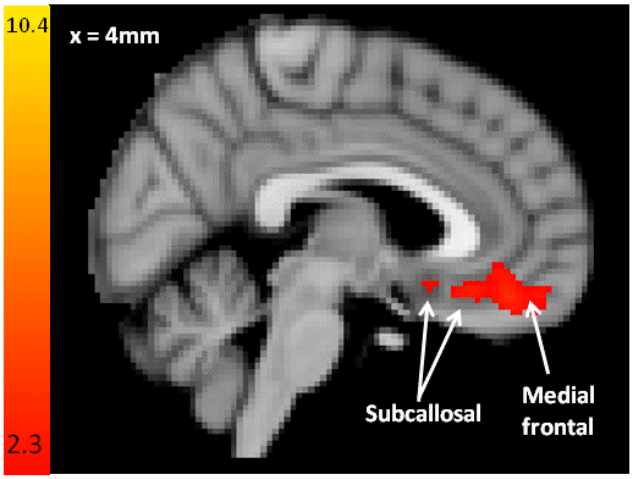
Table 7.7: ACC and insula seed analyses
Table illustrating the resting BOLD ACC and insula seed connectivity regions with voxel wide whole brain comparison showing greater connectivity in controls. Anatomical locations and peak activation co-ordinates (from MNI atlas).

	Co-ordinates x	y	z	z-stat
ACC				
Amygdala (R)	26	-2	-28	2.74
Brainstem (L)	-14	-24	-26	2.74
Insula (L)	-34	-20	8	3.13
Insula (R)	40	-2	-2	3.22
Middle frontal gyrus (R)	30	-2	52	2.60
Parahippocampal gyrus anterior (L)	-22	-22	-26	2.66
Parahippocampal gyrus anterior (R)	20	-20	-26	2.75
Post-central gyrus (R)	42	-28	50	3.02
Precentral gyrus (R)	*34*	*-8*	*50*	*3.24*
Putamen (L)	-28	-2	0	2.92
Superior supramarginal gyrus posterior (L)	-50	-48	50	2.73
Superior supramarginal gyrus posterior (R)	-50	-36	50	2.67
Insula				
ACC (midline)	0	-2	34	3.15
Lateral occipital (L)	-20	-88	34	3.05
Lateral occipital (R)	30	-70	34	2.74
PCC (L)	-6	-20	34	2.64
PCC (R)	6	-18	34	2.74
Postcentral (R)	24	-32	56	3.05
Postcentral gyrus (L)	-58	-18	34	2.50
Precentral (R)	4	-20	56	3.24
Precentral gyrus (L)	-54	-6	34	2.76
Precuneus (L)	-10	-74	34	2.64
Precuneus (R)	18	-74	34	2.45
Superior frontal (L)	-20	2	-56	3.25
Superior frontal (R)	22	-8	56	3.15
Superior parietal (R)	38	-52	56	2.71
Superior partietal (L)	-20	54	60	3.71
Supramarginal gyrus, anterior (L)	-60	-24	34	2.87
Supramarginal gyrus, posterior (R)	34	-40	34	3.48

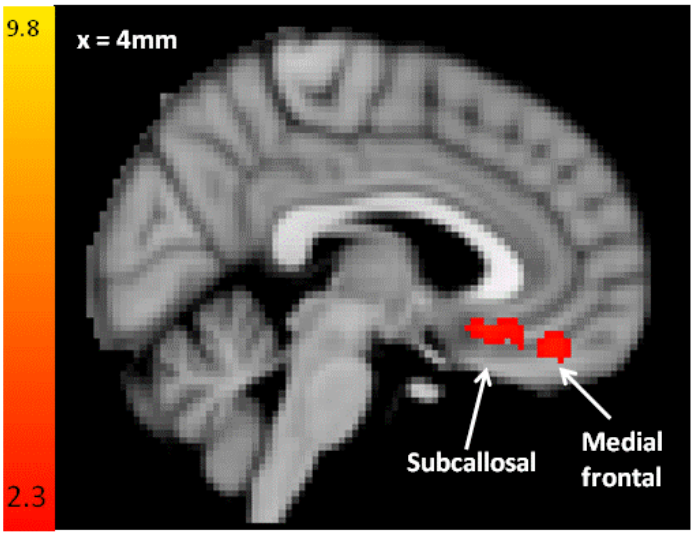
Fig 7.9 DMN and PCC seed analyses
Statistical parametric maps illustrating resting BOLD DMN and PCC seed connectivity analyses correlated to current pain scores in a voxel wide whole brain analysis compared to the seed regions. The colour bar shows the scale of the *z*-statistic (2.3- 10.4 for DMN regions and 2.3 – 9.8 for PCC).

DMN





PCC



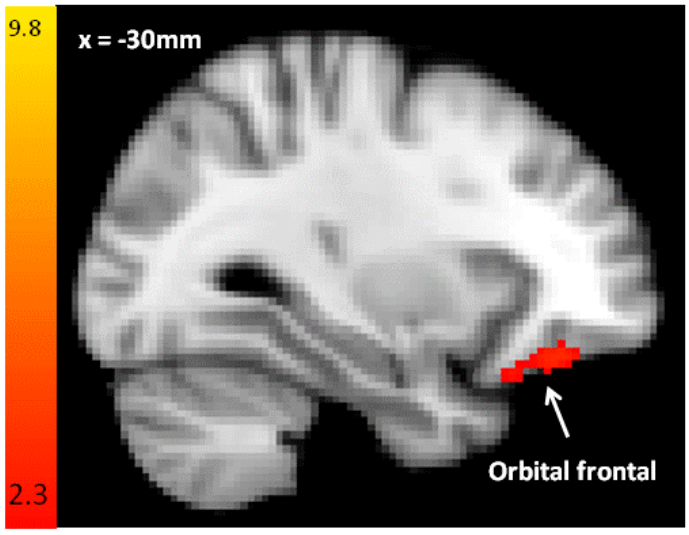


Table 7.8: DMN and PCC seed analyses
Table illustrating the resting BOLD DMN and PCC seed connectivity regions which were correlated to current pain scores. Anatomical locations and peak activation co-ordinates (from MNI atlas).

	Co-ordinates x	y	z	z-stat
DMN				
Medial frontal (L)	-2	50	-16	2.66
Medial frontal (R)	4	40	-16	3.31
Subcallosal (L)	-2	30	-16	3.17
Subcallosal (R)	4	16	-12	2.60
PCC				
Medial frontal (L)	-6	46	-14	3.01
Medial frontal (R)	4	42	-20	2.91
Orbitofrontal (L)	-30	32	-20	3.05
Orbitofrontal (R)	18	28	-16	2.95
Subcallosal (L)	-6	26	-12	2.63
Subcallosal (R)	4	24	-14	2.72

7.5 DISCUSSION

7.5.1 Principal findings

This study illustrates that people with CLBP engage pain-related brain regions when imagining undertaking activities of daily living. Viewing photographs of people engaging in daily activities resulted in BOLD differences between patients and controls in areas associated with the emotional and sensory aspects of pain that would be expected when individuals actually experience physical pain. Covaring self-reported catastrophising and TSK scores into the statistical model revealed brain regions known to be involved with anticipatory anxiety, phobia-related fear and conditioning to fear and threat.

The resting BOLD connectivity analysis using the dual regression approach revealed differences in patients compared to controls only when current pain scores were covaried with the time courses for the patients and controls. The differences in resting connectivity were statistically weak (not corrected across independent component analysis for multiple

comparisons) but did reflect a number of pain related areas (parietal operculum, central operculum, insula, thalamus, etc), regions involved in the visual network (lateral occipital, temporal fusiform, inferior and middle temporal), sensory motor regions (pre and post central, cerebellum) and a few regions involved in the DMN (middle frontal gyrus, precuneus). However, when the ACC and insula were used as seed regions, the control group showed greater connectivity than the patient group for a number of regions in the voxel wide whole brain analyses. When the DMN regions were used as seed regions including the PCC, there was a correlation between pain scores and increased connectivity with the DMN in the medial frontal cortex and subcallosal cingulate cortex and with the PCC, in the orbitofrontal cortex. The seed regions were restricted to those that showed a difference between patients and controls in the PHODA task.

7.5.2 Differences between CLBP patients and pain-free controls in the PHODA task

Pain has been described as having 3 dimensions; (1) the sensory discriminative dimension, (2) the affective-motivational dimension and (3) the cognitive evaluative dimension. A number of regions showing increased BOLD responses in patients compared to controls when viewing pictures and imagining the task involved the sensory-discriminative dimensions of pain. This echoes the findings of the CMSKP study previously discussed (Chapter 6) strengthening the ability of modified PHODA tasks to engage brain regions known to be involved with processing pain. This is discussed further in section 8.1.2.

Within this dimension, we found areas involved with attentional aspects (SI, inferior and superior parietal regions, thalamus, cerebellum) (Duncan and Albanese 2003; Kulkarni et al. 2005; Ralston 2005; Moulton et al. 2011; Worthen et al. 2011), sensory localisation (SI, putamen, ACC, thalamus, caudate) (Bushnell et al. 1999; Oshiro et al. 2007; Worthen et al.

2011), intensity discrimination (SI, SII, superior frontal gyrus, thalamus, ACC, insula, parietal operculum) (Bushnell et al. 1999; Brooks et al. 2002; Buchel et al. 2002; Koyama et al. 2005; Rodriguez-Raecke et al. 2010) and integration with other stimuli and cognitive processes (cuneus, putamen, parietal operculum, thalamus, cerebellum) (Price 2000; Treede et al. 2000; Ralston 2005; Moulton et al. 2011; Starr et al. 2011). We propose that, in the absence of sensory pain input, CLBP patients, when viewing pictures attend to the sensory aspects of pain that they perceive they will physically experience and these are thus represented as BOLD changes in these sensory-discriminatory regions.

The affective-motivational regions that had increased BOLD responses in patients and not controls during the task included insula, ACC, orbitofrontal cortex, parahippocampal gyrus and accumbens (Ploghaus et al. 1999; Phillips et al. 2003; Kulkarni et al. 2005; Roy et al. 2009; Lamm et al. 2011). The insula and accumbens are activated in anticipation of pain (Ploghaus et al. 1999; Leknes et al. 2011); the insula more in relation to the first person perspective (Jackson et al. 2006a; Lamm et al. 2007; Ogino et al. 2007) and the accumbens appears to be related more to dread and pessimism (Leknes et al. 2011). This increased activity in the accumbens may reflect the aversive nature of pain and serve as a useful measure of it (Aharon et al. 2006; Baliki et al. 2010). The ACC, is an area involved in pain, pain affect and with the evaluation of emotional stimuli (Phillips et al. 2003) as is the parahippocampal gyrus (Ploghaus et al. 2001; Apkarian et al. 2005; Moulton et al. 2011). The results from both PHODA studies suggest that the thought of undertaking the activities is processed by regions involved in unpleasantness, dread and increased emotion.

Shimo et al (2011) used visualization of a potentially painful back pain event which they hypothesised would trigger painful memories and provoke the affective dimension of pain

and compared those with low back pain (LBP) to controls. Regions activated included the insula, supplementary motor area, premotor area, thalamus, pulvinar, posterior cingulate cortex, hippocampus, fusiform, gyrus, and cerebellum. These results are similar to those obtained in the current study suggesting that memory retrieval of unpleasant experiences may be associated with CLBP conditions. The parietal operculum is activated when visual pain stimuli are used (Jackson et al. 2006b; Ogino et al. 2007; Benuzzi et al. 2008) and has a substantial role in the cortical representation of pain (Treede et al. 2000).

