Investigating the role of memory on pain perception using FMRI

Katherine M. Fairhurst

Green-Templeton College,

University of Oxford

Thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Oxford

Supervisor

Prof. Irene Tracey

Table of Contents

Acknowledgements

At the conclusion of this manuscript, it is very difficult to imagine any part of it that could have been achieved without the help given so generously throughout. I would like to thank my supervisor Irene, who took me in as an unknown, untried kid from St Andrews, who let me into the FMRIB family. My curiosity was free to play, developing into a deep love of research. Thank you for the intellectual encouragement and letting me turn my "imaginary thesis" into a Real imaginary thesis. To my sister, Merle, one paragraph, or even a good 50,000 words would not be enough to thank you for all the help you have given me. For first welcoming me to join you in this sisterly endeavour, for giving me the biggest feather in my cap, for answering silly questions, for letting me live in your house, for buying me thesis presents, for teaching me when I was too small to appreciate it, for dlPFC-talk at dinner, for being loving and generous—thank you my big sister, I dedicate this to you.

To my friends in the "student room" in the West Wing: Roisin with matlab books, iplayer links, for taking such an interest and being such a good friend, Asma for snickers bars when I was hungry, Chia shu with chats about work and farmyard animals, Andy leaving a lasting impression and lunchtime chats about what we might be doing if not for Science, Anja for tea breaks, psychology talk and sanity, Aleksandar for movie watching, Karl for laughs and burnt CDs, Mari for long lunches and good talks. Thanks to the bunch of FMRIBians who have watched me grow up, and helped shape me as a researcher: Katja, Karolina, Jon Brooks, Katie Warnaby, Vishvarani, Saad, Mike Lee and Sue. Special thanks for those who helped me with my data: Eugene, Peter Hobden, Stuart Wilson, Mark Jenkinson, Jesper and Tamar. More special thanks to Iain Wilson, for SO much patience with work-stuff, dinners and that dancing that never quite happened.

I would not have managed nor had QUITE such a great time while about it, if it weren't for my friends and family. I'm so often overwhelmed by how wonderful everyone has been and always is. To my parents for helping me get so far in life and teaching me to use my brain, but more importantly that it's always better to be good than to be clever. To my brother Paul, for coming to Oxford practically every week, being my friend, and popping in on a Wednesday night for a few hours to spend my birthday with me, watching a movie and ordering in curry. Thank you to Merle (again) for being such a

great sister, BESIDES being so nice to work with. To Juliette for calling me at 6 in the morning because you wanted a chat and couldn't reach the breakfast bowl, also praying every night for me to finish my thesis so we can play. Thank you to Aaron, for putting up with me before you were forced to as a brother, for buying me books, getting breakfast and generally being the best bigger brother I could have hoped for.

Thank you to Ali, for little things and big things, for sharing your college, your house, your bed at 7 in the morning after the G and S marathon, for dinners and too many movies to count. Thank you Angshu for first suggesting I try do my project at Oxford, and waking up at 4 in the morning to listen to me ramble about neuroanatomy and my "theories". Thank you Michael always for checking up on me, and interrupting me when I may be busy. Thank you to Rob and Julia, my surrogate Oxford family, for always giving me such kindness and friendship I will miss so much out of Oxford. Thank you Dominic, for cheeses and breads and music and sweetness. Thank you Caitlin and Andrew for coming to see my shows, coming for cake, consequences and helping me move. Thank you to Linda for care packages, macaroni and Yul Brynner.

Thank you to my friends from St Andrews, and since relocated. Thank you Ann and Sean for letting me stay at your house, giving me tea. Special thank you to Ann for calling me in the lab late at night to see how I am going. Thank you to Lesley Fish, for fishiness and helping me with research too. Thanks to Flossy for Flossiness and giving me the tea-mug that got me through a good 2 years tea-drinking.

Thank you to my friends from College, Rob the soup (for soup), Serini and Katie Gaynor for dinner, and Angela for potatoes. To my friends from G and S—for strange people who like to sing choruses in public, thank you for the music, the songs we're singing (thanks for all the joys they're bringin').

I would also like to thank all those who so generously took part in my studies.

This undertaking would mean very little if it weren't for the people, life and fun (not to mention tea and cake) it involved. It's been the best thing in my life.

Thank you.

Declaration

I declare that the work presented in this thesis is my own and has not been submitted for any other degree in this or in any other University or Institute of learning.

Abbreviations

ACC	Anterior Cingulate Cortex
BOLD	Blood Oxygenation Level Dependant
CBT	Cognitive Behavioural Therapy
Ces-d	Center for Epidemiologic Studies Depression Scale
CNS	Central Nervous System
COPE	Contrast of Parameter Estimates
Crps	Complex Regiona Pain Syndrome
dlPFC	Dorsolateral Prefrontal Cortex
dmPFC	Dorsomedial Prefrontal Cortex
DTI	Diffusion Tensor Imaging
DWI	Diffusion-Weighted imaging
EPI	Echo-Planar Imaging
EV	Explanatory Variable
FA	Fractional Anistropy
FEAT	FMRIB's Expert Analysis Tool
FILM	FMRIB's Improved Linear Model
FLAME 1	FMRIB's Local Analysis of Mixed Effects
FLIRT	FMRIB's Linear Image Registration Tool
FMRI	Functional Magnetic Resonance Imaging
FMRIB	Functional Magnetic Resonance Imaging of the Brain
FNIRT	FMRIB's Non-linear Image Registration Tool
GLM	General Linear Model

Hp1	Trial B first physical pain event
Hp2	Trial B second physical pain event
Hr	Trial B recalled pain event
IFG	Inferior Frontal Gyrus
M	Mean number of voxels
MCFLIRT	Motion Correction FMRIB's Linear Image Registration Tool
MD	Mean Diffusivity
MVF	Mirror-visual feedback
NRS	Numerical Rating Scale
P1	First physical pain event
P2	Second physical pain event
PAG	Periaqueductal Grey
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
Pp1	Trial A first physical pain event
Pp2	Trial A second physical pain event
PPC	Posterior Parietal Cortex
Pr	Trial A recalled pai event
RL	Recalled pain after a long delay condition
RM	Recalled pain after a medium delay condition
ROI	Region of Interest
RS	Recalled pain after a short delay condition
SD	Standard Deviation
SE	Standard Error

SI	Primary Somatosensory Cortex
SII	Secondary Somatosensory Cortex
SMA	Supplementary Motor Area
STAI	State Anxiety index
STC	Superior temporal cortex
STT	Spinothalamic tract
Tbss	Tract-based spatial statistics
TE	Echo Time
TR	Repeat Time
V	Volume of voxels
VAS	Visual Analogue Scales
vlPFC	Ventro-lateral Prefrontal Cortex
vmPFC	Ventro-medial Prefrontal Cortex

Identifying the role of memory in pain perception using FMRI

Katherine M. Fairhurst

It is now widely accepted that the experience of pain is subject to cognitive influences that may determine the severity of subjectively perceived pain. Many of these top-down factors rely on memory-based processes, which in turn are related to prior experience, learned beliefs and behaviours about pain. As such, memory for pain heavily contributes to the physical pain experience. We posit that pain memory is bidirectional in that following each painful event a trace is stored and that these traces in turn may modify future pain perception prospectively. The following body of work explores aspects of what we have termed a memory template for pain. The results of these chapters taken together, examine these bidirectional aspects of short-term memory for pain employing a recall pain task. Specifically, we explore how, after an acute pain event, a short-term mental representation of the initial event persists. We show that during this time, sensory re-experiencing of the painful event is possible. Furthermore, we investigate aspects of recalled pain, namely intensity and vividness. Data suggests that the intensity and the vividness of this mental representation are determined by the intensity of the initial stimulus, as well as the time-to-test delay. We identify regions that characterise short-term memory for pain. Following on from studies in motor and visual imagery, we explore how pain imagery in the form of recall may affect subsequent pain perception. Our results demonstrate that the inclusion of pain-related imagery preceding physical pain events reduces affective qualities of pain. Testing healthy, naïve subjects, we replicate the effect observed in studies using attention management and imagery strategies, which normally require extensive training. Finally, in a cohort of neuropathic pain patients we show significant reductions in white matter connectivity between areas responsible for working and prospective memory. Collectively, these studies emphasise and elucidate the role of short-term memory of pain in physical pain perception. Acting both retrospectively and prospectively, cognitive reinforcement can increase or decrease the subjective feeling of pain, and therefore manipulating how pain is recalled may have therapeutic potential.

White Queen: “There’s one great advantage…is that one’s memory works both ways.”

…

Alice: “Can *you* keep from crying by considering it?”

White Queen: “That’s how it’s done.”

Alice through the looking Glass,

Lewis Carrol

“A man is affected by the image of a past or future thing with the same emotion of pleasure or pain as he is by the image of a present thing…As long as a man is affected by the image of something he will regard the thing as present, even though it does not exist.”

Ethics, proposition 18

Baruch Spinoza

Chapter 1

Introduction

1.1 Background

Pain is a universal feeling, and yet varies greatly from individual to individual. This is because pain is a subjective experience and results from various forms of internal modulation. This may occur at either the peripheral or the central nervous system level. Pain perception in the absence of peripheral input, or centrally mediated pain, illustrates the concept of pain beyond nociception. In cases such as phantom limb pain, for example, central pain processing may independently be responsible for a vivid pain experience (Brodie et al., 2007). Emotion and both psychological and cognitive factors all contribute to and can modify the pain experience (Wiech et al., 2008). Many of these processes are firmly rooted in memory and can be learned (Apkarian et al., 2009). Therapy for chronic pain has targeted these cognitive aspects of pain perception with some success using cognitive-behavioural therapy, hypnosis, imagery and meditation, with the assumption that individuals can replace maladaptive cognitive behaviour with beneficial coping strategies (Elomaa et al., 2009, Morley et al., 2008). The following thesis highlights the importance of pain memory and posits that how each new pain event is perceived depends on a "memory template" of pain determined by previous experience and learning. This memory template can subsequently be altered by each pain experience as well as during the encoding into long-term memory. A better understanding of how pain is remembered and the role of memory in pain perception could lead to long-term strategies for better pain management, specifically for chronic pain sufferers.

1.1.1 Nociception and pain

Pain is defined by the International Association for the Study of Pain, as "an unpleasant sensory and emotional experience associated with actual or potential damage, or described in

terms of that damage" (Merskey, 1994). The variable nature of this experience is inherent in its physiological complexity. There remains much to learn from this system, and how healthy signals for tissue damage or potential damage can develop into chronic pain conditions.

In the periphery, noxious or painful signals are transmitter via nociceptors; sensory neurons activated at high thresholds capable of potentially causing damage to the tissue (Sherrington, 1903). These exist as thinly myelinated Aδ fibres or unmyelinated C fibres, which respectively, when stimulated cause different qualities of pain perception (Bishop et al., 1958). Nociceptors terminate on projection neurons located on the spinal dorsal horn (Price et al., 2003). Proposed ascending pathways originating from the dorsal horn include most notably the spinothalamic tract (STT). This tract connects neurons from Lamina I and V of the spinal dorsal horn directly to the thalamus (Price, 2000, Price et al., 2003).

From the thalamus, sensory information is gated and transmitted to cortical areas. Discrete areas of the thalamus are said to connect to cortical areas that relate different aspects of the sensory experience (Blomqvist et al., 2000, Craig and Blomqvist, 2002, Craig et al., 1994). Projections from the lateral STT activate the posterior part of the ventral medial dorsal nucleus, the ventral caudal portion of the medial dorsal nucleus and the ventral posterior inferior nucleus of the thalamus. Projections from these regions activate the insula, anterior cingulate cortex and the primary and secondary somatosensory cortex (SI and SII), respectively. The anterior part of the STT projects to the ventral posterior lateral nucleus of the thalamus and information is relayed from here to the SI and SII (Price and Dubner, 1977, Price and Verne, 2002, Treede, 2002, Willis and Westlund, 1997, Willis et al., 2002). A long held theory postulates that lateral parts of the thalamus and subsequent projections to cortical regions process sensory-discriminative aspects of pain perception, while medial parts process affective and motivational qualities of pain perception (Melzack and Chapman, 1973b).

1.2 Cognitive control

1.2.1 Attention

As the field of pain has developed, a greater appreciation for the significant role played by emotional, cognitive and behavioural components of pain perception originating in the brain has occurred (Meagher et al., 2001, Melzack and Chapman, 1973a, Wiech et al., 2008, Wiech and Tracey, 2009, Melzack and Chapman, 1973b). The primary aspects of cognitive control include attention, expectation and reappraisal (Wiech et al., 2008). The most widely studied of these is attention (Tracey et al., 2002, Wiech et al., 2008). Attentional control refers to the allocation of cerebral resources, which ultimately affects cognition and perception. The focus of attention toward or the presence of a distraction away from a painful stimulus has been shown to have consequential respective increases or decreases in both sensory and affective aspects of pain perception (Miron et al., 1989, Villemure and Bushnell, 2002). Brain activation corresponding to lower pain ratings related to distraction include prefrontal areas, the anterior cingulate cortex (ACC), and the periaqueductal grey (PAG), otherwise involved in opioid-mediated analgesia, which acts at the level of the dorsal horn in the spinal cord (Tracey et al., 2002). Distraction has been shown to increase functional connectivity between these areas of descending pain control (Valet et al., 2004). Decreased activation in pain-related areas such as the primary and secondary somatosensory cortices (SII and SII), the thalamus and the ACC has also been associated with distraction, which ultimately may facilitate behavioural responses (Bantick et al., 2002b, Frankenstein et al., 2001, Petrovic et al., 2002).

Expectation

Expectation is characterised by pain-related processes that either increase or decrease before the onset of the pain stimulus. These regions include SI, ACC, the insula, the thalamus, the

PAG, the cerebellum and the putamen (Fairhurst et al., 2007, Ploghaus et al., 2001a, Porro et al., 2002). Anticipating higher levels of pain has been shown to increase subsequent pain perception. Expectation serves to prepare behavioural responses to incoming stimuli. The degree to which the expectation of pain is matched to the sensory input from the periphery can determine the level of perceived pain intensity (Koyama et al., 2005b). Furthermore, associative learning derived from this mismatch between expectation and event could contribute to chronic pain states (Ploghaus et al., 2000).

Reappraisal

As well as attention and expectation, pain perception depends on the subjective meaning given to the pain. Perceived threat is based on the degree of perceived controllability the individual has in managing the pain (Lazarus…, 1984). Individuals with realistic expectations may perceive a higher degree of controllability, relying on effective coping mechanisms (Wiech et al., 2008). Others with higher levels of fear, lower perceived controllability and perhaps with tendencies toward high anxiety or catastrophic thinking will perceive higher intensities of pain and increased associated distress (Feldner…, 2001, Skinner, 1996, Sullivan et al., 2006a). As these factors are purely cognitive, they may be manipulated to change the final outcome – that is the degree of perceived pain. Reappraisal of the painful stimulus and changing the subjective meaning of the pain has been shown to result in a decrease in activity in the ACC, the insula and SII in conditions where perceived threat is lower than in conditions with the same nociceptive input and higher perceived threat (Sullivan et al., 2006a). The prefrontal cortex is thought to coordinate this process of reappraisal (Wiech et al., 2010).

Emotions

While closely related to cognitive effects, pain perception is heavily modulated by emotion. Positive moods are said to decrease pain perception, while the opposite effect is

observed with negative moods. The motivational priming model has been put forward to explain this effect (Lang, 1995). The model predicts that moods can be primed to be either positive or negative. The direction of this priming will subsequently facilitate brain activation for future events. In this way, numerous studies have demonstrated that mood inducers in other modalities such as visual images, olfaction, or humorous videos can increase or decrease pain perception given the nature of the other sensory stimuli (Villemure and Bushnell, 2002). Besides contextual influences, trait-like differences can also affect perception. Individuals who are prone to higher anxiety levels, or depressive symptoms perceive higher intensities of pain (Magni et al., 1994, Wiech et al., 2008). However, as affective qualities of pain can affect mood, the causal relationship between anxiety, depression and pain is difficult to disentangle.

A further difficulty with the emotional component of pain is that it is often difficult to separate from the effects of attention. Emotion is said to significantly affect attentional processes (Keogh et al., 2001). Furthermore similar structures in the brain are associated with both emotion and attention, including areas in the frontal cortex and the brainstem (PAG). However, pain perception modulated by emotion often has significant reductions only in the affective qualities of pain as opposed to the sensory qualities modulated by attention (Villemure and Bushnell, 2002). This distinction is also demonstrated in experimental models involving hypnosis, possibly highlighting important and distinct processes (Rainville et al., 1999a).