Increased BOLD activity was observed in patients but not controls when viewing the PHODA-LBP pictures in regions that have been identified as pertinent to the cognitive-evaluative dimension of pain (Devinsky et al. 1995; Vogt et al. 1996; Kelly et al. 2007). Again, very similar to the findings seen in the previous study (Chapter 6) supporting the use of PHODA as a non-painful, pain-related stimuli that can be used within a scanning environment. The ACC appears to be active in arousal and attention, the orbitofrontal and superior parietal cortices are thought to be involved in the cognitive modulation of pain (Rainville 2002; Duncan and Albanese 2003; Villemure and Bushnell 2009; Baliki et al. 2010); the latter showing stronger activation on viewing negative rather than positive emotional pictures (Roy et al. 2009). When individuals view pictures of body parts in painful situations, it has been shown that regions such as the inferior parietal cortex (supramarginal gyrus) and ventral premotor areas (inferior frontal gyrus, pars opercularis) are activated (Lamm et al. 2011). This joint activation appears to be a key feature of action observation (Van Overwalle and Baetens 2009) and action understanding is the core function of this network (Rizzolatti et al. 2006). We therefore suggest that the recruitment of this network observed in our study relates to predicting and understanding the outcome

of the shown situation, which in turn triggers inferences in patients but not controls about the pain-related negative consequences.

During the task, there was an increased BOLD response in memory processing regions such as the frontal pole (Bonda et al. 1996), the inferior temporal/temporal fusiform region (Brown et al. 2008), the paracingulate which is involved in reality monitoring in relation to memory processing (Buda et al. 2011) and the inferior frontal gyrus, involved in memory retrieval of unpleasant pain (Ushida et al. 2008). The supplementary motor cortex also has a role in memory in that it is important for tasks that demand retrieval of motor memory (Tanji 1994) and also has a role in internally generated planning of movement and the planning of sequences of movement (Grafton et al. 2000). The role of the cerebellum in pain processing is attributed to its role in motor control and withdrawal (Moulton et al. 2011). It may be involved in the inhibition of movement execution during the imagery task (Lotze et al. 1999). The cerebellum, in combination with the basal ganglia, are also active during motor imagery of both simple and complex movements (Lotze and Halsband 2006; Guillot et al. 2008) (Munzert et al. 2009); its role here may not necessarily be pain specific. However, PHODA was salient and realistic enough to generate memory centres in patients but not controls suggesting that the patients' brain was preparing for an unpleasant impact from movement which was not present in controls.

Increased BOLD responses in the precuneus, posterior cingulate, angular gyrus and medial frontal cortex were seen in patients viewing PHODA. This response is consistent with a number of studies, including our previous study in a CMSKP population (Chapter 6), illustrating that the DMN is dysfunctional in patients with chronic pain (Gusnard et al. 2001; Baliki et al. 2008; Mantini et al. 2009; Qiu et al. 2011). When undertaking a task, the

DMN should decrease its activity during task performance when compared to the average brain activity at rest (Baliki et al. 2008; Mantini et al. 2009; Kong et al. 2010).

7.5.3 The role of fear and catastrophic thinking

The findings of our study suggest that while there was an increased level of BOLD responses in areas associated with the affective -motivational processing of pain-related stimuli in CLBP in general, this was accentuated in those with higher scores on the catastrophising and kinesiophobia self-report measures. Specifically, higher TSK scores were reflected in occipital fusiform, parahippocampal, temporal occipital fusiform and lingual gyri activity and high catastrophising scores were associated with increased BOLD responses in the superior and middle temporal gyri, orbitofrontal cortex, insula, putamen, amygdala and temporal pole. This was consistent with previous research that has indicated that catastrophising and kinesiophobia are characterised by anticipatory anxiety (fusiform gyri, insula, orbitofrontal cortex) (Chua et al. 1999; Ploghaus et al. 1999), phobia-related fear and conditioning to fear (amygdala, fusiform gyrus, insula, putamen) (Etkin and Wager 2007) and threat (amygdala, fusiform gyrus) (Cools et al. 2005). The superior temporal gyrus and temporal pole play a central role in emotional processing (Takahashi et al. 2009) and increased fusiform activation (2000; Pizzagalli et al. 2002) and increased amygdala activation (Taylor et al. 2000) to visual emotional stimuli is facilitated by the saliency of the images shown. The lingual gyrus has been implicated in visual memory (Kapur et al. 1995).

We suggest that the mechanisms for increased activation in these regions is that projections from the limbic circuitry enhance activation in the ventral stream when viewing emotional content and affective salience of a stimulus (PHODA), and memory directly influences

visual activity (Duncan and Barrett 2007). The middle temporal cortex plays a role in the extinction of fear through inhibition of amygdala function (Bremner et al. 1999). Increased BOLD responses in this region in the present study may therefore indicate that this region is working to reduce the fear.

In the CMSKP study (Chapter 6), high anxiety and catastrophising scores correlated with BOLD differences between patients and controls during the task but this was not seen with the self-reported TSK scores. However, in the CLBP study, anxiety did not correlate with BOLD differences whereas higher TSK and catastrophising scores did. The differences here may be due to a number of reasons. Firstly, it may be explained in the populations studied, which supports the replication of the paradigm in this more discrete musculoskeletal population of CLBP patients. In CLBP, the prospect of movement engaged fear and catastrophising probably related to the fact that this group were highly kinesiophobic whereas, in the CMSKP, it may be more a sense of general apprehension about any movement resulting in anxiety and catastrophising rather than fear per se. This may be associated with the current pain ratings which were different between groups; CMSKP group mean being 49mm and the CLBP group mean being 62mm.

Secondly, PHODA was designed for addressing fear-related activity avoidance in CLBP and while pilot studies were conducted to identify salient pictures for the CMSKP population and the resulting neuroimaging study did produce interesting findings, the pictures may have been more salient for patients with CLBP, especially given the latter group had high kinesiophobia. Indeed, Leeuw et al (2007b) suggested that PHODA may have greater or more specific relevance to the pain and harm-related cognitions of high fear individuals as opposed to low or moderate fear individuals. Therefore, it appears that

while fear and anxiety are related they appear to be slightly different constructs in the studies presented here. In the literature fear is seen as a response to a specific threat, where as anxiety is more of a generalised shift in mood (Öhman 2000). Anxiety is more of a diffuse, unpleasant, vague sense of apprehension, whereas fear relates to a real, definite an immediate threat (Öhman 2000). Again, the fact that PHODA was designed for CLBP may mean that the pictures are more salient to this group and are seen as a real threat whereas in the CMSKP population, there is a sense of apprehension regarding any movement.

While criticism has been levelled at the TSK and self-report measures (Pincus et al. 2010), in terms of the BOLD responses, it appears that TSK and catastrophising self-report is associated specifically with increased activation in motivational-affective processing of pain. This indicates that there is a fair bit of accuracy in the awareness patients with CLBP have of their fear and so self-report is not totally unreliable and TSK and self-report should still be considered potentially useful tools.

It was anticipated that across the CMSKP and CLBP groups, the high scores, if they correlated to BOLD differences between patients and controls, would share similar brain regions but this was not the case. High catastrophising scores correlated with BOLD differences in the orbitofrontal cortex, amygdala, temporal pole, insula, middle temporal, putamen and superior temporal regions in the CLBP population whereas, in the CMSKP group, BOLD differences were seen in the inferior temporal cortex, lateral occipital cortex, precuneus, cerebellum and brain stem. Only the middle temporal gyrus was common to both groups. This may be the result of the CLBP study being better powered to detect differences (40 participants versus 30 participants in the CMSKP study) or may illustrate that catastrophising is processed differently in different pain groups (CLBP versus CMSKP

group) and/or in groups with differing TSK scores (high versus low kinesiophobia) or when current pain levels differ between groups.

7.5.4 VBM

The voxel-based morphometry analysis did not detect any differences between the patient and control groups. Differences in grey matter density between patients with chronic pain and healthy controls has been detected previously, but results are inconsistent and regions that show differences may vary with the type of chronic pain, for example phantom limb pain compared to frequent migraine (May 2008). VBM studies specifically examining chronic lower back pain have only been partially replicated. Three studies have shown a decrease in grey matter density in the dorsolateral prefrontal cortex in patients compared to controls (Apkarian et al. 2004b; Schmidt-Wilcke et al. 2006b; Ruscheweyh et al. 2011) but conflicting results in grey matter changes in the thalamus have been reported (Apkarian et al. 2004b; Schmidt-Wilcke et al. 2006b). It may be that differing types of back pain, such as radiating pain or pain extending to other parts of the body may additionally confound results (May 2008) but this information was not gleaned from participants. Although those patients that were analysed for the VBM had pain for at least 1 year, there was a range of pain duration, therefore long-term dynamics cannot be evaluated and the sample sizes for the range of pain years are to small to compare. If grey matter changes take years to develop, this component of the study may be underpowered.

7.5.5 Resting Bold: functional connectivity

Studies examining resting state BOLD fluctuations have been performed in chronic pain populations (Baliki et al. 2008; Caudu et al. 2009; Malinen et al. 2010; Napadow et al. 2010; Baliki et al. 2011; Farmer et al. 2012) and many of these studies show alterations in

the default mode network (DMN) and insula connectivity, and it has been proposed that the increased nociceptive input from the insula disrupts the DMN (Farmer et al. 2012). It transpired that only one of the 25 independent components in our study, when used in a dual regression illustrated differences between patients and controls when the current pain scores were included in the model (orthogonalised with respect to the regressor describing the patient/control group). This revealed a positive relationship between pain scores and network connectivity (Fig7.6) driven principally by the variability of current pain scores within the patient group as there was little variation of pain scores in the control group.

This dual regression analysis revealed that elevated intrinsic brain connectivity positively correlated with current pain intensity in some of the DMN regions and a number of pain related regions including the insula, orbitofrontal cortex, thalamus, central and parietal operculum. Studies of resting state brain activity by means of fMRI have shown that connectivity within the DMN (Fox and Raichle 2007) is altered in chronic pain, together with task-related deactivation within this network (Baliki et al. 2008; Cauda et al. 2009). This is the picture we present in this chapter. The insula has been implicated as being a key node in elevated intrinsic connectivity in patients with fibromyalgia (Napadow et al. 2010; Napadow et al. 2012), in patients with chronic pain (Malinen et al. 2010), temporomandibular disorder (Ichesco et al. 2011) and in connection with the middle frontal gyrus in chronic back pain patients (Tagliazucchi et al. 2010). Increased DMN-insula connectivity has been linked to spontaneous pain in fibromyalgia (Napadow et al. 2010). There has been little research undertaken comparing the thalamus with DMN in resting BOLD studies in pain populations and yet this region was by far the largest found in the dual regression analysis.

In the seed analysis, greater connectivity was seen in the control group compared to the patient group when ACC and insula were used as seed regions. Malinen et al (2010) found that the insula and ACC were functionally connected in their healthy controls but not in the patient group (10 patients with chronic pain and 10 controls). They found that in the patient group, the ACC and insula were not functionally connected. Taylor et al (2009) found that intrinsic connectivity between the posterior insula and DMN areas such as the PCC has been shown to exist in healthy subjects and this was also found in Napadow et al (Napadow et al. 2010) in both patient and control groups. Our study reflects these findings and may reflect, in controls, the interoceptive input with its emotional salience (anterior insula-ACC system) or the process of environmental monitoring and response selection (whole insula-mid ACC) (Taylor et al. 2009).

In our patient group, the reduced connectivity with the ACC and insula as seeds could result from constant noxious input. It was suggested by Malinen et al (2010) that this may be the reason for the observed disruption in connectivities in their patient group. However, in patients with diabetic neuropathic pain, functional connectivity was strengthened in networks including anterior insula (Cauda et al. 2009). In Napadow et al (2010), the DMN seed connectivity revealed that greater spontaneous pain at the time of scanning was associated with right anterior and middle insula connectivity enhancement and a positive covariation with the intensity of spontaneous pain was also noted in the dorsolateral prefrontal cortex, cerebellum and subgenual anterior cingulate cortex. In our study, DMN and PCC seed analysis revealed connectivity in frontal lobe structures correlated to current pain scores.

Resting BOLD analysis is in its infancy and this may explain differences in findings in our study compared with what is currently published; more research is needed to reach firm conclusions about what it is we are measuring with resting BOLD. Tracey (2011) argues that the functions of resting state networks are unknown and at present, under debate (Morcom and Fletcher 2007). Other factors that be responsible for the differences between the existing studies and ours. Napadow et al (2010), for instance, used a different patient group, that of female fibromyalgia patients. We did not have sufficient patients with good physiological data recordings to perform a regression-based physiological correction and we chose to use a data driven approach. Tracey (2011) again argues that the while our understanding of neurovascular coupling and how this phenomenon influences resting state networks is limited, the possibility exists that vascular-vascular coupling and rhythms in blood vessel networks contribute to these signals; thus caution is required when interpreting resting state networks. Napadow et al (2010) used spontaneous pain reports when in the scanner to correlate their BOLD resting data with, where as we used current pain scores recorded before the scanning procedure. All these could explain the differences found.