1.3 Pain and memory

Pain is intimately linked with learning and memory. One review paper has posited that chronic pain may be regarded as “a persistence of the memory of pain and/or the inability to extinguish the memory of pain evoked by an initial inciting injury ” (Apkarian et al., 2009). Although this view may be regarded as extreme, it might be conceded that much of the cognitive aspect of pain is rooted in personal beliefs, emotions and behaviour formed by previous

experience (Tracey, 2010, Wiech et al., 2008). Chronic pain has been associated with poor recall performance (Oosterman et al., 2011). As the same areas are involved in recall as future prediction, dysfunction in recall tasks may contribute to false or biased expectation of pain, and a subsequent heightening of the hyperalgesic effects of anticipation (Ling et al., 2007, Marty et al., 2009). There have also been cases of memory impairment eliminating pain in humans, and reducing pain in mice (Choi et al., 2007, Pickering et al., 2004). The contribution of memory to pain perception is complex, and is currently poorly understood.

At a neurobiological level, similarities between pain and memory systems have been identified. Synaptic plasticity is crucial to both memory as well as central sensitization in pain (Ji et al., 2003). The link has also been made in terms of observed synaptic strengthening, as in learning and memory, occurring after spinal cord injury possibly contributing to the maintenance of neuropathic (Ji et al., 2003, Tan et al., 2008, Zhuo, 2007). Plasticity involved in learning has been explored as a possible treatment in chronic pain. Specifically, training in discriminating between sensory stimuli has been shown to reverse cortical de-afferentation of SI in phantom limb patients after amputation (Flor, 2004).

It is still unclear whether memory impairment contributes to the development of chronic pain or whether the pathology associated with chronic pain causes damage resulting in disrupted memory processes. Memory dysfunction has been strongly linked to different types of chronic pain. Patients suffering from chronic back pain perform poorly on prospective memory tasks (Ling et al., 2007). Another study demonstrated deficits in verbal episodic memory associated with chronic pain. The most widely reported effect is working memory impairment related to chronic pain (Charlton et al., 2010, Dick and Rashiq, 2007b, Etherton et al., 2006, Grisart et al., 2007). This is thought to be a result of a prolonged increase in cognitive load, and subsequent disruption in

attention processes, which finally affect the working memory trace (Dick and Rashiq, 2007b, Grisart et al., 2007).

1.3.1 Memory

As in pain research, seeking to define and investigate memory processes has revealed increasing levels of complexity. Many different kinds of memory have been identified and discussed and these have been shown to have both overlapping and distinct mechanisms. As individuals perceive the world, a stream of information is fed to the working memory system, which evaluates which aspects are necessary for long-term storage (Baddeley, 2003, Zacks et al., 2007). It is within this short-term, working memory system that memories can be manipulated (Baddeley, 2003). In pain, this short-term store exists as a memory trace of the initial stimulus (Albanese et al., 2007a, Melzack, 1990b, Morley, 1993, Rainville et al., 2004b). As this trace degrades over time, information is converted from a rich analogue representation to a catalogue long-term memory (Albanese et al., 2007b, Rainville et al., 2004b).

Memory specific to pain

Few studies have explored memory processes specific to pain. One possible reason for this might be the inherent complexity of the pain experience. Just as pain includes many factors such as sensory and affective information, proprioception, emotion, as well as cued motor responses to possible threat; the memory for pain may contain each of these components or may be selective as to which survive into long-term storage (Baddeley, 2003). Furthermore, successful and accurate encoding of this information into memory may depend on the specific qualities of the initial stimulus (Albanese et al., 2007a, Morley, 1993). For example, a pain stimulus with a higher threat value, or high emotional value would theoretically be encoded more strongly than a mild pain or non-nociceptive, unthreatening event (Morley, 1993, Phelps, 2004, Robinson and Clore, 2002).

Several studies have demonstrated that sensory information, such as accurate pain intensity levels, are not retained in long-term memory, but exist as a short-term mental trace that degrades over time (Albanese et al., 2007a, Morley, 1993, Niven and Brodie, 1996a, Rainville et al., 2004b).

The earliest reference to this mental trace of "somatosensory memory" was first explored in phantom limb patients. As the described pain in this case had, by definition, no related nociceptive peripheral input, it was assumed that information concerning the location and sensation must originate in the brain as a "neuromatrix." It was suggested that although it was normally not consciously retrievable, it could be activated given a salient sensory cue (Melzack, 1990b). Memory for sensory information, and the ability to re-experience pain was further defined and differentiated relative to other types of pain memory, including "pain event" memory (Morley, 1993).

The temporal nature of this memory trace has been explored measuring the ability for healthy subjects to accurately discriminate between successive painful stimuli. It seems that accuracy to discriminate between sensory cues degrades after 10-14 seconds (Rainville et al., 2004b). This study focused on short-term working memory for accurate sensory recall. Accuracy in pain reporting was investigated extending the time at which subjects rated the pain from immediate reports, an hour and finally a full day following the initial stimulus. Results of this study found that the later subjects were asked to rate the painful stimulus, the closer the correlation between this score and a rating for the same stimulus a week later. These results suggest that during the conversion from short-term to long-term memory, sensory information is evaluated and subsequently remains consistently retrievable (Jantsch et al., 2009a).

Accuracy of reporting

Many studies have found inaccurate recall of previous pain events (Rainville et al., 2004b). Recall of previous pain events depends on the context surrounding memory encoding with the

context determining the level of memory bias (Godinho et al., 2006, Kikuchi et al., 2006, Kuhajda et al., 2002, Terry et al., 2008a). Even the simple presentation of highly emotional images concurrent with a pain event, significantly increases the subsequent pain report (Godinho et al., 2006). These results support the accessibility model of emotional self-report put forward by Robinson and Clore (Robinson and Clore, 2002). This theory holds that pain reports are derived by accessible knowledge. Thus pain reporting at the moment of experiencing pain will be biased by highly affective cues. However, pain reporting *after* the experience will be based on situational cues, and identity-related beliefs (Houtveen and Oei, 2007, Robinson and Clore, 2002). Although recalled pain scores are inaccurate relative to initial pain reports at the time of the painful event, it is the memory of previous pain that influences future reporting, not the original pain score (Gedney and Logan, 2006).

1.4 Short-term pain memory

The recalled pain score influences future pain reporting, and the recalled pain score depends on the context and processing during encoding from short-term memory to long-term recall. In order to develop effective strategies to lessen the perception of pain, we need to explore this crucial conversion time window. Very few studies have explored the short-term memory of pain, and only one using functional magnetic resonance imagining (FMRI). It has been proposed that a mental trace persists in the short-term memory for a limited time after the initial stimulus is presented. After a certain time, this trace, rich in information pertaining to the event, is converted to a categorical memory representation for long-term storage and retrieval. It has also been demonstrated that subjective ratings of pain during this time may differ from those retained, and later accessed in long-term memory. It is therefore crucial to our understanding of pain perception to better our understanding of how this memory of pain is encoded, which aspects of the pain event are retained and how these influence subsequent pain perception.

The context during which memory encoding occurs will vary depending on the many aspects of the related previous pain event. Pain perception is affected by several factors that precede the stimulus, such as expectation and personal beliefs about pain based on previous experience, anticipation and attention, emotion and mood. Evaluation of a pain event at the moment of receiving the noxious stimulus can then change how it is stored long-term. Therefore, each pain experience does not equate to a single evaluation, linearly based on the level of nociceptive input. Previous experience, appraisal and re-appraisal, while the painful experience is still current can determine how each individual pain score is stored in the long-term memory and subsequently accessed to evaluate future pain events. This feedback and feed-forward learning and memory system could be termed a memory template for pain. In this model, maladaptive behaviours borne from false expectations or highly emotional painful experiences, as an example, reinforces the perception bias with each subsequent pain event.

1.4.1 Clinical benefits

Cognitive behavioural therapy aims to target these learned maladaptive approaches to pain and replaces them with beneficial coping strategies. This treatment has shown clinically significant gains in up to 1 in 3 patients, demonstrating the role for memory and learning in establishing this mental template, which can significantly change pain perception (Morley et al., 2008). Other experimental approaches exploring centrally mediated pain perception have used hypnosis, mental imagery and meditation. Clinically, hypnosis has proven effective at relieving phantom limb pain and it has subsequently been used experimentally to explore pain perception in the absence of nociceptive inputs (Faymonville et al., 2000a, Ramachandran and Altschuler, 2009). Similarly mental imagery in different modalities related to pain, such as motor imagery, or visual illusions have demonstrated clear benefits for a variety of pain disorders (Moseley, 2007, Ramachandran and Altschuler, 2009). Recently, the processes underlying meditation have been

explored as a means of dissociating sensory and affective qualities of pain, after specific training (Grant et al., 2011).

1.4.2 Hypnosis

Hypnosis has been defined as "a social interaction in which one person, designated the subject, responds to suggestions offered by another person, designated the hypnotist, for experiences involving alterations in perception, memory, and voluntary action" (Kihlstrom, 1985). Further emphasizing the relationship between hypnosis and memory, hypnosis has been shown to distort the long-term recollection of pain, recalling a greater reduction in pain ratings compared to a control group (De Pascalis et al., 2008). Hypnosis has been shown to be clinically effective for patients that are susceptible, as well as cost efficient (De Pascalis et al., 2008, Lang et al., 2000, Patterson…, 2003, Rainville, 2008). Hypnosis has also been used experimentally to explore pain in the absence of a noxious stimulus, alongside imagined pain relevant to the study design implemented in this study (Derbyshire et al., 2004a).

The efficacy of hypnosis in altering perception by suggestion highlights the importance of subjective reality of pain. The subjective reality of pain can be manipulated by hypnosis, virtual reality and imagery tasks. Virtual reality has been shown to attenuate pain during painful procedures (Gold et al., 2007). Furthermore, in patients suffering from phantom limb pain, affected individuals are given cues in different modalities such as visual feedback or motor imagery with significant effects on their pain condition. While these tasks "trick" the brain into perceiving a functioning limb, it can correct for pain which exists as a subjective reality, but which is physically absent.

1.4.3 Imagery

As observed by Kosslyn and colleagues (Kosslyn et al., 2001) “Imagery is no longer seen as an awkward leftover from a previous, less rigorous age — a topic unfit for polite company”; an increasing number of studies have explored imagery as having potential clinical applications in chronic pain. Both visual and motor imagery manipulations produce promising reductions in pain reports in healthy volunteers as well as patients suffering from a variety of pain syndromes, including neuropathic pain, complex regional pain syndrome and phantom limb pain. The efficacy of these treatments can be attributed to several factors: pain perception relies on the integration of multi-sensory cues, including motor and visual input, which may be simulated using imagery (Kosslyn et al., 2001, Ramachandran and Altschuler, 2009); imagery activates the same neural structures engaged in perception (Derbyshire et al., 2004a, Hugdahl et al., 2001, Kosslyn et al., 2001, Kosslyn et al., 2003); and structures activated during imagery are specific and specialized to the task and modality imagined by the individual (Dvir et al., 2004, Ebisch et al., 2008, Gerardin et al., 2000, Hanakawa et al., 2008, Kosslyn and Thompson, 2003, Kosslyn et al., 2001).

Visual imagery

A memory trace for visual stimuli exists for a short time after exposure to a visual stimulus. This memory trace is dependent on the initial stimulus, but may be recalled during mental imagery activating the same neural structures involved in perception. Memory retrieval in the form of visual imagery has been proposed to influence future perception (Kosslyn et al., 2001, Kosslyn et al., 2003, Pearson et al., 2008, Ramachandran and Altschuler, 2009). The neural correlates of this visual mental representation are specific and specialised to the desired imagery task (Kosslyn et al., 2001). In recent years, visual imagery tasks relying on these processes have been proven to effectively reduce pain reports in patients suffering from a variety of pain conditions (Anderson et al., 2010, Chen and Francis, 2010, Hugdahl et al., 2001, MacIver et al., 2008, Moseley, 2007,

Ramachandran and Altschuler, 2009, Sumitani et al., 2008). One explanation for its efficacy may lie in multi-sensory integration fundamental to pain perception (Ramachandran and Altschuler, 2009).

Vision can play an important role in pain. As early as 1962, the concept of "visual capture," which describes the phenomenon of visual cues altering sensory perception was put forward. This theory argued that sensory cues from different modalities are given different weights according to their statistical reliability. As such, vision can alter perception (Gibson, 1962). This concept has been employed to alter pain perception in phantom limb pain sufferers in the form of mirror-visual feedback (MVF), the rubber hand illusion, and virtual reality paradigms (Chen and Francis, 2010, MacLachlan et al., 2004, Ramachandran and Altschuler, 2009, Sumitani et al., 2008). One theory has been put forward to explain why these visual illusions produce pain reduction in patients suffering from phantom limb pain. It assumes that an important characteristic of this disease is a mismatch between motor output and sensory input, which is subsequently corrected for as the patient receives visual information (as a reflection of their functioning limb, taking the place of the amputated limb) (Harris et al., 2001). Pain reduction using visual feedback has also been demonstrated in patients suffering from neuropathic pain following spinal injury. Mental visual imagery in the absence of mirrors or "real" visual feedback has demonstrated similar pain reducing effects (Moseley, 2007, Oakley et al., 2002); showing virtual visual feedback mimics the effects of external visual feedback.

Motor Imagery

Closely associated with visual memory, mental rehearsal of motor tasks has shown similar effects on physical performance. Motor imagery specifically activates the same cerebral structures involved in motor action (Anderson et al., 2010, Kosslyn et al., 2001). Mental rehearsal of motor tasks has been shown to result in significant improvements in subsequent performance; further

demonstrating that recall of a mental trace can influence subsequent perception. Motor areas and motor responses are also integral to the pain experience. Many studies have demonstrated motor pathways in the brain overlapping with pain processing pathways (Anderson et al., 2010, Coslett et al., 2010, Grafton et al., 1996). Like vision, motor imagery has been implemented as an experimental tool to alter pain perception (Anderson et al., 2010, Gustin et al., 2008, MacIver et al., 2008, Moseley, 2007). The benefits of motor imagery, however, may depend on the nature of the initial injury or pain condition (Gustin et al., 2008).

Pain imagery

Vision and motor imagery have been explored so as to better understand the link between cognition and perception in pain, as they each play a role in pain perception. However, exploration of imagery of pain has been very limited. One study explored imagined pain relative to real physical pain and hypnotically induced pain. The cohort of eight subjects was chosen according to a high score on a suggestibility for hypnosis index. The "imagined pain" condition in this study was used as a control to compare the level of activation relative to hypnosis-induced pain. Imaging results showed strong activation during both real pain and hypnotic pain conditions, yet little in the purely imagined pain condition. However, this result may be due to the relatively small cohort size. Some subjects reported warming of the hand in a post-scan interview, however, no measure for this was acquired as this was not the effect of interest (Derbyshire et al., 2004a).

Mindfulness meditation

As discussed above, attention has a significant effect on pain perception. Attention management is included in CBT to allow people suffering from chronic pain to reduce attentional disturbance and the disabling contribution of attention and emotion to their persistent pain (Eccleston and Crombez, 2007, Elomaa et al., 2009). One aspect of this therapy employs mindfulness meditation practices, which is an acceptance-based method of attention

management (McCracken, 2007). The technique of mindfulness meditation attempts not to distract the patient from pain but engage in non-elaborate awareness (Baer, 2003, Grant et al., 2011, Hayes…, 2004, McCracken et al., 2007a, McCracken et al., 2007b). This technique has been shown to reduce the distressing aspects of pain perception, and reduce pain related anxiety (Elomaa et al., 2009, Grant et al., 2011, Perlman et al., 2010). Attention-management has yet to be refined and a variety of strategies is suggested to and adopted by patients. In one study exploring these techniques, some participants adopted a pain imagery strategy to focus on lessening the effects of pain. Although the number of subjects was few (n=8), and the separate focus of the study did not specifically control for type of imagery used, these patients showed significantly reduced pain ratings (Elomaa et al., 2009).

1.5 Difficulties studying pain memory

The relative paucity of studies exploring memory of pain might be due to the fundamental difficulty involved in isolating the effects of centrally modulated pain, controlling for peripheral nociception. Previous studies have explored hypnotically induced pain, although these manipulations introduce confounds related to the intrinsic complexity of hypnosis and suggestibility. Other studies employing word or image cues are limited by confounds of empathy or language processing. In the studies presented here we utilise pain memory to isolate nociception from cognitive aspects of pain. As a mental trace for pain memory has been suggested and explored in other modalities, we hypothesise that “imagined pain” can induce sensory re-experiencing of a previous pain event and affect subsequent pain perception.