7.5.6 Strengths and limitations

In this study, a set of images were piloted and tailored specifically for use with a CLBP population. A population with clinicially diagnosd CLBP were included in the study, on whom neuroimaging data is still relatively sparse. The paradigm used demonstrated that it was possible to differentiate between CLBP patients and pain-free controls BOLD responses observed. Scanner related fear and the use of pain medications are limitations and have already been discussed in Chapter 6.

The resting BOLD component had a reasonable number of participants but we were unable to establish corroborative physiological data on all participants. Removing those that did not have the physiological data would have left the study with very small numbers. Therefore, physiological noise correction was undertaken with a published data driven approach which influence the connectivity estimates. We also chose to examine all 25 components for connectivity differences between patients and controls rather than choose specific components and this opens the study to issues of multiple comparisons so any differences seen between patients and controls is statistically weak.

7.5.7 Implications and conclusions

The current study has shown that by imagining an activity shown in a picture, CLBP patients show demonstrable BOLD changes in pain related regions of the brain that may reflect fear and catastrophising with similar regions being activated as seen in previous studies, including the CMSKP study previously discussed, when a physical noxious stimulus is presented.

The sensory-discriminative, affective-motivational and cognitive-evaluative dimensions appeared to be represented by BOLD differences in patients compared with controls that were similar in both PHODA studies (CMSKP and CLBP populations). However, there were inconsistencies within the regions found to be correlated to high catastrophising scores between the CLBP and the CMSKP groups and in the fact that anxiety correlated to regions in the latter, and TSK to regions in the former group. As previously discussed, the reasons for these inconsistencies are many and include differences in the type of patients, levels of kinesiophobia, current pain and PHODA itself. These inconsistencies reinforce the need for further study. However, this may be the start of studying the neural correlates

of those who are low and high kinesiophobic, low and high catastrophisers and those who have low and high levels of anxiety in order to establish whether it is possible to stratify groups and align them to different management options as proposed by Pincus et al (2010).

The resting BOLD connectivity results preformed using dual regression, although statistically weak, are supported by other studies in pain populations. This is a relatively new technique and therefore, there are only a few studies currently available. Our results suggest, in combinations with the DMN activity during the picture task, that there is disrupted intrinsic connectivity within multiple brain regions in patients with CLBP. Of importance may be the link between the insula, and the large thalamus representation with the medial frontal and precuneus, part of the DMN as the former regions are involved with evoked pain processing. The seed analyses did not support intrinsic networks between ACC and insula with the DMN regions in patients but there was intrinsic connectivity between these regions but more of this present in the controls. We did find that the DMN and PCC seed regions had increased connectivity with frontal regions when pain scores were higher.

The literature surrounding fear of movement and catastrophising is controversial and although therapies to manage these maladaptive cognitions can be effective for some individuals they have not had a major impact on a population level. There is enormous potential to explore how neural responses for chronic pain patients change in response to different treatment modalities (e.g. counter-stimulation, manual therapy, pharmacotherapy, and psychotherapy) and neuroimaging is likely to have an important role in helping us to better understand chronic pain and improve outcomes in the future. A couple of studies to date, both within the pain population and within psychiatric populations (depression and

social anxiety disorders) have illustrated how neuroimaging can help in predicting outcomes (Doehrmann et al. 2012; Siegle et al. 2012) and possibly as an objective marker of pain (Napadow et al. 2010).

CHAPTER 8: DISCUSSION AND RECOMMENDATIONS

8.1 Main findings

The main finding from this set of studies is that patients with CMSKP demonstrated BOLD differences when compared to non-pain controls when viewing non-painful, pain-related stimuli (that which does not use nociceptive stimulation). Patients attend to both pain words and pictures of activities of daily living but an emotional Stroop response did not appear to be found in either the behavioural or the neuro-imaging research.

Voxel based morphometry showed no differences in a sub-section of patients and controls with CLBP but this finding may be due to the analysis being underpowered and the large differences in duration of chronic pain. Further analysis was not possible in examining the difference between long and short durations of chronic pain by splitting the population because of small numbers in the resultant groups.

The dual regression analysis of resting BOLD data showed a positive association with pain scores (but no average difference between patient and controls) in one of the 25 independent components. These regions involved motor areas (pre and post-central gyrus), areas that are commonly found in pain-related studies (central and parietal operculum, insula, thalamus, orbitofrontal cortex), visual centres (inferior temporal gyrus, temporal fusiform, lateral occipital) and default mode network (middle frontal, precuneus). However, the findings were not corrected for multiple comparisons across the 25 independent components identified and so remain statistically weak. When ACC and Insula were used as seed regions, there appeared to be reduced connectivity in the patient group. However, when the DMN regions and PCC were used as seed regions, high current pain scores correlated with increased connectivity driven by the patient group, in medial

frontal, subcallosal cingulated cortex and in the PCC analysis, orbital frontal also. Differences in methodologies, patient groups and how pain scores were recorded between the small number of exisiting studies and ours may explain why the results did not concur in the seed analyses especially.

8.1.1 Attentional bias

As previously discussed, pain demands attentional resources (Eccleston and Crombez 1999) which humans possess in limited quantities resulting in detrimental effects that have been commonly found in attention-demanding tasks (Kuhajda et al. 2002; Veldhuijzen et al. 2006). Attentional bias also demands cognitive resources and as such a further load is placed on the individual leading to detrimental effects in general cognitive performance. The implications can be far-reaching and include negative impact on employment, academic performance and outcomes from psychological interventions, for instance. Attention to pain may be indicative of patient coping (Pincus and Morley 2001).

The Stroop study discussed in Chapter 5, showed that patients attended to pain words derived from the McGill Pain Questionnaire. This was demonstrated in the small but statistically significant BOLD differences between patients and controls when viewing the pain words but was unlikely to be the result of Stroop interference. The brain regions involved were those that have been seen to respond in pain, emotion and attention to pain studies and have been demonstrated to have behavioural consequences and contribute to pain chronicity (Wang et al. 2009; Henschke et al. 2010). This is further supported in the PHODA studies presented in Chapters 6 and 7 and reflected upon later in this section (8.1.2).

A number of models of pain predict bias for pain-related information and cues (Vlaeyen and Linton 2000; Pincus and Newman 2001; Eccleston and Crombez 2007; Van Damme et al. 2009) but studies have failed to address the time course of bias in CNMP and attentional bias forms only part of these theoretical accounts. The Stroop study examined patients with a long history of CMSKP but it would be interesting and pertinent to compare pain-related attention and bias in those with relatively 'new' CMSKP and those with long established pain. This may provide some insight into time course differences.

The finding that the bias demonstrated in the Stroop study (Chapter 5) was stronger to sensory words is consistent with the literature (Edwards et al. 1992; Crombez et al. 2000). A previous study (Edwards et al. 1992) failed to find the predicted biases for affective pain words and initially the Stroop study was similar but fortunately, the protocol permitted the combination of sensory and affective words to replicate the clinical use of the MPQ. When combined, we saw greater BOLD responses in patients compared to controls than were accounted for by just the sensory word descriptors, suggestive of a bias to affective words as well as sensory.

Affective pain words may be processed differently to sensory pain words. Certainly, sensory pain descriptors portray the physical consequences of pain and therefore may cause more sensitisation than the affective pain words which tend to convey the emotional aspects of the pain experienced. This would support Pincus and Morley (2001) who propose that there are two separate schema relevant to CMSKP; a pain schema which responds to sensory pain stimuli and an illness schema which responds to affective pain words, disability and threat words.

The lack of a Stroop response is interesting given the BOLD signal differences in patients compared to controls. Pincus and Morley provided some interesting thoughts that may be relevant to interpreting the lack of Stroop activity in our study. Cognitive processing of pain patients, they contend, may be more similar to depression than anxiety and attentional bias is smaller and less reliable in depressive groups than in anxious ones. Biases in cognitive processing that are typical for depression have been observed in pain populations with regards to memory bias and interpretation. Although we controlled for depression in that we regressed depression scores into the higher level analysis, this may not have been sufficient and a comparison of CMSKP patients with and without depression may provide a greater insight to these contentions. Pincus and Morley (1998) also propose that having chronic pain may eliminate the attentional bias to pain-related words as pain is the object of threat. There has been some evidence in phobia research that supports the notion that attentional bias to words is absent in the presence of the object of threat (Mathews and Sebastian 1993; Amir et al. 1996) and suggest that high anxiety and an increase in effort strategically overrides the Stroop interference.

The Stroop study showed that patients with CMSKP showed an attentional bias to pain words illustrated in the differences in BOLD responses in emotional and pain-related brain regions. This might be clinically relevant because if patients pay less attention to fear-disconfirming information and remain engaged in avoidance, it may eventually lead to prolonged anxiety states and increasingly poor cognitive function maintaining pain-related disability and distress.

8.1.2 Anxiety, fear and catastrophising

The findings suggest that anticipatory anxiety, fear and catastrophising and memory of pain play an important role in how patients in chronic pain respond to pain-related stimuli. When patients viewed photographs of people engaging in activities of daily living and in which they would find painful, areas associated with emotion and sensory aspects of pain are seen to have an increased BOLD response. These are the regions that are seen in non-pain participants who experience nociceptive stimuli.

While the Stroop study involved exposure to pain-related stimuli rather than nociceptive stimuli and demonstrated different BOLD activity in patients compared to controls, viewing PHODA and imagining undertaking these resulted in a whole host of other brain regions being involved. This neural activity in response to observing people engaging in day to day tasks may be happening in everyday life in patients. If this is the case, observing others undertaking activities could potentially exacerbate and perpetuate an individual's pain even when he or she is not engaged in an activity. This may help explain why group exercises in a pain management programme are useful and pain-related behaviour is discouraged. If patients see other patients engaged in purposeful activity, not exhibiting pain behaviour it may desensitise fear. It also suggests that, in the clinical management of pain, psychological methods for reducing anxiety in relation to pain may need to focus on the social context (i.e. how people view the activities of others) as well as how they experience their own pain.

Therapies to manage anxiety, fear and catastophising have not shown a major impact (Pincus et al. 2010). Examining the social context of pain could be undertaken through helping people to reduce their responses to pictures and pain words could. This may, for

example, be useful as a starting point for ‘graded exposure’ to the thing that individuals fear, building up to situations where they actually start to engage in activities where they have pain. Getting people to engage in activities despite their pain is already part of routine practice in pain management programmes, but for patients that are particularly fearful and resistant to this approach, this could offer a starting point to help learn to control anxiety and build confidence.

The research undertaken in this thesis may support further research on the use of graded exposure as in phobia management in general where graded exposure has been effective (Schienle et al. 2007; Haukebo et al. 2008). In low back pain, unfortunately, it appears no more effective than a minimal intervention or graded activity (Macedo et al. 2010; Pincus et al. 2010). However, it may not be the paradigm that is wanting but inherent methodological weaknesses in studies on graded exposure to date, the poor training of health professionals supporting graded exposure and lack of recognition of sub groups within the population of avoidant CMSKP patients (Pincus et al. 2010) may have led to unreliable research outcomes.

It is also possible that kinesiophobia may be more complex that other phobias, for instance, in arachnophobia, the fear is related to one discrete variable, the spider. In kinesiophobia it is still not clear whether it is the fear of pain, fear of the movements themselves and/or fear of injury/re-injury (Pincus et al. 2010). The neural responses seen during the PHODA task suggests that it may be fear of pain because of the pain-related centres that were seen to have different BOLD responses in patients compared with controls. Although the CMSKP study had low kinesiophobic patients and the CLBP had high kinesiophobic patients, there were a number of pain-related regions that were common to both, strengthening the ability

of PHODA to engage regions known to be involved in processing pain, including nociception.