Aside from the inherent complexity of separating central and peripheral influences on pain perception, the experimental investigation of memory produces its own difficulties. Many of these are highlighted in a meta-analysis of autobiographical memory (Maguire, 2001). These include the novelty of the suggested event, the distinctiveness of the memory, the predictability, the number

and type of sensory modalities involved, the cognitive and emotional significance of the events and finally how long the subjects were made to imagine and how often. Another important consideration is the "time to test" interval, which is to say how long after the event the subject was prompted to recall the event. Free-recall itself is difficult to obtain in an experimental context as some direction or cue must be given, adding bias.

1.5.1 Previous work

Many experiments aiming to isolate the effect of pain imagery on pain perception have concentrated on presenting images to which the subject must then respond. An example is a study by Ogino and colleagues (Ogino et al., 2007), where subjects were asked to imagine localised pain on themselves after looking at painful representations. More specifically, this study sought to disentangle pain from a sense of fear of pain inherent in looking at painful images. The group's imaging results revealed activation in the second somatosensory cortex (SII), the right anterior insula, the caudal bilateral ACC, the cerebellum and the rostral part of the posterior parietal cortex (PPC). The group highlighted the fact that they did not observe thalamic or subcortical activity. The use of images, however, introduces the possible confound of empathy pain processing, and that the mechanism by which it is processed may differ from thoughts of pain which influences self.

As an alternative to using images, Kelly and colleagues (Kelly et al., 2007) looked at recall of autobiographical memories by presenting pain related words. These were contrasted with non-pain related words in order to initiate the semantic retrieval process. Subjects were told to imagine a scenario featuring themselves while reading the words. This particular study looked at the affective-motivational and cognitive-motivational aspects of pain memory. The study did not explore the sensory discriminative aspect of pain, however, as these subjects were not asked to try to recreate the pain involved. The group reported activation in the left caudal anterior cingulate and the inferior frontal gyrus implicating these structures in cognitive-evaluative

memory recall. The results also demonstrated the ability for structures within the pain matrix to be activated in the absence of sensory input. The use of verbal cues can introduce the complication of activation of brain areas associated with language processing, which would be difficult to disentangle from those specific to memory retrieval.

Accuracy and time-to-test interval

Another consideration when running or interpreting memory studies is the importance of time elapsed between event and recall. Niven and Brodie (Niven and Brodie, 1996a) conducted an experiment looking at memory of labour pain three to four years after delivery of the baby. The group found that after this time period, the women had very poor recollection of the quality of the pain, while still maintaining quite accurate memories of the context of the pain. The memory of the context surrounding the birth could be very vivid; however the memory of the intensity of the pain was poor.

The relationship between vividness and intensity was rigorously examined by Stephen Morley (Morley, 1993). Specifically, he proposes that vividness influences intensity. He looked at memory of pain several years after the pain event and the ability of individuals to subsequently recall the pain. He surmised that there was no evidence of any somatosensory aspect of the memory, but hypothesised that at this stage of memory recall, only evaluative judgements of the pain have been encoded, which agrees with Niven and Brodie (Niven and Brodie, 1996a). He also found that non-painful events were less well remembered, implying that painful events were in this way, somehow unique (Morley, 1993).

Rainville and colleagues investigated the processes underlying pain memory by looking at shorter time-to-test intervals (Rainville et al., 2004a). More specifically, these experiments

explored the effect of varying the length of the inter-stimulus interval on subsequent sensory discrimination (Laverdure-Dupont et al., 2009). The results describe the "rapid deterioration of pain sensory-discriminative information in short term memory." This paper concludes that accuracy of memory for thermal stimuli is severely diminished in short-term episodic memory after a period of 12 seconds. The group hypothesize that after analogue storage, memory is converted to a more categorical interpretation at around this time, and therefore subjects cannot accurately make judgements on exact temperature magnitudes.

1.6 FMRI

As the focus of the following chapters is to explore the neural correlates of pain memory, we employed functional magnetic resonance imagining (FMRI). The temporal limitations suggested by Rainville and colleagues are well within the limitations of BOLD (blood oxygenation level-dependent response) FMRI (Rainville et al., 2004a). This technique allows for the acquisition of task-related neuroimaging data, as well as online behavioural measures. This enabled the investigation and disentangling of different aspects of pain perception and pain recall. Previous studies exploring short-term pain recall have focused on sensory-discrimination, and therefore focused purely on sensory aspects of pain (Albanese et al., 2007a, Jantsch et al., 2009b). Using our imagined-pain paradigm, we attempted to capture a more inclusive picture of pain memory including neural activation related to sensory-re-experiencing in the absence of nociceptive input.

1.6.1 Neural correlates of short-term pain recall

The benefits of high spatial resolution in functional magnetic resonance imaging allows us to explore the neural correlates of short-term pain memory. As yet, only one study has explored which areas are responsible for sensory-discriminative aspects of pain memory. Although a short-term mental trace was suggested more than 20 years ago, it has not been explored in the same

capacity as the phenomenon of a mental representation in other modalities such as motor and visual memory. Melzack put forward the concept of a "neuromatrix", defined by a widespread network "sculpted by sensory inputs" and "modified by experience". It includes thalamocortical and limbic loops with areas specific to processing aspects of major sensory events (Melzack, 1990b). Although not consciously retrievable, it may be accessed given a relevant sensory cue (Melzack, 1990b, Morley, 1993).

In other modalities, "imagining", recalling and mental rehearsal involves brain regions specific to the task. It would therefore be reasonable to assume that a neuromatrix for pain recall would comprise areas specific to pain, or the precise (in this case) noxious thermal stimulus. As there is no "pain" cortex, in the same way as there is a motor or visual cortex that is identifiable in a mental rehearsal task, in the following experiments we attempt to distinguish areas commonly activated during pain from those involved in pain memory. Areas hypothesized include those identified during short-term sensory-discrimination paradigm such as the primary somatosensory cortex, which has also been suggested as the region involved in short-term tactile memory (Albanese et al., 2007a, Harris et al., 2002, Harris et al., 2001) as well as the anterior insula, the ACC, premotor and posterior parietal cortex. The posterior parietal cortex and the premotor cortex have been identified as the most commonly activated regions in memory tasks involved in recall of context associated information (Kim, 2010). They are also both involved in imitation and simulation (Molenberghs et al., 2010). The anterior insula is involved in interoception relevant to the pain recall task. We also expected activation in the prefrontal cortex related to working memory, expectation and appraisal (Grant et al., 2011, Harris et al., 2002, Lorenz et al., 2003a, Wiech et al., 2010).

In Chapter Seven, we investigate how memory mechanisms involved in pain processing explored in previous chapters may be applied to patient populations. We isolate the posterior

portion of the superior temporal cortex (STC) as a seed region, and explore white matter connectivity changes to target regions classically associated with sensory and affective pain processing (Apkarian et al., 2005, Tracey, 2005). The posterior STC plays an important role in sensory awareness, sensory integration and both working and prospective memory (Charlton et al., 2010, Hein and Knight, 2008, Hooker et al., 2008, Piras et al., 2010). As the development of chronic pain conditions is marked by both structural and functional changes associated with the specific pathology, we hypothesise that white matter connectivity changes between the posterior STC and areas involved in pain and memory may be present in patients suffering from neuropathic pain. This hypothesis is supported by findings of decreased grey matter in the STC identified in fibromyalgia patients, individual's with pelvic pain and post-traumatic stress disorder (Geuze et al., 2008, Schmidt-Wilcke et al., 2007, Schweinhardt et al., 2008).

1.7 Aims and hypotheses

In the following studies, we attempt to explore the concept of a memory template for pain: how pain-related information is encoded in short-term memory; how the mental representation degrades over time; what aspects of the individual event are retained in long-term storage; how pain-recall can affect subsequent perception; and finally what morphological changes in white matter connections in neuropathic pain patients may be related to memory impairments. The primary aim of the experiment presented in Chapter 3 was to test the ability of normal healthy volunteers for immediate recall of the sensory aspects of pain at different intensities. Using FMRI and behavioural ratings of intensity and vividness of imagined pain, we sought to find the neural correlates of recalled pain and to compare the activation of recalled and physical pain.

Having proved the ability to re-experience pain after a short delay, in Chapter 4 we manipulate the "time-to-test" delay between a "high pain" stimulus, from within to beyond the

limits of short-term recall. The hypothesis held that the mental representation of pain would degrade after the “short” delay of 11 seconds, and subjective ratings for intensity and vividness will significantly decrease.

In Chapter 5, having established the effect of manipulating the intensity of the initial physical pain stimulus and the time-to-test delay on recalled pain, we then explore how recalled pain affects subsequent pain perception. This behavioural study was a variation of study 2 and explored the effect of learning based rehearsal and recall of physical pain events on the ratings of subsequent physical pain experiences.

In chapter 6, we employ FMRI again to explore the effect of pain recall and pain-unrelated recall on subsequent pain perception. We establish similarities between recall of different unrelated stimuli, as well as aspects of recall specific to pain, with the hypothesis that modality of the recalled event will have a specific effect on subsequent pain perception.

Finally, in Chapter 7 we explore what significant differences exist in white matter connectivity between healthy controls and patients suffering from neuropathic pain. We use a region of interest (ROI) probabilistic tracking analysis looking specifically at a region involved in memory and perspective switching. As chronic pain is associated with lower scores in working memory and other memory functioning (Etherton et al., 2006, Grisart et al., 2007), we hypothesise that less connectivity between the STC and other regions involved in pain and memory will be present in the patient cohort relative to the healthy controls.

By exploring how pain recall relies on the initial stimulus, the time-to-test delay and how recall can affect subsequent perception coupled to a better understanding of the neural underpinnings of these processes, we hope to shed light on an important yet relatively unexplored aspect of pain perception and how this may be pertinent to the maintenance of chronic pain.

Chapter 2

Methods

Chapter 2: Methods

Magnetic resonance imaging (MRI) is a safe, non-invasive tool used to produce a 3 or 4-dimensional representation of anatomical structures. MRI uses non-ionising radation taking advantage of the inherint qualities of protons in water to measure a signal. When exposed to a powerful magnetic field, the magnetic moments, that is the torque created by the unpaired spin of thr proton, align along the field (B_o). By subsequently applying a radio frequency pulse, the spin on these protons is flipped. One can then measure how these protons return to equilibrium using three parameters (T1, T2 an T2*). T1 is given as the time needed for the spin to return to equilibrium, exchanging energy between the spin system and surroundings. T2, however, is a measure of energy exchange between spins and is generally faster. T2* is a useful measure combining both these rates. As different tissue types, at different magnetic field strengths have different relaxation rates, this creates the contrast which is used to create the image.

MR imaging can be used for both functional (FMRI) and structural imaging (including diffusion weighted imaging (DWI). In chapters 3, 4 and 6 we use an event-related design using FMRI to investigate the neural correlates of recalled pain. In these chapters, signal change from baseline is measured as a BOLD (Blood Oxygenation Level Dependant) response, which is a vascular response to event-related neural activity. BOLD describes a contrast between oxyhaemoglobin (diamagnetic) and deoxy-haemoglobin (paramagnetic) content in the form of a ratio, which changes during activation of brain areas due to increased flow of oxygenated blood to the area of neural activity. As the ratio of deoxy-haemoglobin to oxyhaemoglobin decreases, there is an increase in T2*-weighted signal. This technique enables *in-vivo* experimentation, without additional risk to experimental cohorts of healthy volunteers, who receive no direct benefit from their participation. Furthermore spatial resolution is good, allowing the interpretation of results up

to a magnitude of millimetres. Our experiments work within the temporal resolution limitations, as we explore pain and short-term recall at the magnitude of seconds.

The first two functional imaging studies presented (Chapters 1 and 2) were conducted using a 3 Tesla Siemens/Varian MRI system with a birdcage radio frequency coil and four channel phased-array receiver coil. A gradient echo-planar imaging (EPI) sequence was used with a TR = 3 s; matrix = 64 x 64; TE = 30 ms; 41 x 3 mm axial oblique slices; volumes = 537; FOV=192 x 192; voxel size = 3 x 3 x 3 mm^3.

In chapter 4, a new scanner (Siemens Verio) of the same field strength was used. The EPI sequence was used with a TR = 2.41 s; matrix = 64 x 64; TE = 35 ms; 44 x 3mm axial oblique slices, volumes = 370; FOV=192 x 192; voxel size = 3 x 3 x 3 mm^3. Scans were acquired continuously throughout the experiment. High resolution, T1-weighted, structural scans (64 slices at 1 x 1 x 1 mm^3 voxel size) were obtained for each individual for anatomical overlay of brain activation.

The diffusion tensor imaging data in chapter 7 were acquired on a Siemens Sonata 1.5 T MR scanner. The diffusion-weighted images were acquired using an echo planar imaging sequence defined by Johansen-Berg, (Johansen-Berg and Behrens…, Woolrich et al., 2001a) (72 x 2mm thick axial slices, matrix size 128 x 104, field view 256 x 20mm^2 giving a voxel size of 2 x 2 x 2 mm^3) (Johansen-Berg and Behrens…, 2004). The diffusion weighting was isotropically distributed along 60 directions by using a b-value of 1000 s mm^{-2}, according to research suggesting that isotropic voxels and a greater number of diffusion-encoding gradient directions improves estimation of the diffusion tensor (Ni et al., 2006). For each diffusion-weighted set, five volumes with no diffusion

weighting (b=0) were acquired. Averaging of three diffusion-weighted data sets were acquired to increase the signal-to-noise ratio.

2.1.1 Imaging Analysis: FSL tools

Analysis of all neuroimaging data sets was performed using FEAT (FMRIB Expert Analysis Tool) Version 5.63, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Statistic processing included: motion correction using MCFLIRT (Motion Correction FMRIB's Linear Image Registration tool, (Jenkinson, 2001 #662), non-brain removal using BET (Smith et al., 2002), B0 fieldmaps for unwarping distortion in the images (Jenkinson, 2003), spatial smoothing using a Gaussian Kernel of 5 mm full width at half-maximum and non-linear high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=40.0 s). Registration included co-registration of the functional scan onto the individual T1 high-resolution structural image and then registration onto a standard brain (Montreal Neurological Institute MNI 152 brain) using FNIRT (FMRIB's Non-linear Image Registration Tool, (Jenkinson, 2001 #662)). Statistical analysis at the first, individual subject level was carried out using a general linear modelling (GLM) approach (Friston et al., 1993). Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al., 2001b). Second level analysis grouped the data of all subjects using the data from the first level of analysis. For group statistics, analysis was carried out using FEAT (FMRI Expert Analysis Tool) with higher-level analysis carried out using FLAME 1 (FMRIB's Local Analysis of Mixed Effects). This analysis method allows for incorporation of variance within session and across time (fixed effects) and cross session variances (random effects). Cluster thresholding was performed with a Z-threshold of 2.3 and a corrected p-value of < 0.01 in Chapters 3 and 4 where the default p value was changed from $p < 0.05$ and made to be more conservative as our results were shown to be quite robust. This was set to the default p-value for Chapter 6 at $p < 0.05$. For chapters 3,4 and 6 a cluster-based

correction for multiple comparisons was applied using Gaussian Random Field Theory (Friston et al., 1993, Worsley et al., 1992).

2.2 Participants

The recruitment of all subjects involved screening for any previous history of pain, neurological or psychiatric disorders. Written informed consent was obtained in accordance with the Declaration of Helsinki and the studies were approved in full by the Milton Keynes Research Ethics Committee (09.H0603.31). Subjects all underwent comprehensive screening to ensure that they did not meet any of the exclusion criteria for MR experimentation.

2.3 Pain Devices

In-house built thermal pain devices were used to deliver thermal warm and noxious stimuli. This device has been reliably used within several previous studies published by the PaIN Group (Bantick et al., 2002b, Ploghaus et al., 2001b). The thermode was attached to the dorsum of the left hand for all subjects throughout the experiment. All subjects are thresholded using a randomised staircase approach to find a temperature at which the desired subjective rating is consistently obtained. This temperature is then delivered by the thermode. In Chapters 3-5, the temperature was controlled via the in-house developed software, Paingain. This software ensures timed presentation of noxious, sensory and visual stimuli for the experiment, including presentation of behavioural rating scales and recording of subjective ratings. In chapter 4, both visual and pain stimuli were delivered using Presentation 5. While no baseline is preset using these thermodes, the temperature of the skin is measured throughout the experiment. One minute was allowed between painful stimuli in order to allow for cooling of the skin.