The common regions shown to have BOLD differences between patients and controls when undertaking the PHODA task in both studies can be seen in Table 8.1. The regions common to both groups are mainly those that are involved in processing pain or in the DMN. It suggests that patients in both groups responded to the pain-related information in ways that healthy volunteers respond to physical pain stimuli and the patients also had abnormal DMN activity. The regions that differ between the groups may be due to a number of reasons, some of these regions are involved in pain processing, but others have roles in motor control, memory and emotion (see Chapters 6 and 7 for full discussion of these regions).

Table 8.1 Comparison of the regions that demonstrated BOLD signal change difference in patient compared to controls across the three studies.

L = left, R = Right, B = Bilateral

Regions	CMSKP group PHODA	CLBP group PHODA	CMSKP group Stroop
ACC (B)	✓	✓	✓
Accumbens (L)	×	✓	×
Accumbens (R)	✓	✓	×
Amygdala (L)	✓	×	×
Angular gyrus (B)	✓	✓	✓
Caudate (L)	×	✓	×
Caudate (R)	✓	✓	✓
Central operculum (B)	×	×	✓
Cerebellum	×	✓	×
Cuneus (B)	✓	✓	×
Frontal pole (L)	✓	×	✓
Frontal pole (R)	×	✓	×
Inferior frontal gyrus pars triangularis (L)	×	✓	×
Inferior frontal gyrus, pars opecularis (L)	×	✓	×
Inferior frontal gyrus, pars opercularis (R)	✓	×	×
Inferior frontal gyrus, pars temporalis (R)	✓	×	×
Inferior temporal lobe (temporooccipital part) (L)	×	✓	×
Insula cortex (B)	✓	✓	✓
Middle frontal gyrus (B)	✓	✓	✓
Orbitofrontal cortex (B)	✓	✓	×
Pallidum (L)	✓	×	×
Paracingulate cortex (B)	✓	✓	✓
Parahippocampus anterior (R)	✓	×	×
Parahippocampus posterior (L)	✓	✓	×
Parietal operculum (L)	✓	✓	✓
Parietal operculum (R)	×	✓	✓
PCC (B)	✓	✓	✓
Precuneus (B)	✓	✓	✓
Putamen (B)	✓	✓	
S1 (B)	✓	✓	✓
S11 (B)	×	✓	✓
Subcallosal cortex (B)	×	×	✓
Substantia nigra/ventral tegmental (L)	✓	×	×
Superior frontal gyrus (B)	✓	✓	×
Superior parietal cortex (L)	✓	✓	×
Superior parietal lobule (R)	×	✓	×
Superior temporal gyrus posterior (L)	✓	×	×
Superior temporal gyrus posterior (R)	×	×	✓
Supplementary motor cortex (L)	✓	✓	×
Supplementary motor cortex (R)	×	✓	×
Supramarginal gyrus, anterior division (L)	✓	✓	✓
Supramarginal gyrus, anterior division (R)	✓	×	✓
Supramarginal gyrus, posterior division (L)	✓	✓	×
Supramarginal gyrus, posterior division (R)	✓	✓	✓
Thalamus (B)	✓	✓	×

In section 7.5.3 the discussion attempted to explain the differences between the CMSKP and CNMP in relation to regions showing BOLD activity correlated to higher anxiety, catastrophising and TSK scores. A similar discussion is warranted here in attempting to explain the differences in regions showing BOLD differences in patient compared with controls when undertaking the PHODA tasks. These differences may be explained by the populations studied in that the CLBP group had one source of chronic pain, whereas in the CMSKP group, there were a number of sources of pain. It may also be due to the current pain ratings which were different between groups; CMSKP group mean being 49mm and the CLBP group mean being 62mm. However, lying down did not provoke pain and patients were included if they were comfortable being in the scanner so these differences should not reflect increasing spontaneous pain. It may reflect the differences in being high or low kinesiophobic or may be that the CLBP study was a larger study and therefore it was better powered.

The study findings regarding differences in anxiety and TSK between the high kinesiophobic group of CLBP patients and the low kinesiophobic CMSKP patients may also be due to PHODA itself. Leeuw et al (2007b) suggested that PHODA may have greater or more specific relevance to the pain and harm-related cognitions of high fear individuals as opposed to low or moderate fear individuals, for whom the link between participation in day-to-day activities and immediate concerns regarding pain and harm (elicited during a standardized laboratory set of movements) appears less clear. It may also be explained by the fact that CLBP is prone to be exacerbated by specific (fear provoking) movements, whereas, in more generalised CMSKP it is about general anxiety concerned

with a range of motions. PHODA has been studied is CLBP patients and not in a generalised CMSKP group.

It appears that while fear and anxiety are related they appear to be slightly different constructs in the studies presented here. In the literature fear is seen as a response to a specific threat, where as anxiety is more of a generalised shift in mood (Öhman 2000). Anxiety is more of a diffuse, unpleasant, vague sense of apprehension, whereas fear relates to a real, definite an immediate threat (Öhman 2000). Again, the fact that PHODA was designed for CLBP may mean that the pictures are more salient to this group and are seen as a real threat whereas in the CMSKP population, there is a sense of apprehension regarding any movement.

There are a number of ways of interpreting the studies which, unfortunately, does not shed further light on whether fear is defined as fear of pain, movement or (re)injury. What these studies do show is that it is unwise to put all 'CMSKP' patients together as while there are some similarities in how they respond to pain words, activity pictures and the imagination task, there are differences around anxiety, fear and catastrophising.

It may be that self-report is associated specifically with increased activation in motivational-affective processing of pain in patients with high kinesiophobia. This suggests that there may be a fair bit of accuracy in people's awareness of their fear and so self-report, when they are highly fearful, and using tools such TSK and the catastrophising sub-scale from the CSQ should still be considered potentially useful tools.

8.2 Limitations

The research discussed in Chapters 5, 6 and 7 did suffer from some limitations that have been alluded to within the chapters. However, a more general discussion of some of the limitations of the tools used is required to complete the thesis.

8.2.1 Stroop

It has been contended that the traditional emotional Stroop task may not provide a measure of emotional conflict comparable to the measure of cognitive conflict provided in the colour-word Stroop task (Etkin et al. 2006). In fact, the emotional word counting Stroop may not be a Stroop effect at all. In a traditional Stroop interference task, for any value along one dimension (e.g. a colour word) there must be a value along the other dimension (a print colour) with which it can be combined to create a congruent stimulus. In the emotional counting stroop, the word 'stabbing' is not a number and therefore it cannot be a congruent item in a counting stroop and hence may not be regarded as a Stroop stimulus. Nonetheless, the button pressing for 'stabbing' may be slower than to its matched household object but that slowdown is probably not a Stroop effect.

It also appears that behavioural interference is not detected at all (Williams et al. 1996), in healthy volunteer subjects or habituates rapidly (McKenna 1986; Compton et al. 2003). This lack of behavioural effect limits the conclusions that can be drawn from studies that have used the traditional emotional Stroop task in healthy volunteers (Whalen et al. 1998; Compton et al. 2003; Bishop et al. 2004a).

It would have been appropriate to include a general threat word category in the Stroop study (Chapter 5) to establish whether patients were attending to threat per se or

specifically pain-related threat. A positive word category was justified but both would have been more appropriate in comparing outcomes with other Stroop studies. Also, while combining the sensory and affective word groups was appropriate, the imaging methods might have reflected this decision more appropriately. The block design should have included a combined sensory and affective word component as well as the individual sensory interference and control and affective intereference and control trials.

Words were chosen in a pilot of 20 patients and 20 controls and while this was an improvement in comparison to previous studies where the researchers chose the words, it still may have been limited. The pain words certainly illustrated different BOLD responses in patients compared with controls. However, this was not as pronounced as in the PHODA studies and with no Stroop effect, the salience of the words may not have been as ecologically appropriate as they could have been. It was important to reduce the impact of primacy biasing the research and so asking patients to rate words prior to scanning was not deemed appropriate and hence the use of the separate pilot group. We could have asked participants after the scanning event to rate the words we used, which was a missed opportunity. Also a number of high scoring pain words were lost in the lexical balancing process and these may have been key, salient words; again, if we had asked participants after the scanning session, we may have established this.

8.2.2 PHODA

PHODA has not been extensively studied and there are limitations in studies that have supported the use of this tool (Leeuw et al. 2007b). Methodological concerns have been raised about the small sample sizes in previous research and/or limited participation of individuals with high levels of pain-related fear (Leeuw et al. 2007b). However, a valid

and reliable set of pictures to provide visual stimuli to represent real world functioning is lacking and the PHODA modifications certainly resulted in a range of BOLD differences between patients and controls in the studies presented.

It is also important to note that the PHODA-LBP and PHODA-MSK stimuli were selected based on prior clinical research and a small pilot study and so do not comprise a formal clinical instrument. PHODA-MSK deviated further than the LBP modification from the original administration but both were not used as originally designed. This may, in part account for the differences in anxiety and TSK BOLD regional differences in the CMSKP group and the CLBP group. Therefore, further research is required to validate these as research and clinical tools.

It is commonplace to statistically control for depressive symptoms when investigating relations between pain catastrophising and pain-related outcomes. Nevertheless, it must be kept in mind that catastrophising shares elements in common not only with depression, but also with anxiety and its associated disorders, and perhaps anger and hostility as well (Quartana et al. 2009). Future studies need to consider the impact of these other factors when designing catastrophising studies.

8.2.3 VBM and resting BOLD

As discussed within Chapter 7, there were a number of limitations in the VBM and resting BOLD components. The number of years of pain experience varied considerably in the patient group but the sample was not large enough to divide the group into different duration of pain experience to establish whether this was correlated to structural loss.

The resting BOLD component had a reasonable number of participants but we were unable to record corroborative physiological data on all participants. Removing those that did not have the physiological data would leave the study with very small numbers. Therefore, physiological noise correction was undertaken with a published data driven approach. Given the exploratory nature of the analysis of the resting state data, we also chose to examine all 25 independent components identified for connectivity differences between patients and controls rather than choose components with specific spatial distributions and this weakens the statistical robustness as we did not correct for multiple comparisons across many components.

8.2.4 BOLD signal and fMRI studies

Logothetis states that fMRI is currently the best tool for gaining insights into brain function and formulating interesting and eventually testable hypotheses but there are limitations. One disadvantage is that, like all haemodynamic-based modalities, it is a surrogate measure subject to physical and biological constraints and this surrogate measure reflects neuronal mass activity (Logothetis 2008). Only in very special cases can it be really useful for unambiguously explaining the underlying mechanisms of the topic under consideration. The fMRI signal does not easily differentiate between function-specific processing and neuromodulation between bottom-up and top-down signals and can confuse excitation and inhibition. Therefore, in writing the thesis, it has become paramount that verbs such as ‘activating’ and ‘deactivating’ should be avoided but instead the emphasis is on different BOLD responses. The magnitude of the fMRI signal has not been quantified to measure true neuronal information-processing differences between brain regions, or between tasks within the same region. Therefore results have been discussed in relation to changes between healthy controls and patients and not in relation to changes from zero.

A potential problem in fMRI studies when attempting to understand better the nature of cognition is 'reverse inference', where the engagement of a particular process is inferred from the activitation of a particular brain region (Poldrack 2006). The usual kind of inference that is drawn from neuroimaging data is 'if cognitive process X is engaged, then brain area Z is active', however, there is an 'epidemic' of reasoning that is not taking this form (Poldrack 2006). As advised by Poldrack (2006):

- reverse inference in this thesis has tried to be informal,
- the analyses that have been undertaken and discussed involve sets of regions rather than the analysis and discussion of a single region,
- where possible, the neuroimaging data has been used in combination with behavioural data.

Studies in CNMP populations using fMRI methods are sparse and while reverse inference is an imperfect tool, it can help to advance our understanding of the mind and brain in suggesting novel hypotheses than can be tested in subsequent experiments (Poldrack 2006).

Given these limitations, multimodal approaches are needed to study brain function and dysfunction and hence the inclusion of behavioural questionnaires and tasks in the research presented here. Future research needs to build on early hypotheses that have been based on reverse inference in successfully advancing our understanding of cognitive processing.

8.3 FUTURE RESEARCH

This thesis represents a large component of the PhD activities undertaken over the last 4 years. However, there are still data to be analysed and this will be the initial focus of future

research activity and will include exploring the DMN dysfunction with the behavioural and neuroimaging data from the N-Back study undertaken in the CLBP patients. Cerebral blood flow data will need to be interpreted and presented as well as the diffusion tensor imaging data obtained.

Part of the research plan was also to assess the impact of a pain management programme on the neural correlates of fear, anxiety, catastrophising and attention to pain. If a discrete set of brain regions could be isolated that accompanied successful and unsuccessful treatment outcomes this may help in predicting which groups of patients would be better going to pain management programmes and which would not. Currently, pain management programmes are seen as the last resort due to the cost incurred and yet certain patients may benefit from early intervention and an identifiable pattern of brain regions indicating success may support the utility in exploring the potential for a combined imaging and behavioural assessment process to identify these groups. Classifying groups of patients that would do better with different treatment regimens using behavioural and self-report measures had been largely inconclusive.

Studies have been discussed in this thesis that show that structural changes occur when chronic pain is treated but it is not clear what functional changes occur. Siegle et al (2006) used fMRI to predict recovery following CBT in patients with unipolar depression. FMRI was also used by Laatsch et al (2004) to investigate the neurobiological basis of cognitive rehabilitation therapy in mild traumatic brain injury. Therefore there is potential for examining functional neural changes but recruitment from the in-patient pain management programme was problematic due to funding streams resulting in low treatment numbers. Four patients were scanned and completed the behavioural questionnaires and while the

sample was too small to produce valuable research data, it is sufficient to power calculate the numbers required in a future study where an number of outpatient programmes will be recruited to collaborate.

To understand the impact of emotional disorders on CMSKP, further research is required exploring patients with and without emotional disorders and examining specificity of bias towards various forms of threat. The research paradigms used in this thesis need to be further studied to improve the rigor of the methods used and this would be a suitable way of assessing the validity and reliability of the modified versions of PHODA. This could also be achieved by comparing neuroimaging outcomes with a range of behavioural tools and may help in designing a questionnaire or a set of questionnaires which may be more sensitive in assessing fear, catastrophising and attention to pain.

It is still not clear what patients fear and catastrophise about or why they attend to pain-related information. To date, research has examined a number of different visual stimuli from pictures evoking harm to limbs, facial expressions of pain, movement etc. Using PHODA and a number of other pictorial images, an event-related fMRI design study may now be able to unpick what is feared. At present, those depicted in PHODA express neutral stances but, modifying these and other pictures to have distinct images of injury, pain or movement may be useful. This would not be a simple task and would require a large validation process. Patients would then rate, in the scanner whether the fear is fear of pain, movement or injury.

Due to the issue of causality, longitudinal research will be especially beneficial in tracking structural and functional changes that occur as a result of developing CMSKP and research

that compares those at the beginning of their chronic pain career with those that are well established may be a useful start as longitudinal neuroimaging studies will be costly.

From a personal perspective, this experience has presented new challenges and opportunities for learning new skills. It has allowed for an in-depth study of factors that are important in CMSKP. Having a long history in educational and strategic developments in pain from a local and national perspective, it has complemented the process of trying to improve the management of those with CNMP by helping to better understand some of the factors implicated in maintaining pain-related disability and distress.

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APPENDIX 1: HADS

Please choose one response from the four given below. Please give an immediate response and don't think too long about your answer and answer how it currently describes your feelings.

A	I FEEL TENSE OR 'WOUND UP':	
	Most of the time	3
	A lot of the time	2
	From time to time, occasionally	1
	Not at all	0

D	I STILL ENJOY THE THINGS I USED TO ENJOY:	
	Definitely as much	0
	Not quite so much	1
	Only a little	2
	Hardly at all	3

A	I GET A SORT OF FRIGHTENED FEELING AS IF SOMETHING AWFUL IS ABOUT TO HAPPEN:	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0

D	I CAN LAUGH AND SEE THE FUNNY SIDE OF THINGS:	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3

A	WORRYING THOUGHTS GO THROUGH MY MIND:	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not too often	1
	Only occasionally	0

D	I FEEL CHEERFUL:	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0

A	I CAN SIT AT EASE AND FEEL RELAXED:	
	Definitely	0
	Usually	1
	Not Often	2
	Not at all	3

D	I FEEL AS IF I AM SLOWED DOWN:	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0

A	I GET A SORT OF FRIGHTENED FEELING LIKE 'BUTTERFLIES' IN THE STOMACH:	
	Not at all	0
	Occasionally	1
	Quite Often	2
	Very Often	3

D	I HAVE LOST INTEREST IN MY APPEARANCE:	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care as ever	0

A	I FEEL RESTLESS AS I HAVE TO BE ON THE MOVE:	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0

D	I LOOK FORWARD WITH ENJOYMENT TO THINGS:	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3

A	I GET SUDDEN FEELINGS OF PANIC:	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0

D	I CAN ENJOY A GOOD BOOK OR RADIO OR TV PROGRAM:	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

APPENDIX 2: BECK'S DEPRESSION INVENTORY

There are 21 groups of statements (indicated by letters A to U). Please tick only one statement in each group - i.e. the statement which best describes how you have felt over the past week. If no statement in a group describes exactly how you have felt, just tick the one which is closest. Be sure you only pick one statement per group including groups P (Changes in sleeping pattern) and R (Changes in appetite)

Make sure you read all the statements in each group before answering

A
- ☐ I do not feel sad
- ☐ I feel sad much of the time
- ☐ I am sad all the time
- ☐ I am so sad or unhappy that I can't stand it

B
- ☐ I am not discouraged about my future
- ☐ I feel more discouraged about the future than I used to be
- ☐ I do not expect things to work out for me
- ☐ I feel my future is hopeless and will only get worse

C
- ☐ I do not feel like a failure
- ☐ I feel I have failed more than I should have
- ☐ As I look back I see a lot of failures
- ☐ I feel I am a total failure as a person

D
- ☐ I get as much pleasure as I ever did from the things I enjoy
- ☐ I don't enjoy things as much as I used to
- ☐ I get very little pleasure from the things I used to enjoy
- ☐ I can't get any pleasure from the things I used to enjoy

E
- ☐ I don't feel particularly guilty
- ☐ I feel guilty over many things I have done or should have done
- ☐ I feel quite guilty most of the time
- ☐ I feel guilty all of the time

F
- ☐ I don't feel I am being punished
- ☐ I feel I may be punished
- ☐ I expect to be punished
- ☐ I feel I am being punished

G
- ☐ I feel the same about myself as ever
- ☐ I have lost confidence in myself
- ☐ I am disappointed in myself
- ☐ I dislike myself

H
- ☐ I don't criticize or blame myself more than usual
- ☐ I am more critical of myself than I used to be
- ☐ I criticize myself for all of my faults
- ☐ I blame myself for everything bad that happens

I
- ☐ I don't have thoughts of killing myself
- ☐ I have thoughts of killing myself, but would not carry them out
- ☐ I would like to kill myself
- ☐ I would like to kill myself if I had the chance

J
- ☐ I don't cry anymore than I used to
- ☐ I cry more than I used to
- ☐ I cry over every little thing
- ☐ I feel like crying, but I can't

K
- ☐ I feel no more restless or wound up than usual
- ☐ I feel more restless or wound up than usual
- ☐ I am so restless or agitated that it is hard to stay still
- ☐ I am so restless or agitated that I have to keep moving or doing something

L
- ☐ I have not lost interest in other people or activities
- ☐ I am less interested in other people or things than before
- ☐ I have lost most of my interest in other people or things
- ☐ Its hard to get interested in anything

M
- ☐ I make decisions about as well as ever
- ☐ I find it more difficult to make decisions than usual
- ☐ I have much greater difficulty in making decisions than I used to
- ☐ I have trouble making any decisions

N
- ☐ I do not feel I am worthless
- ☐ I don't consider myself as worthwhile and useful as I used to
- ☐ I feel more worthless as compared to other people
- ☐ I feel utterly worthless

O
- ☐ I have as much energy as ever
- ☐ I have less energy than I used to have
- ☐ I don't have enough energy to do very much
- ☐ I don't have enough energy to do anything

P
- ☐ I have not experienced any change in my sleeping pattern
- ☐ I sleep somewhat more than usual
- ☐ I sleep somewhat less than usual
- ☐ I sleep a lot more than usual
- ☐ I sleep a lot less than usual
- ☐ I sleep most of the day
- ☐ I wake up 1-2 hours early and can't get back to sleep

Q
- ☐ I am no more irritable than usual
- ☐ I am more irritable than usual
- ☐ I am much more irritable than usual
- ☐ I am irritable all the time

R
- ☐ I have not experienced any changes in appetite
- ☐ My appetite is somewhat less than usual
- ☐ My appetite is somewhat more than usual
- ☐ My appetite is much less than usual
- ☐ My appetite is much more than usual
- ☐ I have no appetite at all
- ☐ I crave food all the time

S
- ☐ I can concentrate as well as ever
- ☐ I can't concentrate as well as usual
- ☐ It's very hard to keep my mind on anything for very long
- ☐ I find I can't concentrate on anything

T
- ☐ I am no more tired or fatigued than usual
- ☐ I get tired and fatigued more easily than usual
- ☐ I am too tired or fatigued to do a lot of the things I used to do
- ☐ I am too tired or fatigued to do most of the things I used to do

U
- ☐ I have not noticed any recent change in my interest in sex
- ☐ I am less interested in sex than I used to be
- ☐ I am much less interested in sex now
- ☐ I have lost interest in sex completely

APPENDIX 3: CATASTROPHISING COMPONENT OF THE CSQ

Please indicate using the scales below how often you tend to think in the way described when you are experiencing pain where 0 indicates that you never do; 3 indicates that you sometimes do; and a 6 indicates that you always do.

Q16 **When I feel pain**	Never			Sometimes			Always
	0	1	2	3	4	5	6
I think it is terrible and I feel that it is never going to get any better	☐	☐	☐	☐	☐	☐	☐
I think it is awful and I feel that it overwhelms me	☐	☐	☐	☐	☐	☐	☐
I feel my life isn't worth living	☐	☐	☐	☐	☐	☐	☐
I worry all the time about whether it will end	☐	☐	☐	☐	☐	☐	☐
I feel I can't stand it anymore	☐	☐	☐	☐	☐	☐	☐
I feel like I can't go on	☐	☐	☐	☐	☐	☐	☐

APPENDIX 4: TSK

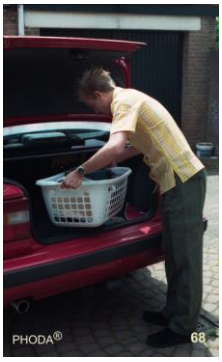
This is a list of statements which other people have used to describe their condition. Please indicate the extent to which you agree with each statement.

1 = strongly disagree
2 = disagree
3 = agree
4 = strongly agree

1. I'm afraid that I might injury myself if I exercise	1	2	3	4
2. If I were to try to overcome it, my pain would increase	1	2	3	4
3. My body is telling me I have something dangerously wrong	1	2	3	4
4. My pain would probably be relieved if I were to exercise	1	2	3	4
5. People aren't taking my medical condition seriously enough	1	2	3	4
6. My accident has put my body at risk for the rest of my life	1	2	3	4
7. Pain always means I have injured my body	1	2	3	4
8. Just because something aggravates my pain does not mean it is dangerous	1	2	3	4
9. I am afraid that I might injure myself accidentally	1	2	3	4
10. Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening	1	2	3	4
11. I wouldn't have this much pain if there weren't something potentially dangerous going on in my body	1	2	3	4
12. Although my condition is painful, I would be better off if I were physically active	1	2	3	4
13. Pain lets me know when to stop exercising so that I don't injure myself	1	2	3	4
14. It's really not safe for a person with a condition like mine to be physically active	1	2	3	4
15. I can't do all the things normal people do because it's too easy for me to get injured	1	2	3	4
16. Even though something is causing me a lot of pain, I don't think it's actually dangerous	1	2	3	4
17. No one should have to exercise when he/she is in pain	1	2	3	4

APPENDIX 5: EXAMPLES OF PICTURES USED

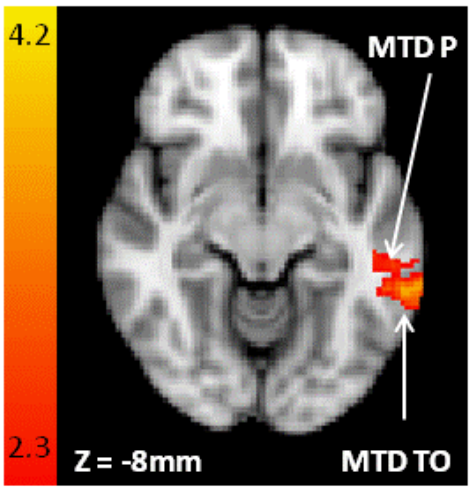
N.B all pictures were presented to participants at a standardised size



APPENDIX 6: WITHING GROUP RESPONSES FOR THE STROOP STUDY

During the prcStroop task, using affective and sensory words compared to control words, the control group had BOLD signal changes in middle temporal gyrus, posterior part (peak voxel at x -66, y-38, z -8, z-stat 3.09) and in the temporo-occipital part (peak voxel at x -66, y -44, z -8, z-stat 3.32) (see Fig A6.1).