2.4 Ratings

2.4.1 Behavioural ratings

Visual analogue scales (VAS) were used to obtain various behavioural ratings to further define subjective perception of both physical and imagined pain experiences (Sriwatanakul et al., 1983). The scales were anchored with minimum and maximum extremes of the behaviour being measured. As an example, for intensity of imagined pain, the scale was anchored with no pain, and extremely painful. The output of the visual analogue scale is then converted into a numerical value between 0 and 10. In this way, we are able to obtain quantitative behavioural measurements in the scanner. This data was then analysed using PASW statistics 18.0 and Microsoft Excel to explore significant correlations and differences across measures and conditions. In chapter 5, PASW statistics were used to run repeated measures ANOVA on subjects' ratings. For analyses where Mauchly's test of sphericity found epsilon > 0.75 the Huynh–Feldt correction was applied, where epsilon < 0.75 the greenhouse-geisser correction was applied. In Chapters 3 and 4, behavioural measures were incorporated into the imaging data to further elucidate the neural correlates of imagined pain intensity and vividness. In Chapter 6, pain unpleasantness scores were analysed in the same way.

2.4.2 Visual Rating Scales

Collecting subjective ratings for both physical pain qualities as well as psychometric evaluations of recalled pain was crucial to the outcome of the following experiments. Although the task of assigning a numerical rating or word to describe a multi-dimensional experience such as pain or memory is difficult, and perhaps limited, care was taken to fully explain each task to the participant before the start of the experiment. Several types of ratings scales were used in the

various chapters, each adapted from a 10cm visual analogue scale (VAS) anchored on each side with a descriptor.

In Chapters 3-6 we use visual ratings scales (VAS) to record subjective ratings. In each of these, we acquired subjective ratings for recalled pain dissecting the experience into recalled pain "intensity" and recalled pain "vividness". We use these related yet distinct measures to tease apart different aspects of pain memory. As our paradigm instructs participants to match the previous pain stimulus in all aspects of the pain experience, including intensity, then recalled pain intensity could be used as a measure of success as to how well subjects were able to achieve this goal of matching "imagined pain" with the previous physical pain stimulus. It can also be used as a measure of accuracy, as perfect recall would match the intensity of the imagined event to the intensity of the physical pain. Vividness is a measure of subjective reality. This measure was explained to subjects as "how real did the imagined experience feel"; where the upper limit of this scale represented a painful experience identical to receiving noxious thermal input.

In chapters 4 and 6, we acquired a measure of pain perception using physical pain intensity and physical pain unpleasantness as well as subjective ratings for the recalled pain conditions. Pain unpleasantness, while related to physical pain intensity, gives a measure for the affective, rather than sensory qualities of the physical pain experience. In chapters 4 and 5, physical pain intensities and measures of physical pain unpleasantness are compared between trials to establish any significant effects of recalled pain on physical pain. More detailed information, specific to each experiment, can be found in the methods section of each chapter.

2.4.3 Thresholding

Prior to each experiment subjects were "thresholded" to determine the temperature at which subjective perception of physical pain is consistently rated. Subjects are instructed to give a verbal rating on a scale from 0 to 10, where 0 is not painful, and 10 is the pain at which you would withdraw. Between each painful event an interval lasting at least one minute was left between stimuli for skin temperature to recover. Skin temperature was checked before the next stimulus was administered. In order to accustom participants to this scale, the first stimulus was administered to elicit a "warm but not painful" stimulus, which subjects rated as 0/10. Following this a "staircase" method was administered gradually increasing the temperature in measured increments. This staircase would continue until the desired subjective rating was achieved. Following on from this, temperatures of stimuli were administered at random, and checked against previous ratings to ensure consistency. When this was achieved, participants were asked whether they were happy to use that temperature in the experiment. More specific details pertinent to each study are described in the methods section of each chapter.

2.5 Verbal instruction

2.5.1 VAS rating scales

Both before entering the scanner and after thresholding subjects were instructed how to use the visual analogue scale (VAS) and given an opportunity to acquaint themselves with the slider (used in chapters 3, 4 and 5) or button box (used in chapter 6). The visual analogue scale is used to give a standard visual representation of subjective ratings, which can be taken online or out of the scanner. In these studies the VAS consisted of a horizontal line anchored on each end with verbal descriptors. For the "imagine pain" scales of "Intensity" and

"Vividness" subjects were told to rate only the quality of the recalled pain, not the physical pain. Imagined pain intensity was defined as the intensity of pain felt during the "imagine pain" event. Subjects were told if they did not feel any pain to rate "not painful" on the scale, however if they did re-experience pain they were to rate the magnitude of pain toward the other verbal anchor "extremely painful".

In addition to the measure of intensity for recalled pain, a measure for vividness of the recalled memory was taken. This measure is frequently used in studies of pain memory and imagery; related but distinct from recalled pain intensity (Melzack, 1990a, Morley, 1993, Moseley, 2007). Recalled pain vividness was described as "how close to reality was the pain you re-experienced?". Participants were told that if they were unable to re-experience pain then they were to move the slider to the verbal anchor "not vivid", however if they were able to re-experience the painful sensation they were to rate "how real it felt relative to the initial physical pain event". If the vividness of the re-experienced pain was perceived as if they were receiving a physical stimulus they were to move the slider to the verbal anchor marked "extremely vivid."

Care was taken to explain that they were to rate as accurately as possible, and to encourage no incentives to rate the recalled experience if they did not perceive any re-experiencing of the pain. During post scan interviews individuals were all asked the degree to which they were able to re-experience the painful stimulus; this was to verify that their answers matched their scores given during the experiment.

For chapters 3 and 4, physical pain ratings were only taken verbally on a 10-point scale, where 0 is not painful, 3-5 is a medium pain and 6-8 is a high pain, and 10 is extremely painful. In chapters 5 and 6, after thresholding, VAS scales for physical pain were used in the scanner, with verbal anchors "not painful" and "extremely painful". Subjects were told to use the visual analogue scale describing physical pain intensity in the same way as the verbal ratings given during

thresholding. Physical pain unpleasantness was used only online. The measure of pain unpleasantness was described as “distress” and was emphasised to be distinct from pain intensity. Verbal anchors used for the VAS scale for pain unpleasantness were “not unpleasant” and “extremely unpleasant”.

2.5.2 Imagined events

Prior to the experiment, care was taken to ensure subjects understood the “imagine pain” task (in chapters 3, 4, 5, and 6) and “imagine house” task (in chapter 6). Participants were told to recall the initial physical stimulus as soon as they were prompted with the visual screen describing “Imagine Pain” and refrain from recalling the event as soon as the prompt left the screen. Subjects were told to recall as many aspects of the painful experience as they were able to, specifically including: the location of the painful stimulus; and the intensity as it rose, and fell. No training was given prior to the experiment. For the “imagine house” event, subjects were instructed to only visualise the last house in the series when the prompt “imagine house” appeared on the screen and to stop visualising the house as soon as the prompt disappeared.

2.6 Fixation cross

Participants were shown all visual stimuli used in the experiment prior to taking part, including the fixation cross. This fixation cross consisted of two white lines with squared edges centred on a black background, measuring 5cm x 5cm. Subjects were instructed that when viewing the fixation cross they were not to perform any task until the emergence of another visual prompt. They were instructed to focus on the centre of the cross, and not close their eyes. In the experiments performed in the scanner, only imaging data acquired during viewing of the fixation cross, presented between epochs (not within epochs), was used as a baseline.

2.7 Timing of events

All pain events were kept at six seconds for all experiments. Imagined events were also kept at six seconds to facilitate comparisons between the two events. Delay times between the physical pain event and the recalling pain event was at least eleven seconds to ensure as much of the haemodynamic response curve might be sampled in the scanner. In Chapter Five, this was kept at the same time-delay to attempt to mimic the same design as the previous two experiments. An interval of at least a minute was kept between physical pain stimuli in order to ensure cooling down of the skin. Finally, the time between epochs was jittered for all scanned experiments. Further information particular to individual study designs can be found in the methods section in the respective chapters.

Chapter 3

The effect of varying intensity on pain recall

This work was done in collaboration with Merle Fairhurst, and therefore many of the results were previously reported in her D.Phil thesis, Michaelmas 2009.

Chapter 3: The effect of varying intensity on pain recall

3.1 Introduction

Pain memory plays a crucial role in chronic pain, however, very few conclusive neuroimaging studies of pain memory, particularly in healthy individuals, have been performed to explore how experiences of pain events may be stored and recalled. From various imaging and behavioural studies, we are aware of the influence of previous experiences of pain on subsequent pain perception. Specifically, judging the intensity of future pain events is heavily dependent on pain related recall (Gedney and Logan, 2006). With this as a starting premise, the present study looked at short-term episodic memory (working memory), as subjects were asked to recall a specific noxious event eleven seconds after it was experienced. We explore neural correlates of short-term pain recall, as well as quantify and dissociate different aspects of the imagined event by acquiring perceptual measures of intensity and vividness. We hypothesise that a mental representation of pain persists after the initial physical stimulus. When cued within a specific time limit, this mental representation can manifest in sensory re-experiencing of the original stimulus. By initiating sensory re-experiencing, we are able to isolate and distinguish centrally from peripherally generated pain.

3.1.1 Imagining Pain

Earlier attempts to explore cognitive aspects of pain processing have concentrated on imagined pain based on presentation of pain-related images (Ogino et al., 2007) or words (Kelly et al., 2007). These studies attempted to explore pain-related recall as activation related to retrieval

in response to a non-noxious, but pain-related visual stimulus. The inherent limitations of this approach lie in confounds that present themselves as a result of overlapping, yet, distinct processes such as empathy or language processing. Few have looked specifically at recall of the sensory qualities of pain intensity. Several studies have concluded that sensory-re-experiencing or somatosensory memory is not retained after a painful event (Niven and Brodie, 1996b, Kelly et al., 2007, Morley, 1993). Contrasting these claims, some subjects in a study by Derbyshire reported warming of the hand during the imagined pain event (Derbyshire et al., 2004b). Specifics of this data, however, were not collected. While other studies have explored short term memory for pain as a sensory discriminative task (Albanese et al., 2007b, Rainville et al., 2004b), the present study is the first to measure recalled pain as an imagined event within a time frame close enough to the event itself to reliably record re-created pain.

3.1.2 Time to test

The time between the pain event and recall is assumed to be a crucial factor for an accurate and vivid memory of the sensory experience to be retrieved (Rainville et al., 2004a) Although the level of pain intensity and emotional valence of pain events can affect encoding (Morley, 1993), even labour pain is poorly recollected by women when tested three to four years following delivery of the baby (Niven and Brodie, 1996a). Although they were able to accurately remember the context of the pain, recall for the sensory aspects of the event was limited. This clearly demonstrates dissociable aspects of pain processing, which may not all persist into long-term storage. In the present study, we acquire and utilise subjective measures of recalled pain intensity and vividness to better quantify successful recall, as well as to try to dissect different aspects of the imagined event. Morely et al. explored the relative contributions of these perceptual measures in recall of pain experienced years prior to testing. This study concluded pain

memories are readily retrievable, but sensory and affective qualities of the event are encoded separately. Despite not finding any evidence for sensory re-experiencing years after the initial event, based on the work by Morley and others, it is posited that it is possible to elicit a vivid mental representation of pain given a salient cue (Melzack, 1990b, Melzack, 1990a, Morley, 1993). Rainville and colleagues looked at shorter time intervals and the effect on pain memory. The group hypothesized that after analogue storage, memory is converted to a more categorical interpretation at around the chosen time of 12 seconds, beyond which point subjects cannot accurately make judgements on exact temperature magnitudes (Rainville et al., 2004a).

The aim of the following experiment was to establish whether healthy subjects were able to recall the physical experience of pain in the absence of nociceptive input, and test the accuracy of recalling distinct pain intensities. Subjects were instructed to "imagine" the previous experience relying on several aspects of the physical experience. This study is unique, as the manipulation relies simply on memory processes involving no hypnosis. We hypothesise that the memory of pain allows the accurate re-experiencing of the physical sensation of pain within the time-to-test interval employed. With the use of FMRI, we investigate the neural correlates of this memory trace as well as being able to identify differences between processing of physical and recalled pain. Furthermore, we attempt to characterise different aspects of varied thermal intensities in memory recall, and isolate areas specific to memory of noxious pain. A better understanding of each of these aspects of pain memory may help in establishing the contribution of memory in pain perception and utilising this knowledge toward the development of more efficient treatment for sufferers of chronic pain.

3.2 Materials and Methods

3.2.1 Study design

The study design consisted of two scanning blocks within the same session. Within both blocks, three conditions were defined by parametrically varied stimulus types: warm, low pain and high pain. The three levels of thermal stimuli were established using subjective thresholding to achieve intensity ratings of 0/10 (not-painful), 2/10 and 6-7/10 (on a scale of 1-10, where 0 is not painful and 10 is a level pain from which one would withdraw). Each thermal stimulus was applied for six seconds. Each condition was repeated ten times over both blocks, pseudo-randomly. Simultaneously with each thermal stimulus, a visual stimulus was presented reading either "feeling pain" or "feeling warm." The low and the high pain conditions were not identified by a specific verbal cue. A gap of eleven seconds separated the thermal stimulus from the prompted recalled event, during which a fixation cross was presented on the screen. The recalled event following the warm stimulus was accompanied by a visual stimulus which read either "imagine warm" or "imagine pain", instructing subjects to recall the preceding thermal stimulus (Figure 3.1).

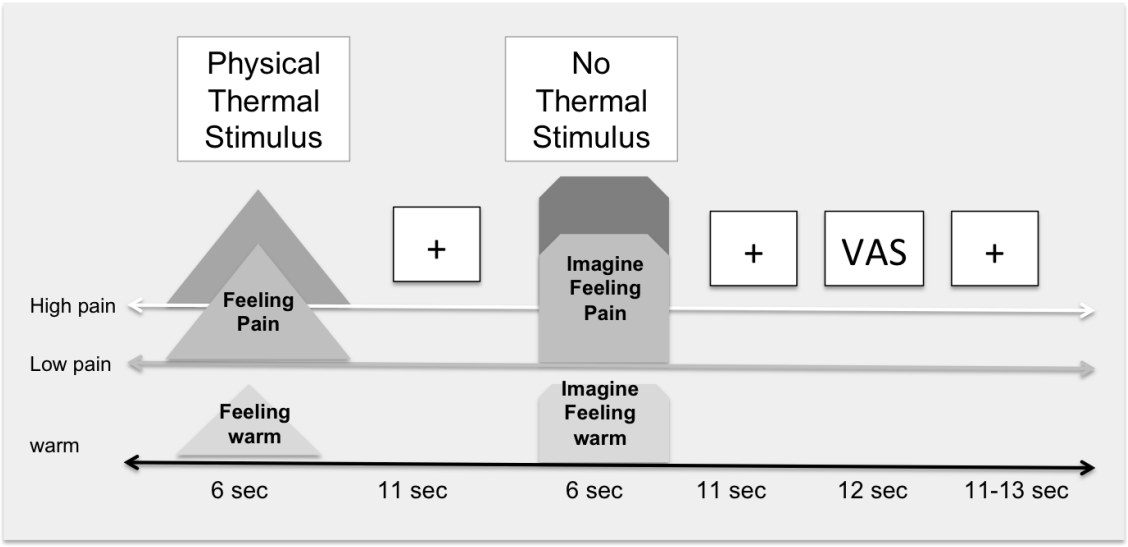


Figure 3.1: Study Design. Thermal and visual stimuli for physical and imagined events followed by visual analogue scales (VAS) for intensity and vividness of imagined pain. Visual stimuli were presented for the duration of the experiment. Low pain and high pain were not cued differently for either the physical pain stimulus or the recall pain event. During the presentation of the fixation cross after the physical stimulus and the "imagine" event, subjects were instructed to not actively recall the previous stimulus until prompted. Two kinds of behavioural ratings were acquired with the VAS: imagined pain intensity and imagined pain vividness. Each of these was presented for six seconds. The time after the final VAS and the beginning of the next condition was jittered for analysis purposes.

3.3 Results

3.3.1 Behavioural data

All of the subjects reported the ability to recall the thermal events during the post scan debriefing. Ratings of both intensity and vividness of imagined pain were observed to significantly increase in a graded manner across conditions: demonstrating accuracy in matching recalled pain intensity to the distinct thermal events (warm mean ± SD = 1.08 ±1.7, low pain mean ± SD = 2.52 ±1.7; high pain mean ± SD = 4.49 ±2.4; one-way ANOVA: $F_{(2,42)} = 10.98$, $p < 0.01$; Figure 3.2). Ratings for vividness of the recalled experience, unlike ratings for intensity, did not show a significant difference between the "warm" and the "low pain" condition. Vividness ratings for both the "warm condition" and "low pain" condition were shown to be significantly lower than ratings for the high pain condition (warm mean ± SD = 4.33 ±2.1, low pain mean ± SD = 4.27 ±1.8; high pain mean ± SD = 5.66 ±1.8; one-way ANOVA: $F_{(2,42)} = 2.32$, $p = 0.11$; Figure 3.2).