Fig.A6.1 Statistical parametric maps illustrating BOLD signal changes in the control group during the prcStroop task
Comparing prcStroop task with control task in the control group using sensory and affective pain words compared to the control words. Each z-statistic map represents BOLD signal change in a whole brain analysis. The colour bar shows the scale of the z-statistic (2.3 – 4.2).

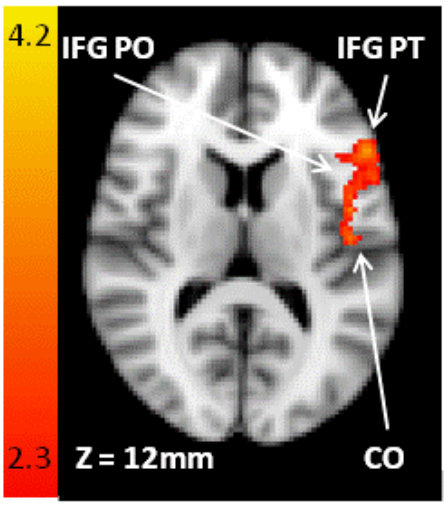


MTD P: Middle temporal gyrus, posterior part
MTD TO: Middle temporal gyrus, temporo-occipital part

During the prcStroop task, using affective and sensory words compared to control words, patients had BOLD signal changes in inferior frontal gyrus, pars triangularis (peak voxel at x -52, y 22, z 12, z-stat 3.25), inferior frontal gyrus, pars opercularis (peak voxel at x -54, y 14, z 12, z-stat 2.89) and central operculum (peak voxel at x -46, y -14 , z 12, z-stat 3.12) (Fig A6.2).

Fig.A6.2 Statistical parametric maps illustrating BOLD signal changes in patients during the prcStroop task

Comparing prcStroop task with control task in the patient group using sensory and affective pain words compared to the control words. Each z-statistic map represents BOLD signal change in a whole brain analysis. The colour bar shows the scale of the z-statistic (2.3 – 4.2).



IFP PT: inferior frontal gyrus, pars triangularis
IFP PO: inferior frontal gyrus, pars opercularis
CO: central operculum

Fig.A7.1. Statistical parametric maps illustrating BOLD signal changes in the control group to the PHODA-MSK task

Illustrating activation during the PHODA-MSK task in the control group when viewing the pictures and imagining undertaking the task depicted. The colour bar shows the scale of the Z-statistic (2.3 – 8.1).

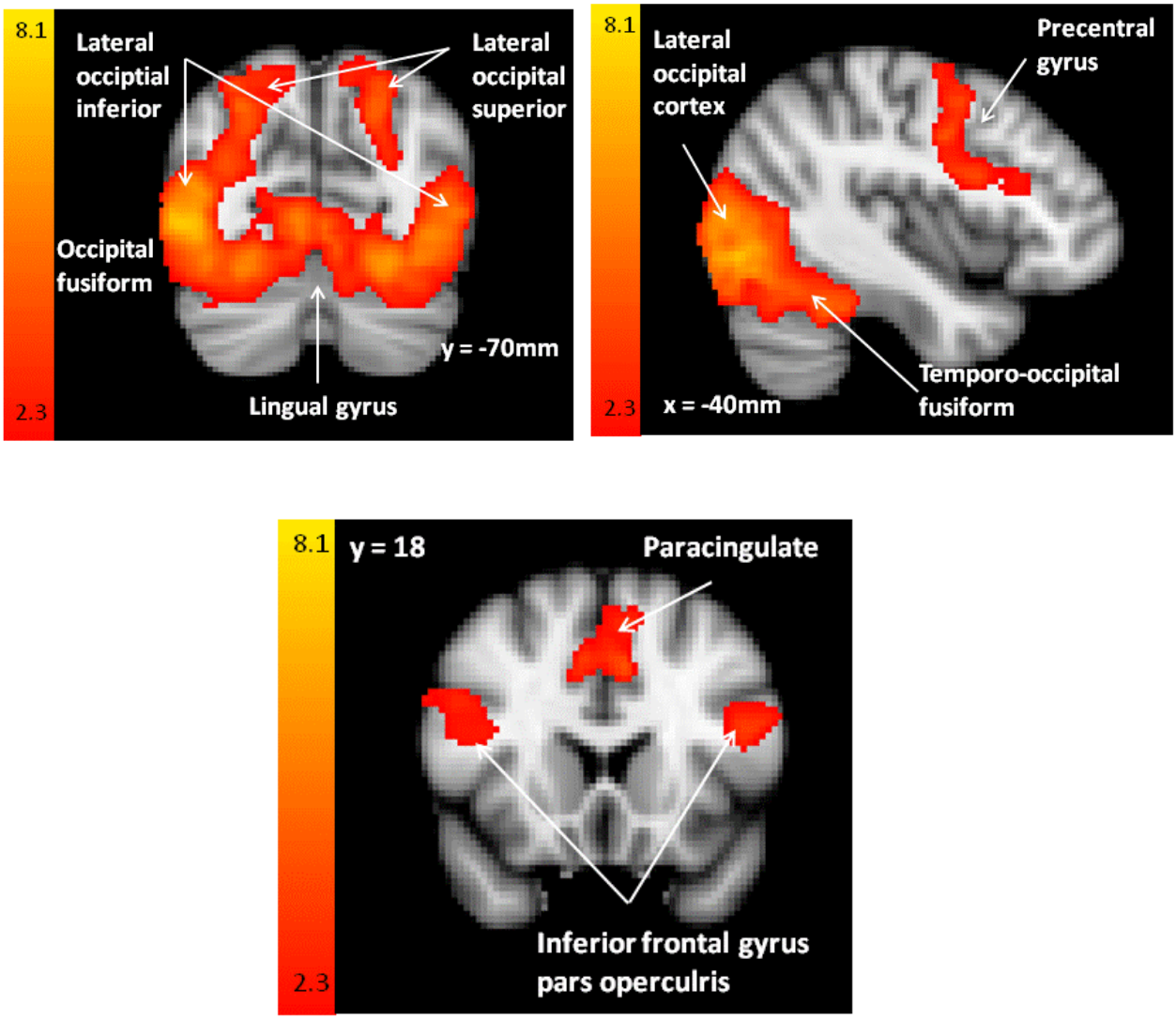


Table A7.1: Control group responses to the PHODA-MSK task
BOLD signal changes in the control group during the PHODA-MSK task. Anatomical locations and peak activation co-ordinates (in MNI 152 space) extracted from brain regions showing significant BOLD signal change at Z>2.3 and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
Inferior frontal pars opercularis (L)	-48	18	20	3.48
Inferior frontal pars opercularis (R)	50	18	24	2.94
Lateral occipital inferior part (L)	-46	-70	4	4.72
Lateral occipital inferior part (R)	50	-70	0	6.89
Lateral occipital superior part (L)	-22	-70	52	4.04
Lateral occipital superior part (R)	28	-70	46	4.11
Lingual gyrus (L)	-4	-70	-2	4.10
Lingual gyrus (R)	6	-70	0	5.07
Occipital fusiform (L)	-26	-70	-16	5.80
Occipital fusiform (R)	-24	-70	-12	4.95
Paracingulate (mid-line)	0	18	42	3.21
Precentral (L)	-42	-2	50	3.47
Precentral (R)	44	-2	50	3.16
Temporal occipital (L)	-36	-40	-26	4.17
Temporal occipital (R)	44	-46	-22	5.40

Fig.A7.2. Statistical parametric maps illustrating BOLD signal changes in the patient group to the PHODA-MSK task

Illustrating activation during the PHODA-MSK task in the patient group when viewing the pictures and imagining undertaking the task depicted. The colour bar shows the scale of the Z-statistic (2.3 – 8.1).

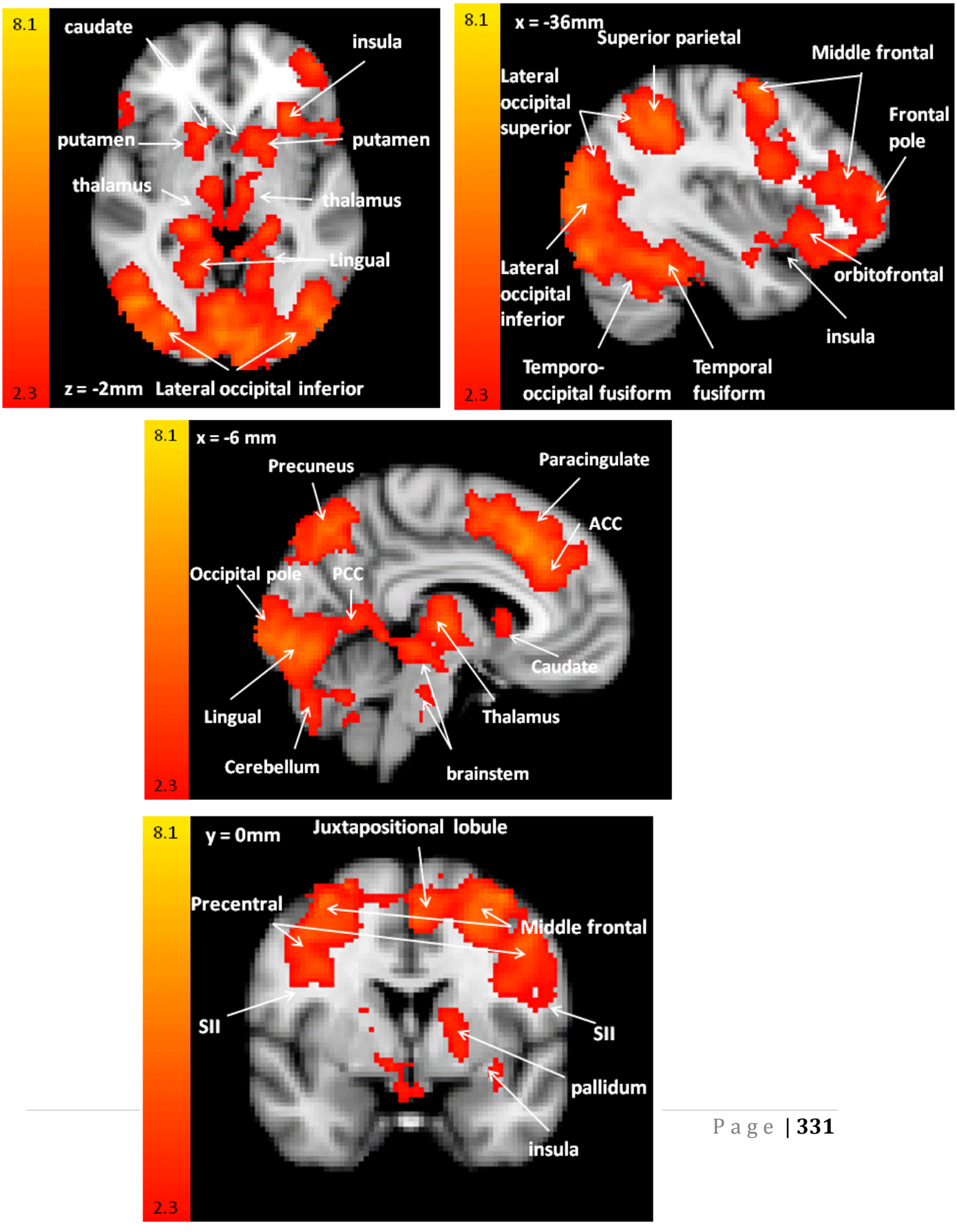
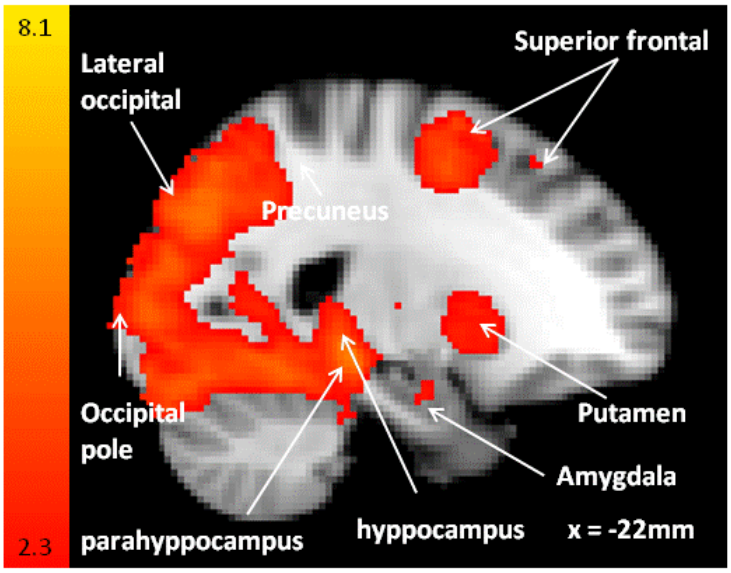
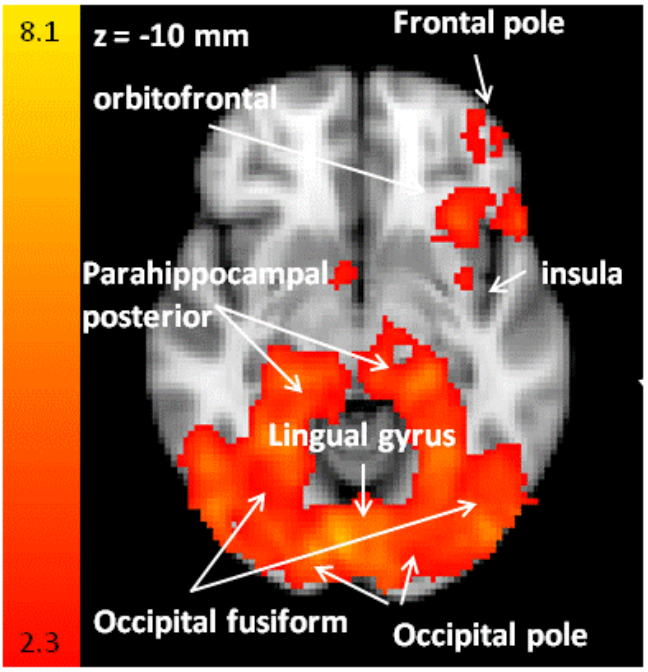
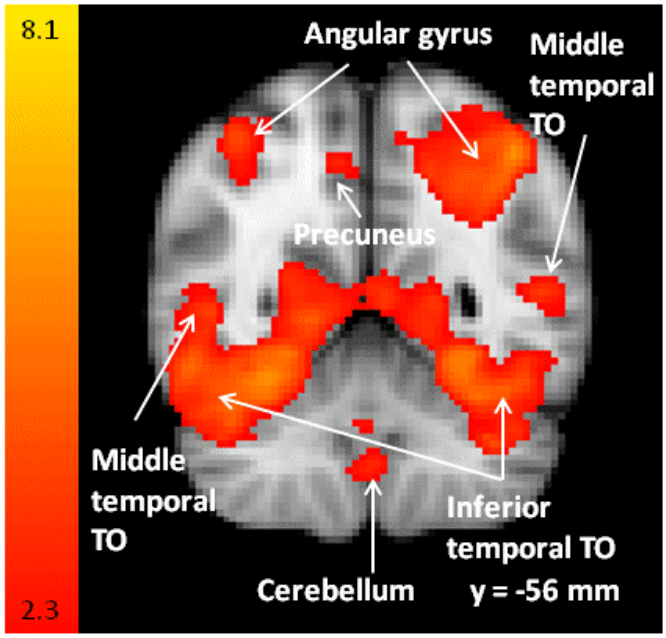


Fig.A7.2. Statistical parametric maps illustrating BOLD signal changes in the patient group to the PHODA-MSK task (cont)
Illustrating activation during the PHODA-MSK task in the patient group when viewing the pictures and imagining undertaking the task depicted. The colour bar shows the scale of the Z-statistic (2.3 – 8.1).







TO = temporo-occipital

Table A7.2: Patient group cortical responses to the PHODA-MSK task

BOLD signal changes in the patient group during the PHODA-MSK task. Anatomical locations and peak activation co-ordinates (in MNI 152 space) extracted from brain regions showing significant BOLD signal change at Z>2.3 and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
ACC (L)	-6	30	24	3.69
ACC (R)	4	22	34	2.35
Angular gyrus (L)	-46	-56	44	3.00
Angular gyrus (R)	38	-56	42	2.59
Frontal pole (L)	-36	56	6	3.49
Frontal pole (R)	48	42	6	3.10
Inferior frontal gyrus pars opercularis (L)	-46	12	24	3.97
Inferior frontal gyrus pars opercularis (R)	50	30	10	2.94
Inferior frontal gyrus pars temporalis (L)	52	26	-2	2.42
Inferior frontal gyrus pars temporalis (R)	50	34	14	3.06
Inferior temporal gyrus, temporo-occipital part (L)	-50	-56	-14	2.55
Inferior temporal gyrus, temporo-occipital part (R)	50	-56	-14	4.33
Insula (L)	-34	20	-2	3.48
Juxtapositional lobule (midline)	0	0	58	3.31
Lateral occipital inferior part (L)	-50	-78	2	4.06
Lateral occipital inferior part (R)	52	-70	2	4.65
Lateral occipital superior part (L)	-36	-84	26	3.96
Lateral occipital superior part (R)	36	-82	26	4.11
Lingual gyrus (L)	-8	-80	-10	4.60
Lingual gyrus (R)	6	-78	-10	5.10
Middle frontal gyrus (L)	-36	-2	60	5.20
Middle frontal gyrus (R)	34	0	60	4.51
Middle temporal gyrus temporo-occipital part (L)	-56	-56	8	2.86
Middle temporal gyrus temporo-occipital part (R)	50	-56	2	3.40
Occipital fusiform (L)	26	-78	-10	3.48
Occipital fusiform (R)	28	-68	-10	3.07
Occipital pole (L)	-12	-94	-10	4.18
Occipital pole (R)	18	-94	-10	4.20
Orbitofrontal gyrus (L)	-32	22	-10	4.12
Paracingulate (L)	-6	26	36	4.75
Paracingulate (R)	6	24	36	3.93
Parahippocampus posterior part (L)	-14	-38	-10	3.73
Parahippocampus posterior part (R)	18	-34	-10	4.23
PCC (L)	-6	-48	4	2.77
PCC (R)	8	-48	6	3.07
Precuneus (L)	-6	-68	46	3.91
Precuneus (R)	6	-76	46	3.91
Precentral gyrus (L)	-46	0	30	3.60
Precentral gyrus (R)	40	0	40	3.05
SII (L)	-52	0	40	3.27
SII (R)	44	0	44	4.00
Superior frontal (L)	-22	0	50	4.17
Superior parietal lobule (L)	-36	-50	52	3.87
Superior parietal lobule (R)	40	-48	52	3.83
Supramarginal gyrus (L)	-52	-30	42	3.91
Supramarginal gyrus (R)	48	-30	46	3.57
Temporal fusiform, posterior part (L)	-36	-40	-24	3.69
Temporal fusiform, posterior part (R)	40	-40	-24	4.57
Temporal occipital fusiform (L)	-36	-56	-22	4.38
Temporal occipital fusiform (R)	38	-50	-22	4.80

Table A7.3: Patient group sub-cortical and brain stem responses to the PHODA-MSK task

BOLD signal changes in the patient group during the PHODA-MSK task. Anatomical locations and peak activation co-ordinates (in MNI 152 space) extracted from brain regions showing significant BOLD signal change at Z>2.3 and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
Amygdala (L)	-22	-6	-20	2.63
Caudate (L)	-10	12	-2	3.29
Caudate (R)	12	14	-2	3.44
Hippocampus (L)	-22	-28	-12	4.62
Putamen (L)	-18	8	-2	3.48
Putamen (R)	20	8	-2	5.40
Thalamus (L)	-8	-16	-2	3.81
Thalamus (R)	8	-16	-2	2.95
Pons (L)	-6	-24	-28	2.56
Pons (R)	8	-24	-24	3.29

Table A7.4: Patient group cerebellar responses to the PHODA-MSK task

BOLD signal changes in the patient group during the PHODA-MSK task. Anatomical locations and peak activation co-ordinates (in MNI 152 space) extracted from brain regions showing significant BOLD signal change at Z>2.3 and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
Crus I (L)	-6	-82	-24	2.79
Crus I (R)	30	-64	-32	2.64
Crus II (L)	-6	-78	-34	3.12
IX (R)	4	-58	-42	3.02
V (R)	30	-34	-30	3.30
Vermis VI (R)	4	-76	-22	3.12
Vermis VIIb (L)	-6	-66	-30	3.11
Vermis VIIIb (L)	-6	-60	-40	2.54
Vermix IX (midline)	0	-56	-42	3.07

Fig.A8.1. Statistical parametric maps illustrating BOLD signal changes in the control group to the PHODA-LBP task

Illustrating activation during the PHODA-LBP task in the control group when viewing the pictures and imagining undertaking the task depicted. The colour bar shows the scale of the Z-statistic (2.3 – 8.7).