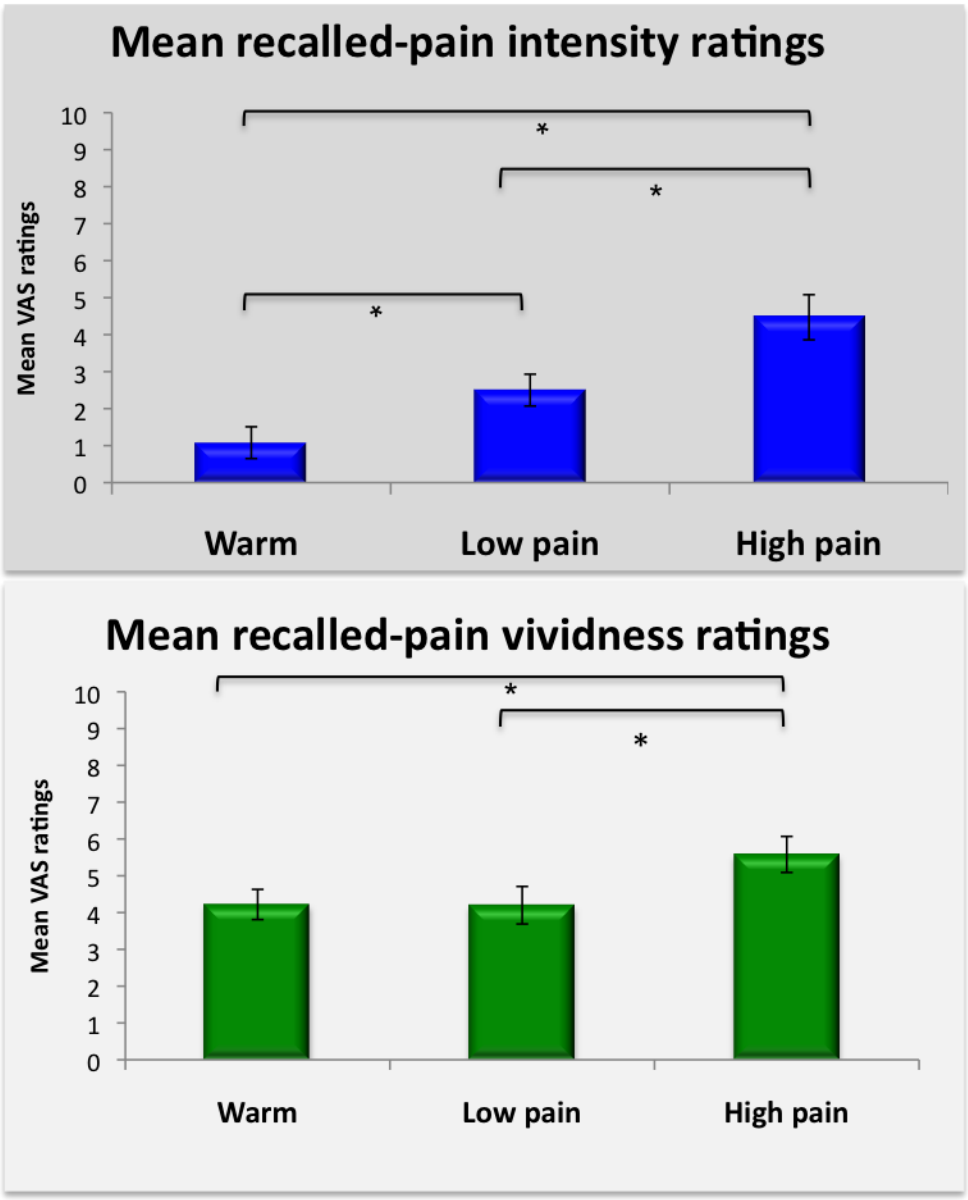


Figure 3.2: Online Visual Analogue Scale (VAS) ratings of Imagined stimulus intensity and vividness compared across warm, low pain and high pain conditions. *: Denotes significant – two-tailed t-test.

Physical pain Intensity ratings were acquired before the start of the experiment, between blocks and after the experiment (warm mean = 0; low pain mean ±SD = 2.2 ±0.47; high pain mean ±SD = 6.29 ±0.6). T-tests revealed a significant difference between physical and recalled warm events ($t_{(14)}$ = -2.364, $p < 0.05$) and between physical high pain and recalled high pain ($t_{(14)}$ =

2.844, $p < 0.05$). No significant difference was observed between physical and recalled low pain events ($t_{(14)} = -0.603$, $p = 0.556$) .

Objective temperature measures

To ensure that nociceptive C-fibres were not stimulated during the imagined events, averages were taken of the recorded temperatures of the stimulating thermode prior to and during the imagined events (mean temperature across subjects = 37.8, SD = ±1.2).

3.3.2 Imaging Data

Neural activation during imagined noxious events

Classical pain processing areas were observed in contrasts exploring both recalled low pain > baseline and recalled high pain > baseline. Furthermore, a conjunction analysis exploring overlap between recalled pain and physical pain conditions revealed significant activation in structures commonly observed during physical pain including bilateral anterior insula, ACC, thalamus, SII, premotor cortex, inferior frontal gyrus and cerebellum (Figure 3.3 and Table 3.1). These results replicate previous findings, where activation of an extensive network of pain-related areas during imagined pain is observed in the absence of noxious input, and in the present study, as a result of a recall task, suggest the existence of a memory trace for pain. Activity during low pain recall > physical low pain and warm recall > physical warm showed extensive overlap. However, comparisons of activation during the imagined events suggest less specificity for recalling a noxious stimulus versus a non-noxious stimulus, particularly when pain intensity is low.

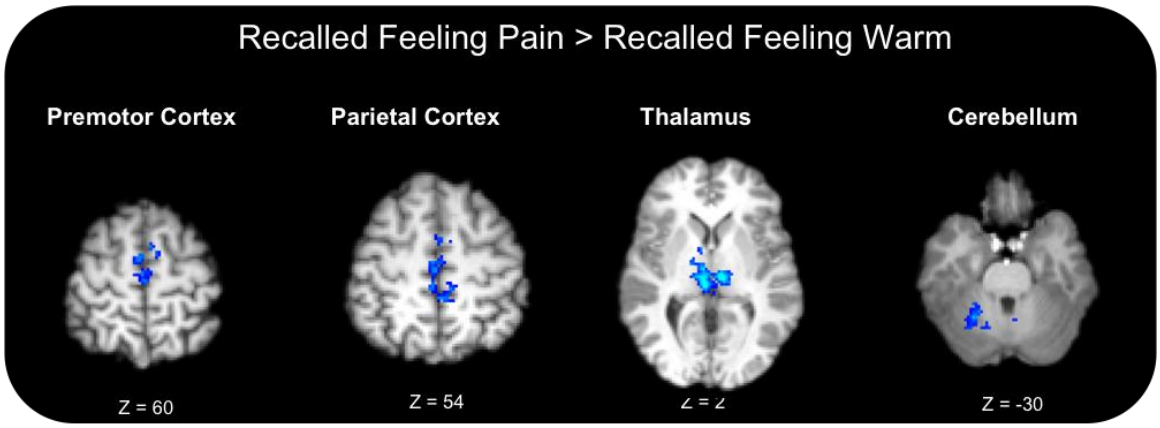


Figure 3.3: Interaction analysis (mixed effects) of Recalled pain > recalled warm. Regions specifically active in combined activation during recalled high pain relative to recalled warm included the premotor, parietal cortex, the thalamus, and the cerebellum (Z = 2.3; p = 0.01). Images are displayed in radiological convention (R – L). For full tables of activation with MNI coordinates, see tables 3.1, 3.3.

By contrast, recalled high pain > high physical pain revealed activity in dlPFC, parietal cortices, putamen, SI, premotor cortex, posterior cerebellar hemispheres and contralateral dentate nucleus (Figure 3.3 and Table 3.2). To explore activity specific to imagining a pain event, a subtraction analysis of imagined recalled high pain from imagined recalled warm was performed revealing activity in the midcingulate, SI, thalamus, PAG and the cerebellum.

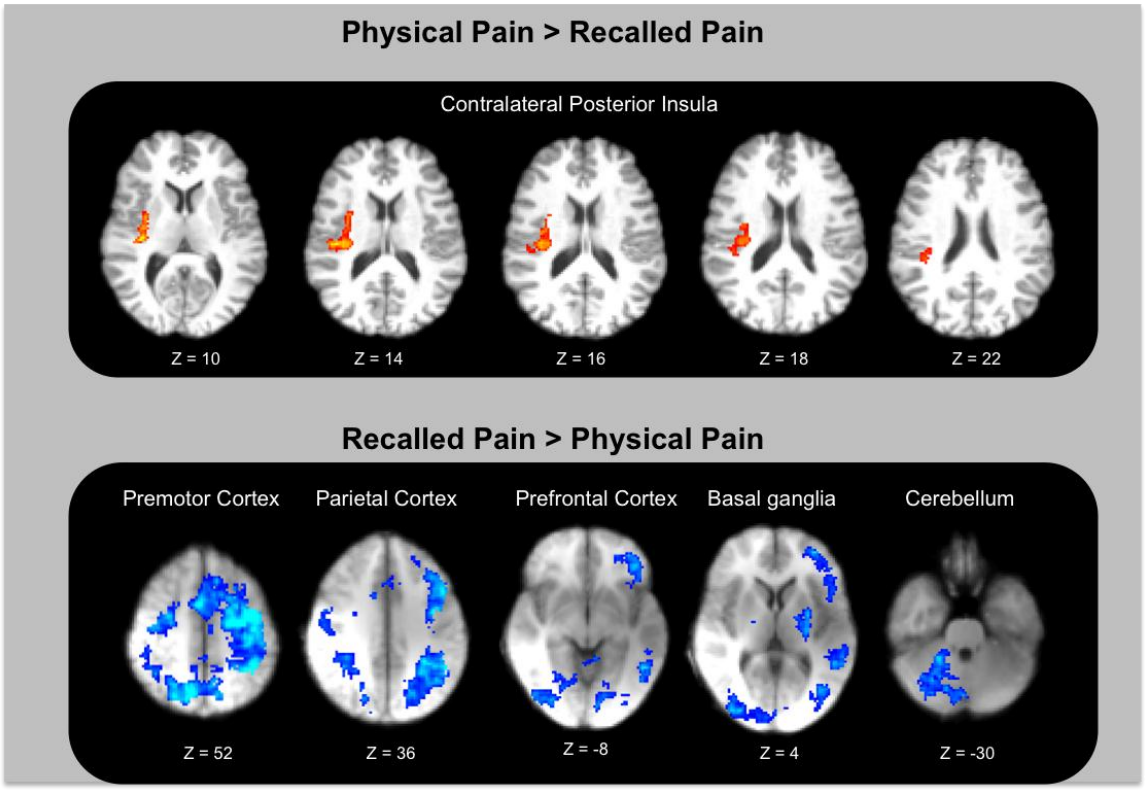


Figure 3.4 Neural correlates of "Physical pain" and "Recalled pain". Group contrast (mixed effects) of "physical pain" (high pain) > "recalled pain" (high pain): isolated activation of contralateral (right) posterior insula. Whereas group contrast (mixed effects) of "recalled pain" (high pain) > "physical pain" (high pain) revealed activation in premotor, parietal and prefrontal cortex, the basal ganglia, cerebellum, areas involved in working memory processing (Z = 2.3; p = 0.01). Images are displayed in radiological convention (R – L). For full tables of activation with MNI coordinates, see tables 3.2, 3.3.

Neural activation specific to noxious thermal events

A group contrast difference between physical pain and imagined pain (high physical pain > high recalled pain) revealed isolated activity in only one brain region: contralateral posterior insula (Figure 3.4, Table 3.3). We found this same unique activity in the contrast of the difference between low physical pain and low imagined pain (low physical pain > imagined low pain).In order to isolate areas specific to physical pain relative to recalled pain, a subtraction contrast was performed looking at areas more active during physical pain relative to physical warm and subtracting this from a contrast of areas more active in recalled pain relative to recalled warm (Physical high pain – physical warm) – (recalled high pain – recalled warm). Areas revealed included bilateral posterior insula, the ACC, contralateral SII, the PAG and the ipsilateral thalamus (Figure 3.5, Table 3.4). No areas were found to be significantly different in the inverse subtraction, specific to recalled pain. Exploring activation significantly more active in this analysis further, region of interest analyses were run to explore relative parameter estimate values for the right posterior insula, SII and the midcingulate, for physical pain, physical warm, recalled pain and recalled warm (figure 3.5a).

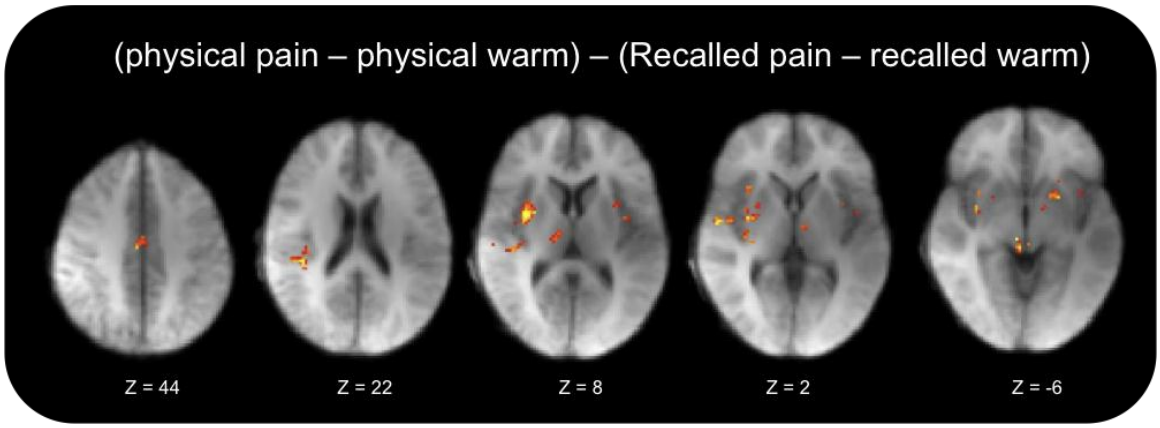
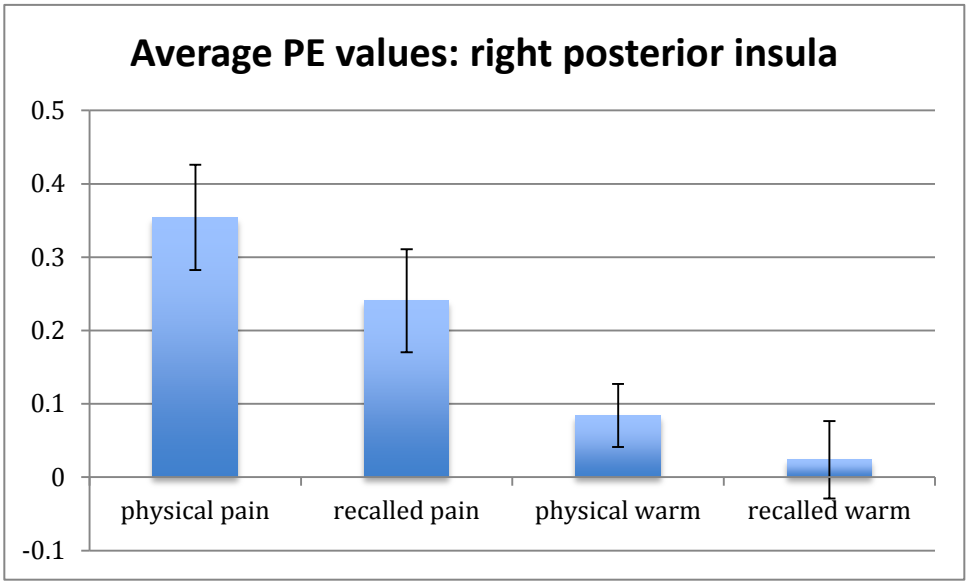


Figure 3.5: Isolating the neural correlates of physical pain relative to physical non-noxious stimuli and activation specific to recalled pain. (Z = 2.3; p = 0.01) Images are displayed in radiological convention (R – L). For full tables of activation with MNI coordinates, see table 3.4.



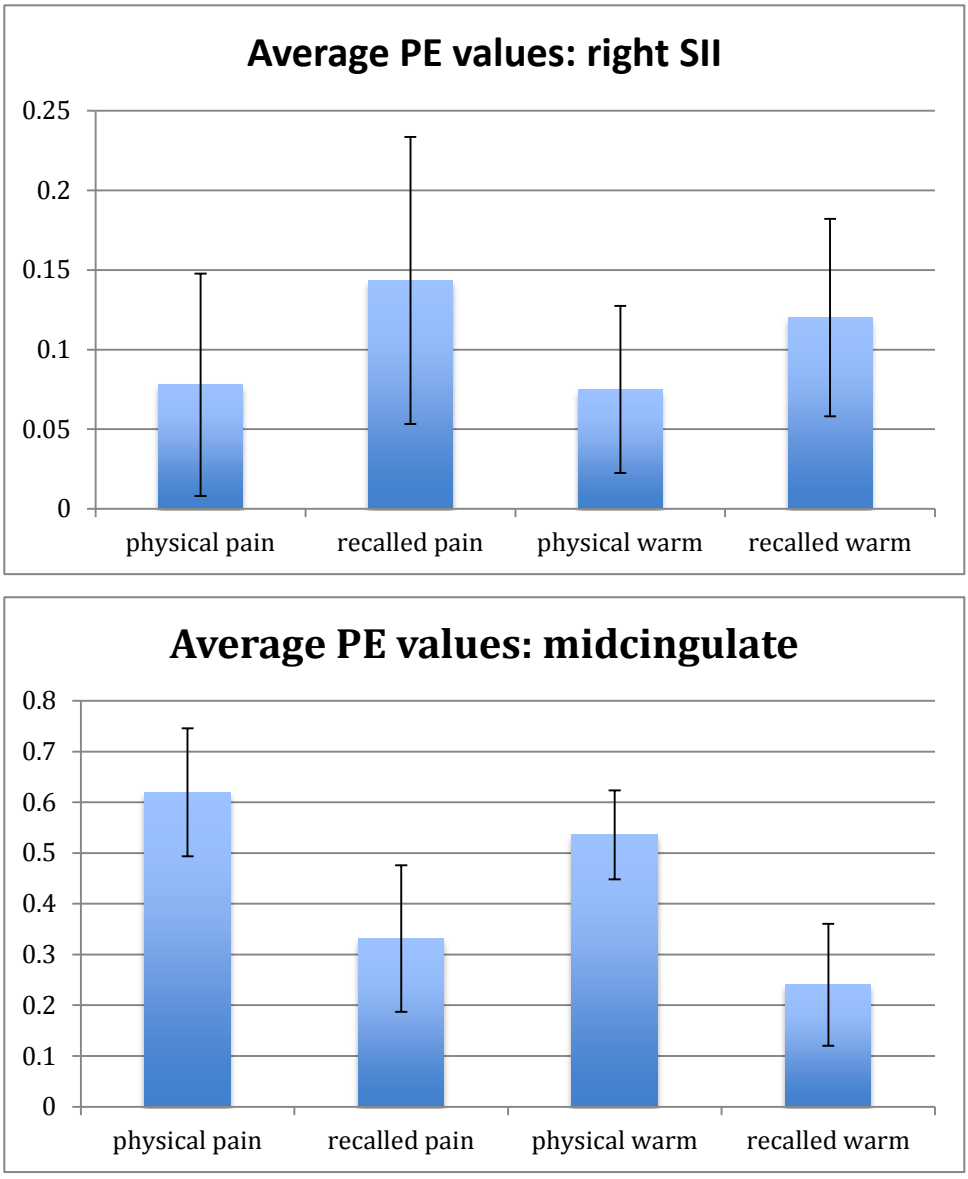


Figure 3.5a: ROI parameter estimates for physical pain, recalled pain, physical warm and recalled warm for the right posterior insula, SII and midcingulate, respectively.

Recalled pain memory areas

Brain activity during imagined events was further investigated using a function-fitting analysis. In this analysis, voxels that showed a significant correlation with the linear trend found in the imagined pain intensity ratings were identified. Regions revealed in this analysis included

bilateral thalamus, mid-cingulate, cerebellum, PAG, putamen, primary motor cortex, bilateral insula, SII, hippocampus, amygdala, and right PPC. (Figure 3.6; table 3.5).

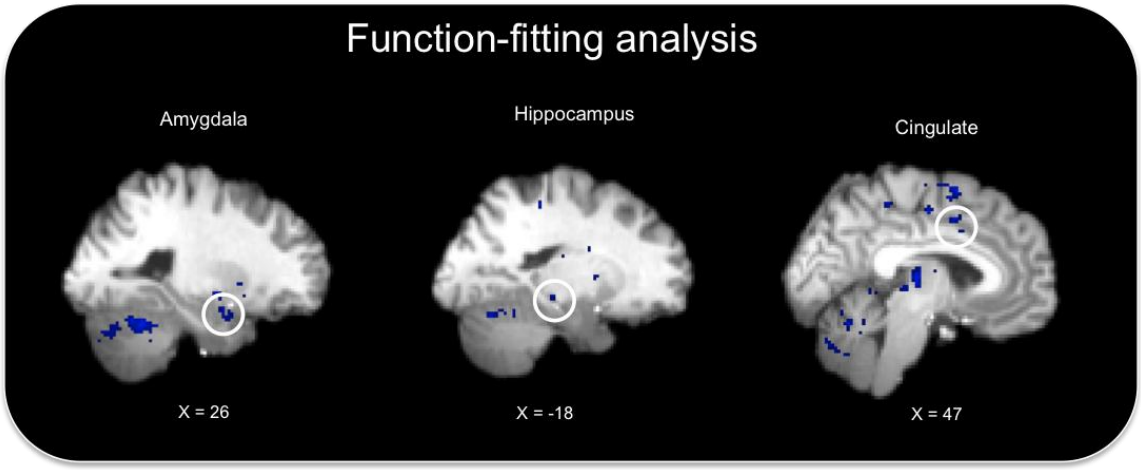


Figure 3.6: Group contrast (mixed effects) using recalled pain intensity scores as a regressor (Z = 2.3; p = 0.01) revealing activation in areas associated with memory that increase in activity with increased intensity of the imagined stimulus. These include the amygdala, the hippocampus and the cingulate (Z = 2.3; p = 0.01) and are not seen in the similar analysis performed to explore vividness encoding. Images are displayed in radiological convention (R – L). See Materials and methods for details of function-fitting analysis and full tables of activation with MNI coordinates, Table 3.5.

This same analysis was applied to explore regions that correlated with the observed trend in vividness ratings across conditions (Table 3.6). Much overlap with the intensity analysis was observed with notable exception of the hippocampus and the amygdala.

3.4 Discussion

Our results demonstrate that within the time-to-test interval employed, healthy individuals are able to accurately recreate the physical pain event and in so doing a sensory re-experiencing of pain, without the aid of hypnosis. Recall of the noxious pain event results in activation of an extensive network of classical pain and working memory structures, which we suggest represent a memory trace or mental representation available shortly after the elicited thermal stimulus. Subjects were able to recall the stimulus intensity accurately according to each thermal stimulus presented. A significant difference between the low and high recalled pain events was found, despite no visual cue differentiating the two conditions. Vividness ratings demonstrate no significant difference between the warm and low-pain condition, yet high pain was shown to be significantly more vivid. Exploring activation specific to physical pain, we reveal posterior insular activity as the only significant difference between the nociceptive thermal pain and recalled pain conditions, and the only neural distinction between recalling and receiving a physical pain stimulus. Results from the function-fitting analysis demonstrate that despite behavioural ratings for intensity and vividness displaying different trends across conditions, both show similar associated activation. Intensity, however, included more areas devoted to memory processing.

3.4.1 Cortical and subcortical pain-related brain activity is not nociceptive-specific

We demonstrate that cued retrieval of a memory of noxious pain events results in extensive pain-related neural activation. Areas that characterize this mental representation of pain are consistent with previous studies of pain imagination under hypnosis, including bilateral anterior insula, ACC, thalamus, SII, premotor cortex, inferior frontal gyrus and cerebellum (Derbyshire et al., 2004b, Raij et al., 2005) (Figure 3.4). Our results prove the hypothesis that healthy subjects can mentally simulate a pain experience without hypnosis and in the absence of noxious input.

3.4.2 Pain memory and the pain template

Activation specific to recalled high pain (recalled high pain > high physical pain) included key structures involved in memory: dlPFC, parietal cortices, putamen, SI, premotor cortex, posterior cerebellar hemispheres and contralateral dentate nucleus. The pattern of activity observed during recalled pain conditions, particularly in the basal ganglia (Li, 2000, Menon et al., 2000), parietal and prefrontal cortices (Lorenz et al., 2003b, Albanese et al., 2007b, Ogino et al., 2007), may represent a network involved in working memory processes and cognitive tasks that require the selection of actions specific to a noxious stimulus and orientating attention to sensory stimuli. The warm condition was used as a control to find activation unique to pain memory. A subtraction contrast (recalled high pain > recalled warm) revealed activity in the thalamus, parietal cortex, premotor cortex, SI, PAG, and the cerebellum (Figure 3.3). The SI and the parietal cortex have been put forward as key structures involved in transitory storage of noxious pain (Albanese et al., 2007a). Furthermore, observed premotor and cerebellar activation might be due to action preparation, in response to the higher pain intensity and more vividly recalled stimulus (Decety,

1996, Farrell et al., 2005). Additionally, activation in the PAG and thalamus might suggest pain anticipation (Fairhurst et al., 2007, Koyama et al., 2005a).

3.4.3 A central biomarker for peripheral nociceptive input

A mixed-effects group contrast isolated activity specific to physical pain revealing only the contralateral posterior insula. An ROI of this region confirmed a unique and significantly different BOLD response during physical pain. The posterior insula has been described as the most frequently activated structure in pain experiments, yet its precise role in pain processing is still debated (Apkarian et al., 2005). Many have suggested the role of the posterior insula to be specific to pain and temperature sensitivity, receiving input from a number of pain processing areas (Brooks and Tracey, 2007a, Craig, 2003). Stimulation of this area can cause contralateral perception of pain (Ostrowsky et al., 2002). By isolating this structure as being uniquely nociceptive specific, we further highlight the extent of neural activation of classical pain structures during pain recall in the absence of peripheral input.

To further identify, more precisely, regions that respond to nociceptive input relative to non-noxious thermal input, and in the absence of memory related areas, we controlled for warm stimulation and recall ((physical high pain > physical warm) > (recalled high pain > recalled warm)) (figure 3.4). Here, we find a more extended network of areas classically associated with pain. Areas revealed in this contrast include bilateral posterior insula, the ACC, midcingulate, contralateral SII, the PAG and the ipsilateral thalamus. One possible explanation as to why this may be is that the recalled conditions are more similar than the two physical conditions. Similarities between the recalled conditions would include similar processing required to recall a sensory stimulus and working memory processing. By contrast, one can expect (from previous studies) that significant differences exist between processing of noxious and non-noxious thermal stimuli. This is further explored in ROI analyses exploring activation in the right posterior insula, SII

and the midcingulate, for physical pain, physica warm, recalled pain and recalled warm. Activation for the posterior insula seems to most clearly support the hypothesis that the posterior insula is more active during physical stimuli than recalled stimuli, and there exists a greater difference in activation between the noxious stimulus and the warm stimulus for the physical stimuli. This is further supported by the midcingulate activation. PE values for SII do not show this same trend, which may indirectly emphasise the role of the posterior insula as being more nociceptive specific than the SII cortex.

3.4.5 Neural correlates of pain recall

By exploring neural activation that increased across conditions and thus mirroring the observed pattern in the behavioural ratings of recalled pain intensity and vividness, we were able to identify regions associated with specific aspects of these two quantifying measures of recall. For intensity, areas that followed the same linear increase in activation included the parietal cortex, dlPFC, SII, bilateral anterior insula, PAG, putamen, cerebellum, ACC, hippocampus and amygdala (Figure 3.6 and Table 3.5). A similar analysis exploring the trend across vividness ratings showed substantial overlap except for ACC, amygdala and hippocampus activity, which were not present (Table 3.6). These areas are characteristic of memory processing and intensity matching (Greenberg et al., 2005). These results support previous work that suggests a very strong relationship between intensity and vividness, while highlighting some intrinsic differences (Morley, 1993). The current study design varied intensity specifically, however, in order to further explore neural activity specific to the vividness of a recalled event. Future work may need to vary this factor more specifically while exploring and controlling for other contributing factors. In the next chapter we explore the effect of the time-to-test interval between the physical and recalled event.

3.4.6 Conclusion

In this chapter, we demonstrated that without hypnosis an imagined recall task was sufficient to create a quantifiable sensory re-experiencing of pain that activated all of the classical pain structures except the contralateral posterior insula. We suggest that this imagined experience of pain was created by using a recent and retrievable pain template with our imaging data identifying structures in the working memory network enabling this retrieval. Regions that characterise high pain recall include memory areas such as the SI, parietal, premotor and cerebellum, and regions associated with pain expectation including the PAG and the thalamus. In our function fitting analysis we find regions specific to a linear increase in pain intensity and vividness. This analysis highlights areas distinctive to intensity encoding and memory retrieval. Clinical benefits of hypnosis are promising but depend on the suggestibility of individuals. By establishing and investigating the potential of retrieving a memory template, we might further our understanding of the cognitive aspects of pain perception, which in turn may lead to more effective therapies (Faymonville et al., 2000b). Access to and the integrity of this mental template, we assume, depends on the time to test delay. In the next chapter we manipulate this delay to explore the limits of this robust mental representation.

3.5 Tables of activation

Conjunction Analysis

		Voxelwise extent	Z score	X	Y	Z
Anterior Insula	right	1532	5.59	34	8	8
Thalamus	right		5.39	12	-22	6
Parietal Cortex	right		5.02	24	-54	36
Visual Cortex	right		3.88	16	-80	0
Cerebellum Crus I	right		5.46	-38	-68	-38
Thalamus	left	444	5.07	-10	-18	6
dlPFC	left		5.19	-42	40	6
Anterior Insula	left		5.48	-34	10	4
Parietal Cortex	left		5.09	-38	-50	36
SI	left		4.76	-26	-36	54
Premotor cortex	left		4.54	-16	-4	64
Cerebellum Crus I	left		5.19	36	-70	-38
Visual Cortex	left		3.47	-18	-80	0
Premotor cortex	right	432	5.93	12	-2	64
Midcingulate	right	369	5.58	0	10	32

Table 3.1: Group contrast (mixed effects) conjunction analysis. Coordinates of structures activated during physical (high pain) and recalled pain. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

High Recalled Pain – High Physical Pain						
		Voxelwise extent	Z score	X	Y	Z
premotor cortex	left	16005	4.99	-26	-10	50
primary motor cortex	left		3.48	-14	-28	60
SI	left		4.68	-34	-46	56
dlPFC	left		4.5	-32	48	20
Parietal cortex	left		4.27	-28	-56	54
visual cortex	left	4078	4.42	-10	-86	-2
Premotor cortex	right	1214	3.79	28	-6	50
parietal cortex	right		4.36	12	-56	54
visual cortex	right		3.82	32	-86	-2
putamen	left	604	3.13	-28	-2	0

Table 3.2: Group contrast (mixed effects) revealing activation specific to high pain recall relative to physical high conditions. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

High Physical Pain – High Recalled Pain						
			Z score	X	Y	Z
posterior insula	right	654	3.81	38	-20	12

Table 3.3: comparing physical pain and recalled pain conditions. Coordinates of structures significantly more active during "feeling pain" (high physical pain) events ("feeling pain" (high physical pain) > "imagine feeling pain" (high recalled pain). Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

(Physical high pain - physical warm) - (recalled high pain - recalled warm)

		voxelwise extent	Z score	X	Y	Z
anterior insula	right	1532	4.07	34	0	10
thalamus	rght		3.22	12	-18	6
PAG	right		3.13	4	-32	-6
putamen	right		3.11	20	6	-10
amygdala	right		3.06	16	-6	-12
putamen	left	444	3.3	-24	6	-6
PAG	left		3.04	-2	-28	-6
thalamus	left		3.04	-12	-14	6
anterior insula	left		3	-32	6	6
amygdala	left		2.57	-20	-4	-12
pallidum	left		3.02	-14	0	-4
ACC	left		3.22	2	12	32
posterior insula	right	432	3.38	38	-22	18
SII	right		3.43	46	-22	12
ACC	right	369	3.33	8	10	34

]