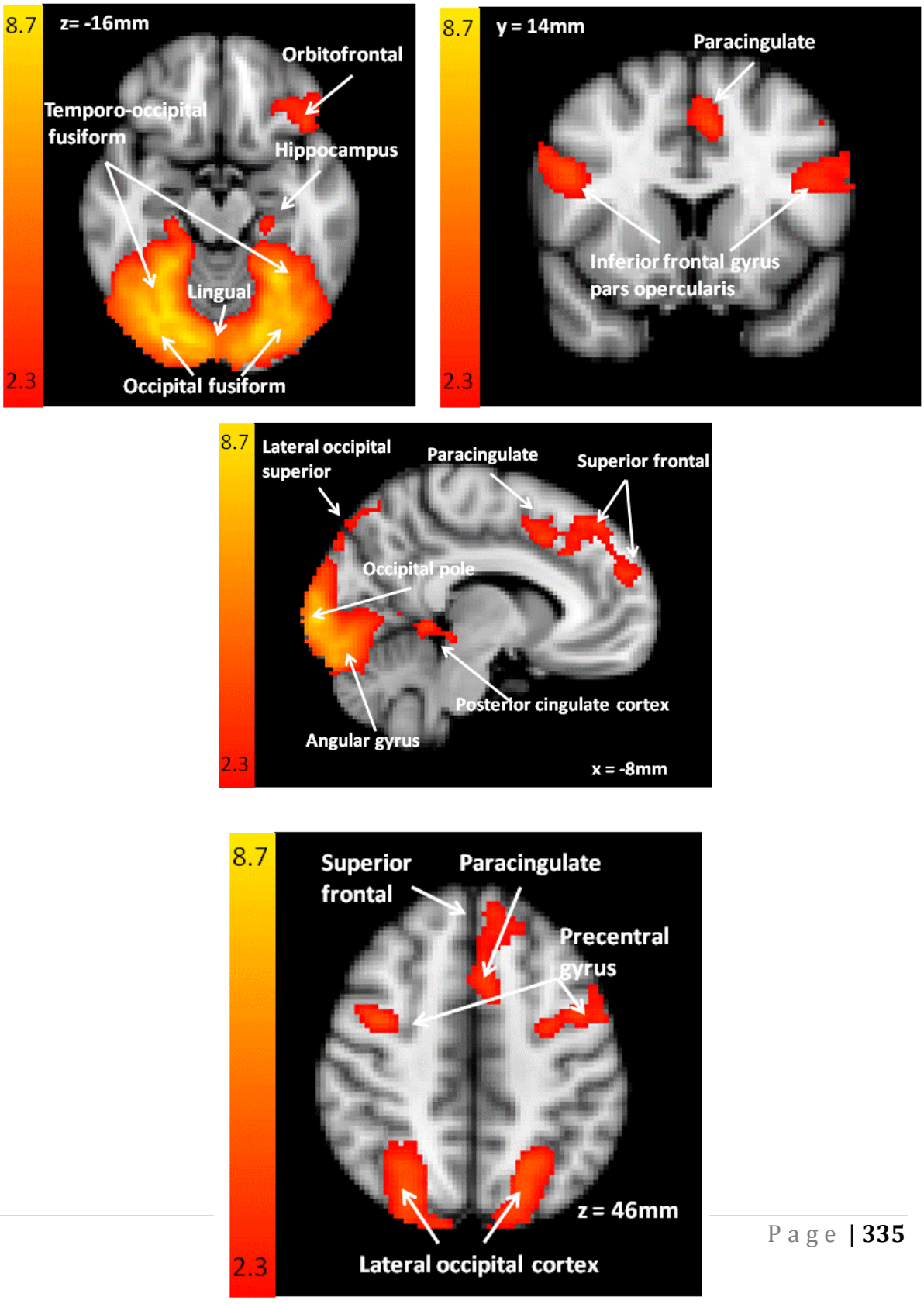


Table A8.1: Control group cortical responses to the PHODA-LBP task
BOLD signal changes in the control group during the PHODA-LBP task. Anatomical locations and peak activation co-ordinates (in MNI 152 space) extracted from brain regions showing significant BOLD signal change at Z>2.3 and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
Hippocampus (L)	-24	-26	-16	3.09
Inferior frontal gyrus pars opercularis (L)	-52	14	24	2.60
Inferior frontal gyrus pars opercularis (R)	54	14	24	3.21
Lateral occipital superior part (L)	-8	-80	52	2.73
Lingual gyrus (mid line)	0	-88	-16	4.99
Occipital fusiform (L)	-28	-78	-16	3.48
Occipital fusiform (R)	30	-74	-16	7.79
Occipital pole (L)	-8	-100	2	7.85
Occipital pole (R)	8	-98	6	6.63
Orbitofrontal gyrus (L)	-40	30	-16	3.12
Paracingulate (L)	-4	14	46	3.78
Posterior cingulate cortex	-8	-44	-2	3.88
Precentral gyrus (L)	-42	0	46	3.83
Precentral gyrus (R)	42	0	46	3.60
Superior frontal (L)	-8	52	30	2.50
Temporal occipital fusiform (L)	-32	-56	-16	7.33
Temporal occipital fusiform (R)	26	-50	-16	7.35

Fig.A8.2. Statistical parametric maps illustrating BOLD signal changes in the patient group to the PHODA-LBP task

Illustrating activation during the PHODA-LBP task in the patient group when viewing the pictures and imagining undertaking the task depicted. The colour bar shows the scale of the *z*-statistic (2.3 – 8.7).

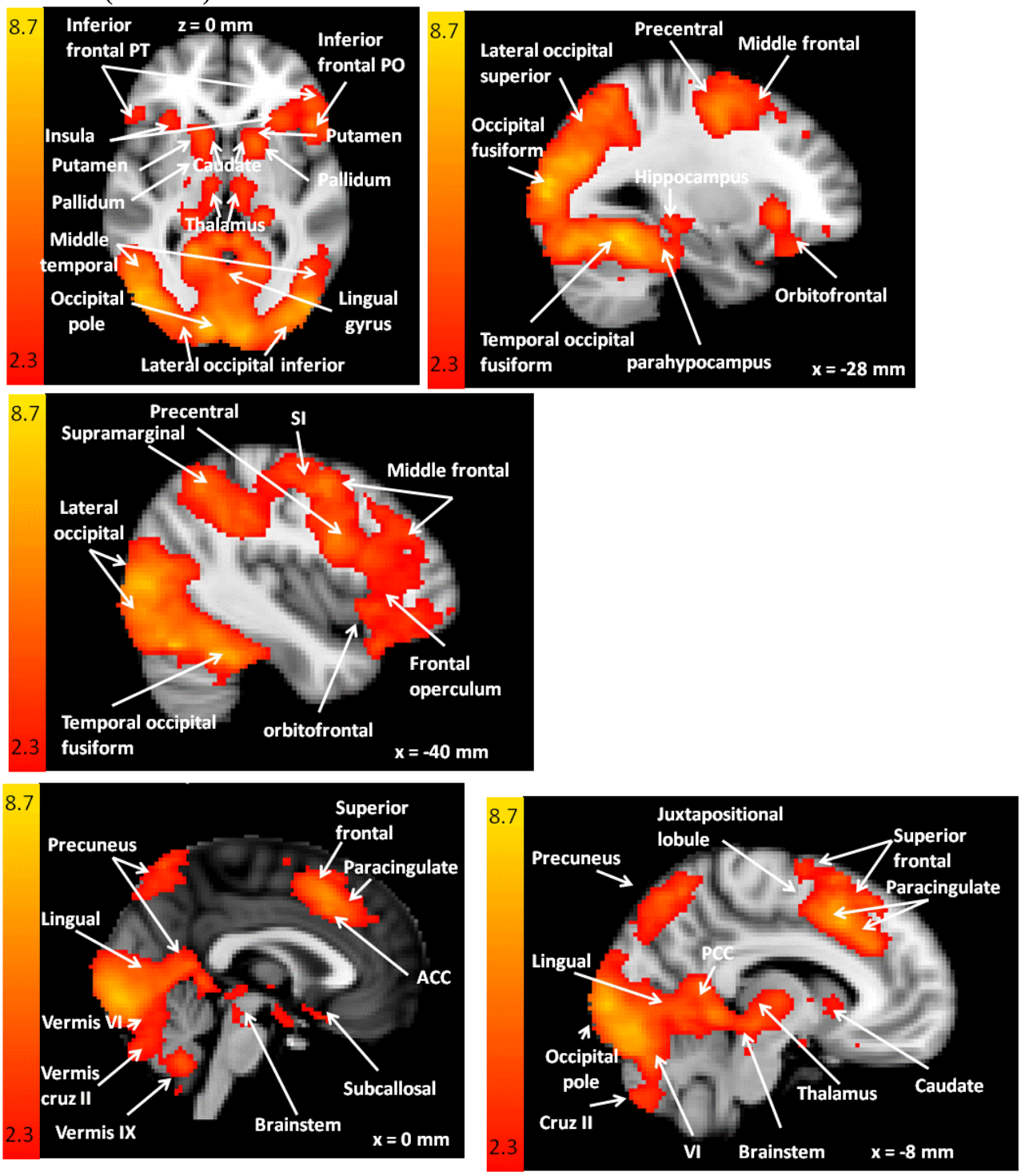


Table A8.2: Patient group cortical responses to the PHODA-LBP task
BOLD signal changes in the patient group during the PHODA-LBP task. Anatomical locations and peak activation co-ordinates (in MNI 152 space) extracted from brain regions showing significant BOLD signal change at Z>2.3 and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
Frontal operculum (L)	-40	26	2	2.59
Postcentral gyrus	-40	-22	50	2.91
ACC (mid line)	0	16	36	4.29
Subcallosal (mid line)	0	14	-16	2.56
Angular gyrus (L)	-46	-52	42	4.47
Frontal pole (R)	28	34	-16	2.78
Inferior frontal gyrus pars opercularis (L)	-52	18	0	4.06
Inferior frontal gyrus pars temporalis (L)	-46	34	0	4.12
Inferior frontal gyrus pars temporalis (R)	52	24	0	2.90
Inferior temporal gyrus, temporo-occipital part (L)	-50	-56	-14	3.98
Inferior temporal gyrus, temporo-occipital part (R)	54	-56	-14	4.22
Insula (R)	34	24	0	3.48
Insula (L)	-34	22	0	3.87
Juxtapositional lobule (L)	-8	2	50	4.42
Juxtapositional lobule (R)	8	6	50	3.79
Lateral occipital inferior part (L)	-46	-80	0	6.89
Lateral occipital inferior part (R)	46	-76	0	6.75
Lateral occipital superior part (L)	-28	-78	26	6.11
Lateral occipital superior part (R)	28	-70	44	4.45
Lingual gyrus (midline)	0	-70	0	4.61
Middle frontal gyrus (L)	-28	18	52	2.89
Middle frontal gyrus (R)	28	8	52	3.05
Middle temporal gyrus temporo-occipital part (L)	-56	-60	0	2.78
Middle temporal gyrus temporo-occipital part (R)	50	-56	2	3.40
Occipital fusiform (L)	-28	-76	-14	6.07
Occipital fusiform (R)	28	-70	-14	7.81
Occipital pole (midline)	0	-98	0	6.02
Orbitofrontal gyrus (L)	-28	32	-20	3.56
Paracingulate (L)	-8	18	42	6.72
Paracingulate (R)	8	22	38	4.50
Parahippocampus posterior part (L)	-28	-30	-20	3.43
Parahippocampus posterior part (R)	28	-26	-22	2.38
PCC (L)	-6	-48	6	4.33
PCC (R)	6	-48	4	4.40
Precuneus (L)	-8	-68	44	3.18
Precuneus (R)	8	-70	56	3.63
Precentral gyrus (L)	-40	10	56	3.05
Precentral gyrus (R)	32	-8	54	3.34
SI (L)	-48	-26	46	2.77
Superior frontal (L)	-8	28	54	4.18
Superior parietal lobule (L)	-40	-48	54	3.55
Superior parietal lobule (R)	34	-48	54	3.91
Supramarginal gyrus, posterior (L)	-40	-36	40	4.38
Supramarginal gyrus, anterior (L)	-56	-34	34	2.98
Temporal fusiform, posterior part (L)	-38	-32	-24	3.62
Temporal fusiform, posterior part (R)	32	-32	-22	4.49
Temporal occipital fusiform (L)	-28	-54	16	7.81
Temporal occipital fusiform (R)	28	-42	-18	7.28

Table A8.3: Patient group sub-cortical and brain stem responses to the PHODA-LBP task

BOLD signal changes in the patient group during the PHODA-LBP task. Anatomical locations and peak activation co-ordinates (in MNI 152 space) extracted from brain regions showing significant BOLD signal change at Z>2.3 and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
Amygdala (R)	-22	0	-22	3.09
Caudate (L)	-12	14	0	3.29
Caudate (R)	12	14	0	4.34
Pallidum (L)	-18	4	0	3.63
Hippocampus (L)	-28	-28	-14	3.07
Hippocampus (R)	28	-22	-12	3.52
Pallidum (R)	14	4	0	3.69
Putamen (L)	-20	10	0	3.74
Putamen (R)	22	10	-4	2.62
Thalamus (L)	-10	-22	0	3.42
Thalamus (R)	8	-16	0	3.17
Brainstem (midline)	0	-28	-18	2.58

Table A8.4: Patient group cerebellar responses to the PHODA-LBP task

BOLD signal changes in the patient group during the PHODA-LBP task. Anatomical locations and peak activation co-ordinates (in MNI 152 space) extracted from brain regions showing significant BOLD signal change at Z>2.3 and cluster corrected $p<0.05$.

	Co-ordinates			z-stat
	x	y	z	
Crus II (L)	-8	-80	-46	3.57
Crus II (R)	8	-78	-38	3.62
VI (L)	-8	-74	-22	4.08
VI (R)	8	-74	-24	4.42
V (R)	8	-58	-18	2.55
Vermis IX (mid line)	0	-58	-42	4.46
Vermis VI (mid line)	0	-68	-20	3.09
Vermis crus II (mid line)	0	-76	-34	3.15
IX (R)	8	-58	-58	2.72