Table 3.4: Group contrast (mixed effects) Isolating the neural correlates of physical pain relative to physical non-noxious stimuli and activation specific to recalled pain relative to recalled warm stimulation. Coordinates in MNI space and associated peak voxel z-scores 0.01 corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Function Fitting Analysis						
Intensity						
		Voxelwise extent	Z score	X	Y	Z
thalamus	left	690	3.58	-6	-20	4
Putamen	left		2.34	-32	0	-2
mid-cingulate	left		2.53	-4	8	36
hippocampus	left		2.39	-18	-26	-12
anterior insula	left		2.29	-40	10	-2
anterior insula	right	685	3.34	42	2	-2
thalamus	right		3.5	6	-20	4
PAG	right		2.06	4	-32	-4
Putamen	right		2.34	28	8	-2
SII	right	467	3.2	58	-30	22
amygdala	right		2.04	26	-2	-20
premotor cortex	right	148	3.1	2	-12	62
parietal cortex	right	121	3.39	38	-50	54
cerebellum midline deep nuclei			2.31	0	-52	-26
cerebelum lobule VI	right		3.36	18	-60	-26
cerebellum crus I	right		3.05	40	-66	-32
cerebellum crus I	left		2.36	-24	-76	-32

Table 3.5: Function fitting analysis for recall pain intensity, Group contrast (mixed effects) of intensity encoding during recalled conditions. Voxels following the linear increasing trend observed in the group mean behavioural data for recalled pain intensity. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Function Fitting Analysis						
Vividness						
		voxelwise extent	Z-score	X	Y	Z
thalamus	right	545	3.46	6	-20	4
putamen	right		2.2	32	-8	-4
cerebellum deep nuclei midline	right		2.19	2	-52	-26
cerebellum crus I	right		2.73	40	-62	-30
thalamus	left	436	3.22	-10	-22	4
premotor cortex	left		2.7	-2	0	52
cerebellum crus I	left		2.66	-26	-74	-30
caudate	right	228	2.85	18	0	16
cerebellum lobule VI	right	84	3.06	26	-54	-30

Table 3.6: Function fitting analysis for vividness rating of recalled pain. Group contrast (mixed effects) of vividness encoding during recalled conditions. Voxels following the trend observed in the group mean behavioural data for recalled pain vividness. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Chapter 4

The effect of delay on pain recall

Chapter 4: The effect of delay on pain recall

4.1 Introduction

In the previous chapter, our design focused on the ability of a healthy individual to recall different pain intensities in the absence of nociceptive input and without hypnosis. During pain recall, we identified a network of brain regions that overlap significantly with classical pain structures. We suggest this network exists transiently as a memory trace or mental representation of the initial noxious stimulus after a short delay between the physical pain event and recall. By increasing the time-to-test delay beyond the limits of short-term memory, we hypothesise that the mental representation of pain will degrade. Specifically, we expect to isolate regions encoding for different aspects of the pain experience as short-term memory is converted to long-term storage. During this crucial transitioning stage, pain memory may still be manipulated before consolidation. Unravelling the key components of short-term memory encoding for pain may therefore be critical for the understanding of how acute peripheral injury develops into centralised chronic pain (Woolf and Salter, 2000).

4.1.1 Mental representations

Evidence for the existence of mental representations using brain-imaging techniques has amassed in the research areas of vision, motor and emotional memory, yet has only recently started to be explored in terms of pain (Bensafi et al., 2003, Decety, 1996, Halpern, 2001, Kosslyn and Thompson, 2003). Behaviourally, it has been established that for a short time following a physical pain experience, an accurate mental representation of pain exists before being converted into long-term storage (Albanese et al., 2007b, Morley, 1993, Rainville et al., 1999b). However, as time between the initial noxious event and retrieval is extended, some of this information is

thought to be lost as the transient analogue representation is converted to a long-term catalogue representation (Albanese et al., 2009, Maguire, 2001).

4.1.2 Short-term recall of pain

Due to the level of complexity inherent to the experience of pain, many aspects may be less desirable to maintain over long periods of time. Previous research has attempted to characterise pain-related recall both within the limits of short-term recall, and after consolidation in long-term memory. Using a sensory-discrimination behavioural paradigm, Rainville and colleagues found that accuracy in sensory matching decreases as the delay between the two painful stimuli increases from four seconds to fourteen seconds. This degradation is said to represent the gradual conversion of a rich analogue representation in memory to a long-term categorical representation (Rainville et al., 2004b). While specific information relating to intensity is lost over this time, Jantsch et al. demonstrated that after memory is consolidated into long-term storage it remains consistent and reliable (Jantsch et al., 2009b). As memory for painful experiences influences subsequent expectations and perception of noxious pain events, exploring the time-window during which memory is manipulated before long-term storage could be central to a greater understanding of the pain experience.

While this type of paradigm is useful for the investigation of the accuracy of subjective ratings as a measure of recall, in the current study we focus on recall as sensory re-experiencing. As such, we hope to capture more completely the memory for a noxious pain event, including both sensory and affective aspects of pain, and investigate how these distinct traces of the pain experience are either maintained or lost over time. In the following experiment, we manipulate the time-to-test delay with a parametric design characterising different time-to-test intervals and thus different stages of pain memory. In this way we hope to accurately model the transition from

short-term memory to long-term storage. Replicating the manipulation in the high pain condition of the previous study, the short delay condition tests short-term pain recall after eleven seconds. The medium delay condition of 20 seconds represents a point beyond the limit of accurate recall for the intensity aspects of pain, and therefore a time at which detailed information characterised by the analogue representation of pain memory would begin to degrade (Rainville et al., 2004b). The one-minute duration of the long delay condition was chosen to be sure that we would be testing beyond the limit of short-term memory (Della Sala et al., 2005).

We suggest that examining short-term memory for pain before long-term storage occurs is essential for a greater understanding of the pain experience, as it can be considered to be the crucial juncture between perception, action and future retrieval (Baddeley, 2003, Gregory, 1980). As perception relies on previous pain memory, expectation and experience, by exploring the neural correlates of the memory template for pain, we may not only improve our understanding of cognitive modulation of pain but also find novel treatments that rely on existing physiological mechanisms (Albanese et al., 2007b, Gustin et al., 2010, Anderson-Barnes et al., 2009).

4.2 Materials and methods

4.2.1 Subjects

Nineteen right-handed healthy volunteers (ten female, nine male; age range: 20-50, mean age: 28.95, Std ± 6.9 years) were recruited for a pain study using FMRI. All subjects were screened for an absence of any prior history of pain, neurological or psychiatric disorders, and did not meet any of the exclusion criteria for MR experimentation. After obtaining written informed consent, subjects were scanned. This study has been approved by the Milton Keynes Research Ethics Committee.

4.2.2 Study Design

The imaging session consisted of 21, six-second thermal stimuli to the dorsum of the left hand. The thermal pain stimulus was defined by subjective thresholding in the scanner before the start of the experiment to identify a 6/10 verbal pain rating. After each painful stimulus there would be an un-cued variable delay condition. The conditions of interest were defined by three parametrically varied time-to-test doelays: short, medium and long (11 seconds, 20 seconds and 59 seconds, respectively). Conditions were pseudo-randomised across the trial with seven repeats per condition. A one-minute interval was allowed between each six-second pain stimulus to ensure the safety of the skin, after which the subjects gave a verbal rating for the previous stimulus.

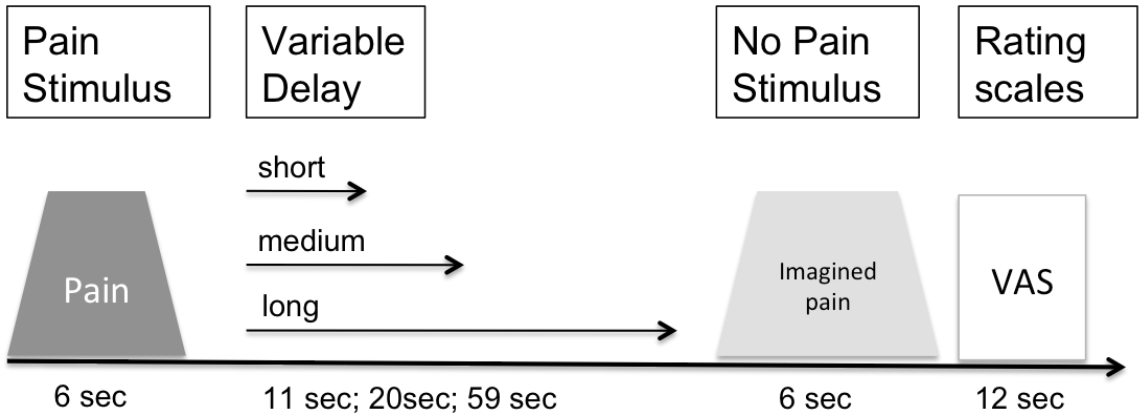


Figure 4.1: Study Design: visual stimuli coinciding with a noxious thermal event followed by the imagined pain event and rating scales; VAS: visual analogue scale, included rating for both intensity of imagined pain and vividness of imagined pain. The delay between noxious and imagined pain events defined the three conditions: short delay (11 sec), medium delay (20 sec) and long delay (59 sec)

4.2.3 Thermal stimuli

An in-house built thermal pain device was used to deliver noxious stimuli. This device has been reliably used in previous studies published by the PaIN Group (Bantick et al., 2002b, Ploghaus et al., 2001b). All subjects were thresholded using a randomised staircase approach to find a temperature at which the desired subjective rating was consistently obtained. This temperature was then delivered by the thermode, controlled via the in-house developed software, Paingain. This software runs both the visual and sensory stimuli for the experiment, including presentation of behavioural rating scales and recording of subjective ratings. Temperatures applied across subjects ranged from 46.5ºC-56ºC (mean ±SD = 50.75ºC ± 2.9).

4.2.4 Visual stimuli

Visual stimuli included a fixation cross and a six-second prompt showing "Feeling pain," presented concurrently with the painful stimulus and "Imagine feeling pain" during which there was no thermal stimulus. Visual analogue scales (VAS) were presented to obtain online ratings for intensity of imagined pain and vividness. Each scale was presented for six seconds. The "Imagined pain intensity" scale was anchored with "no pain" at the minimum, and "extremely painful" at the maximum end. Similarly, the "Vividness" scale was anchored with "not vivid" and "extremely vivid". All visual stimuli were projected onto a screen visible to the subject via prism glasses. Visual stimulation was continuous throughout the experiment.

4.2.5 MRI Data acquisition

Functional imaging was conducted using a 3 Tesla Siemens/Varian MRI system with a bird-cage radio frequency coil and four channel phased-array receiver coil. A gradient echo-planar imaging (EPI) sequence was used with a TR = 3 s; matrix = 64 x 64; TE =30ms; 41 x 3 mm axial oblique slices; volumes = 537; FOV=192 x 192; voxel size = 3 x 3 x 3 mm^3. Scans were acquired continuously throughout the experiment. Signal dropout due to susceptibility-induced field inhomogeneities was minimized for the orbitofrontal cortex (Deichmann, 2005). High resolution, T1-weighted, structural scans (64 slices at 1 x 1 x 1 mm^3 voxel size) were obtained for each individual for anatomical overlay of brain activation. Fieldmap B0 phase and magnitude images were also acquired to correct for any possible distortion of the EPI images.

4.2.6 Data Analysis

Psychophysical Data

Online ratings for intensity of imagined pain and vividness of imagined pain were grouped according to the time-to-test condition (short, medium and long) and the individual means and standard deviations were calculated. After a one-way ANOVAs between all three conditions were shown to be not significant for either recalled intensity, or vividness, two-tailed t-tests were performed to determine the significant difference between conditions, for both intensity and vividness. All t-tests were corrected for multiple comparisons. Temperatures of the thermode at the skin surface were recorded once every 500 ms. The mean and standard deviation of these temperatures across epochs prior to and during the imagined events were calculated per individual and then across subjects to ensure that the temperature of the skin had cooled sufficiently prior to recall. Pearson correlation tests run to see whether the temperature of the thermode just prior to the recall task correlated with recall pain intensity and recall pain vividness scores. Finally the timeseries detailing activation intensity before, during and following physical pain, the delay and the recalled event, for each condition was plotted demonstrating a peak as subjects are asked to recall the stimulus.

Imaging Data

Analysis of all neuroimaging data sets was performed using FEAT (FMRIB Expert Analysis Tool) Version 5.63, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Statistical processing included: motion correction using MCFLIRT (Motion Correction FMRIB's Linear Image Registration tool, (Jenkinson, 2001 #662)), non-brain removal using BET (Smith et al., 2002)), B0 fieldmaps for unwarping distortion in the images (Jenkinson and Smith, 2001), spatial smoothing using a Gaussian Kernel of 5 mm full width at half-maximum and non-linear high pass temporal

filtering (Gaussian-weighted least-squares straight line fitting, with sigma=40.0 s). Registration included co-registration of the functional scan onto the individual T1 high-resolution structural image and then registration onto a standard brain (Montreal Neurological Institute MNI 152 brain) using FNIRT (FMRIB's Non-linear Image Registration Tool), (Jenkinson and Smith, 2001). Statistical analysis at the first, individual subject level was carried out using a general linear modelling (GLM) approach (Friston et al., 1993). Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al., 2001a). Second level analysis grouped the data of all subjects using the data from the first level of analysis. For group statistics, analysis was carried out using FEAT (FMRI Expert Analysis Tool) with higher-level analysis carried out using FLAME 1 (FMRIB's Local Analysis of Mixed Effects). This analysis method allows for incorporation of variance within session and across time (fixed effects) and cross session variances (random effects). Cluster thresholding was performed with a Z-threshold of 2.3 and a corrected p-value of < 0.01 with a cluster-based correction for multiple comparisons using Gaussian Random Field Theory (Friston et al., 1993, Worsley et al., 1992). Contrasts performed explored activation during the three delay conditions as well as physical pain compared to baseline and subtractions between conditions.

A trend analysis that incorporated demeaned values for the delay times for each recalled contrast of parameter estimates (COPE), per subject, was done and a higher level analysis was run using randomise. Randomise employs permutation methods for inference of a statistical map related to recall pain using threshold-free cluster enhancement, corrected for multiple comparisons, p-value of < 0.05. This map was created by adding the activation maps for all the first level recalled COPEs at the group level using fslmaths.

Individual behavioural results for both intensity and vividness were incorporated as a weighting in the explanatory variable (EV) files for each subject for all recalled conditions.

Behavioural results were also incorporated into the pain EV that preceded each recalled pain event, for each individual, for both intensity and vividness. Finally, the time in seconds for each pain stimulus was included as a weighting for each pain event. A higher-level group analysis using mixed-effects statistics was performed for each of the analyses.

4.3 Results

4.3.1 Behavioural data

A one-way ANOVAs between all three conditions were shown to be not significant for either recalled intensity, or vividness (intensity: $F(2, 54) = 0.891$, $p = .416$; vividness $F(2, 51) = 2.326$, $p = .108$). T-tests between ratings for both intensity and vividness show a significant difference between the recalled pain after a short delay condition (RS) and the recalled pain after a long delay condition (RL) (two -tailed t-test significance test between RS and RL for intensity, $t_{(18)} = 2.44$, $p = 0.025$), for RS and RL for vividness, $t_{(18)} = 3.04$, $p = 0.007$), and recalled pain after a medium delay condition (RM) and RL (2-tailed t-test, $t_{(18)} = 3.05$, $p = 0.007$ for intensity, 2-tailed t-test, $t_{(18)} = 3.55$, $p = 0.002$ for vividness). Mean Intensity RS 4.81 ± SE 0.44, RM 4.82 SE± 0.43, RL 4.03 SE± 0.54 . Mean vividness for RS 5.43 SE± 0.44, RM 5.26, SE± 0.46, RL 4.21, SE± 0.54 (See Figure 4.2). Neither recall pain intensity nor recall pain vividness, were significantly correlated with temperature for any of the three delay conditions using the Pearson product-moment coefficient correlation test (recall pain intensity: RS with average temperature ratings $r(19) = -0.06$, $p = 0.79$; RM $r(19) = -0.03$, $p = 0.9$; $r(19) = -0.08$, $p = 0.74$; recall pain vividness: RS $r(19) = 0.16$, $p = 0.51$; RM $r(19) = 0.04$, $p = 0.86$; RL $r(19) = 0.21$, $p = 0.932$).

Pain intensity ratings of the physical pain stimuli were taken during thresholding and in a post-scan interview. A t-test analysis performed to find whether perception of the physical stimulus changed over the course of the experiment showed these ratings to be not significantly different, $p > 0.05$ (mean pain intensity rating at thresholding ±SD 6 ±0.0, post scan interview 6.16 ±0.35, $p = 0.08$).

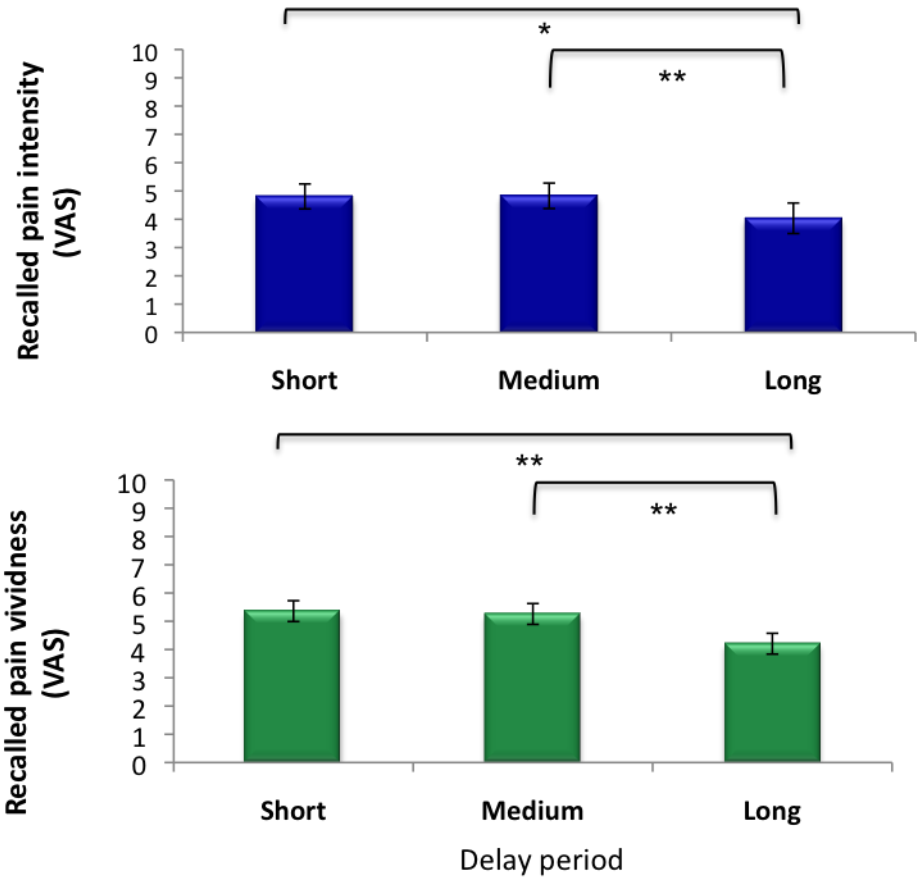


Figure 4.2: Subjective ratings of Recalled pain intensity and vividness of imagined pain (bottom) averaged across individuals across conditions. * denotes significance with a two-tailed t-test $p<0.05$, **denotes significance with a two tailed test at $p<0.01$

4.3.2 Objective temperature measures

To ensure that nociceptive C-fibres were not stimulated during the imagined events, averages were taken of the recorded temperatures of the stimulating thermode prior to and during the imagined events (mean ± SD temperature at onset across subjects and across imagined conditions = 36.46 ±1.4 ^{o}C).

4.3.3 Imaging Data

Recalled pain as a mental representation

As in the previous chapter, our pain recall task results in widespread activation of classical pain and working memory structures as demonstrated by mixed-effects group contrasts exploring activity during recalled pain events relative to baseline. As the time to test delay increases however, these representations of pain show fewer active regions. Several structures, however, remain robustly conserved even after the longest delay (Figure 4.3, see table of activations 4.1, 4.2, 4.3).

It is interesting to note that the posterior insula is not shown to be active in any of these recalled conditions, thereby confirming the results of the first study. The posterior insula was also present when exploring activity specific to physical pain relative to each of the recalled conditions. The contrast Physical Pain > RS condition revealed bilateral activation of the posterior insula, the thalamus, and the putamen, the right anterior insula, and inferior frontal gyrus, the left pallidum as well as the PAG and VTA. When the same analysis was performed relative to RM and RL, more areas were found to be active only during physical pain as the delay increased (see table of activations 4.4, 4.5, 4.6). Interestingly, no areas were more active during any of the recalled conditions relative to physical pain.

Pair-wise comparisons between the three recalled conditions revealed significant differences in activation only in the contrast RS > RM, and RS > RL. This result is consistent with the behavioural data. The data also supports the hypothesis that the mental representation of pain degrades as time increases, and therefore has significantly less activation in RM and the RL conditions (figure 4.4, table 4.4)

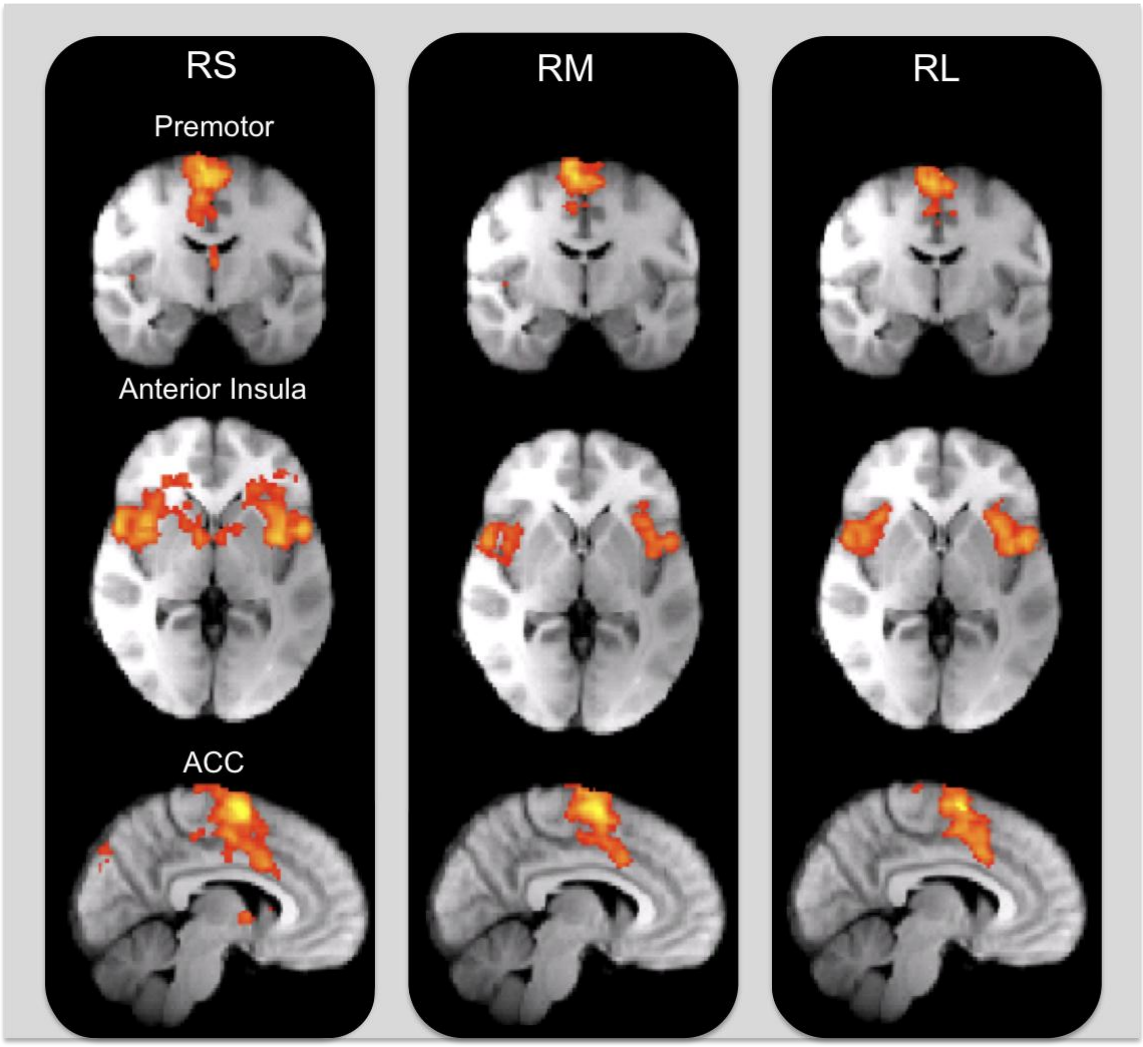


Figure 4.3 Mixed effects group contrast depicting three recalled conditions relative to baseline (Z = 2.3 ; p = 0.01): recalled pain after a short delay (RS), recalled pain after a medium delay (RM) and recalled pain after a long delay (RL). Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates; see table of activations 4.1, 4.2, 4.3.

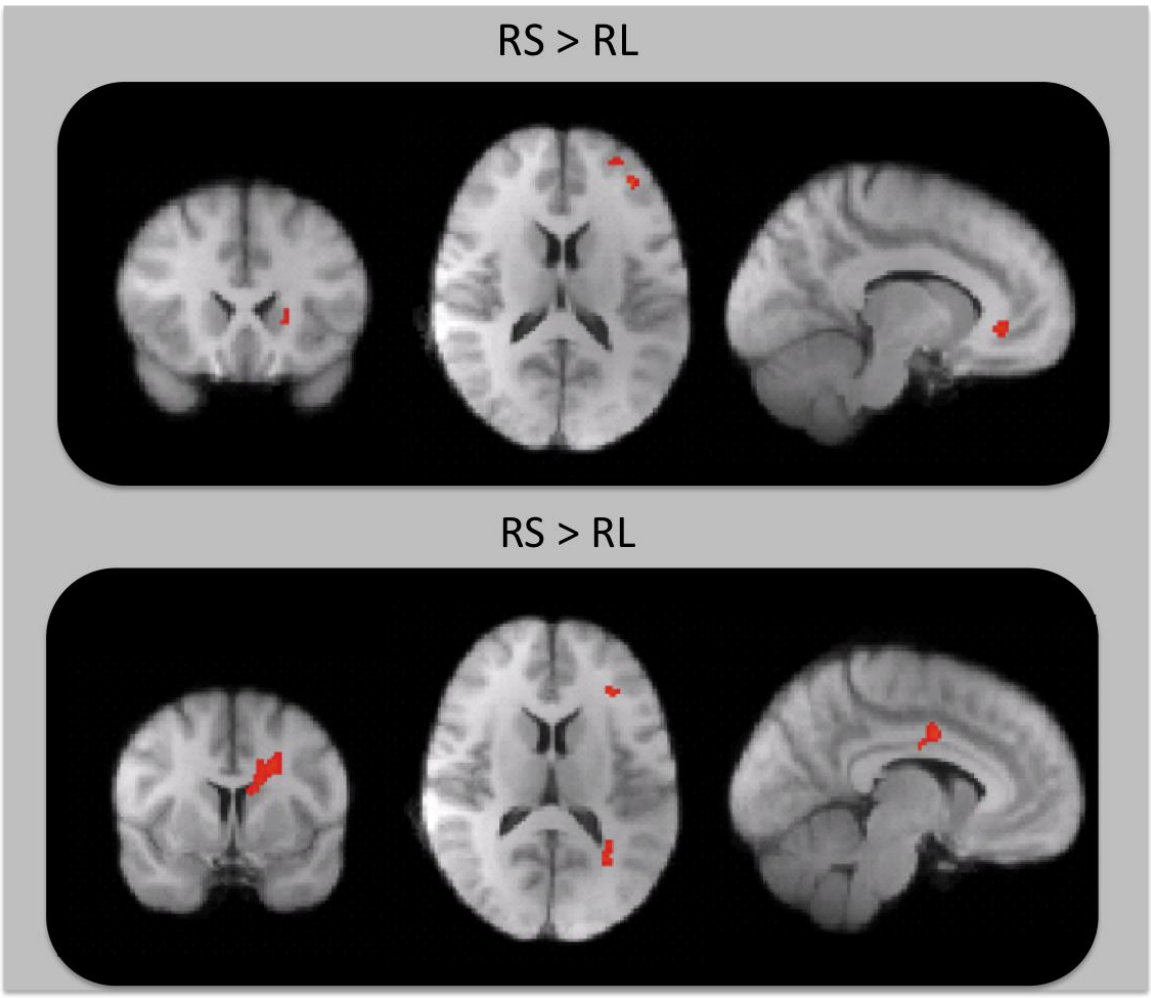


Figure 4.4 Mixed effects group contrast (Z = 2.3 ; p = 0.01): depicting activity significantly more active in the recalled pain condition after a short delay (RS) and the recalled pain condition after a medium delay (RM), and activity significantly more active in RS compared to recalled pain after a long delay (RL). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates; see table of activations 4.4.

Activity during pain predicts recall

We again posit that the observed pattern of activation during our imagined pain task is a mental representation of pain or pain template upon which recall is based. To test this dependence and demonstrate that subjects were able to recall a memory template associated with the previous painful stimulus, individual behavioural ratings were incorporated as an

additional weighting in the explanatory variable (EV) files of the noxious pain events preceding recall. This was run for both intensity ratings and vividness ratings, for each stimulus, for each subject at the first level.

Areas active during the pain stimulus that predicted intensity scores for the subsequent recall event included bilateral activation of an extensive network including the anterior and posterior cingulate, the anterior and posterior insula, the caudate and putamen, the DLPFC, the pallidum, the thalamus, the amygdala, SII, occipital fusiform gyrus, the visual cortex, broadman area 44, and the cerebellum. This same extended network was present when the vividness ratings were incorporated in the same manner, with the only exception of the posterior cingulate cortex (Figure 4.5; see table of activations 4.8, 4.9).

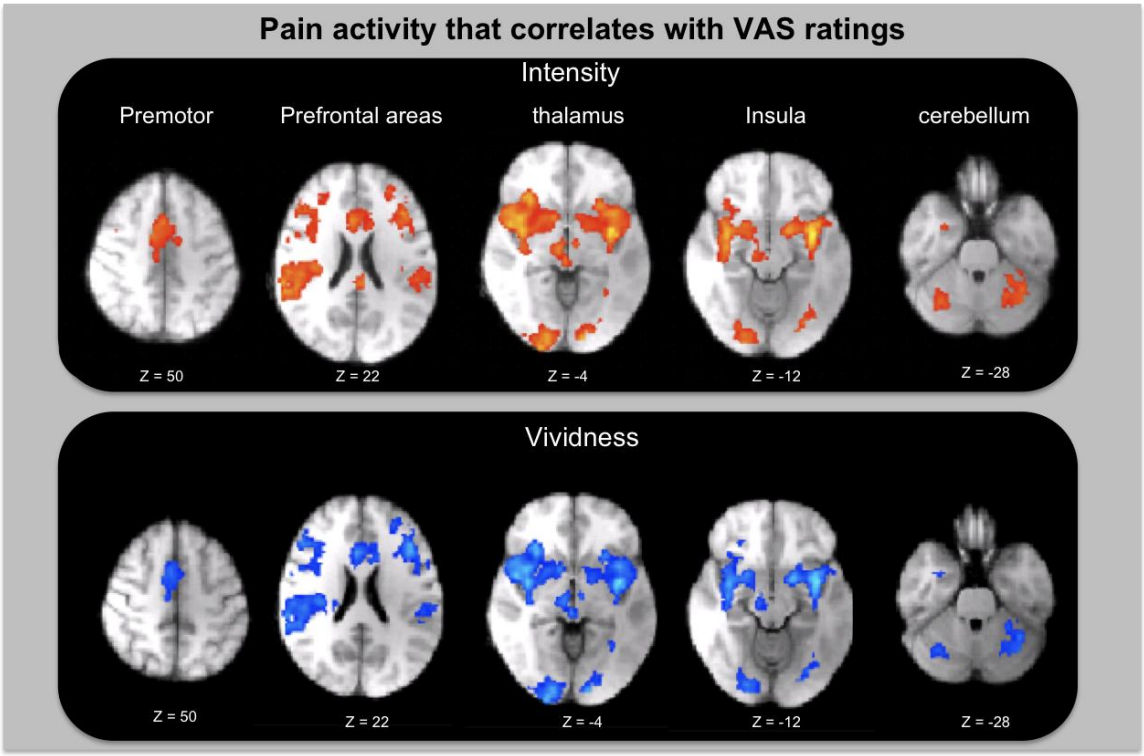


Figure 4.5: Mixed effects group contrast using behavioural data as a regressor for activation during the physical pain event (Z = 2.3; p = 0.01) for both intensity and vividness ratings. This analysis demonstrates the extensive network active during pain that predicts the subjective experience of recalled pain. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates, Table of activations 4.8, 4.9.

Recall activity over time

Regions that characterise short-term recall of pain were defined as structures that significantly attenuate as the time delay increased beyond the limits of short-term recall. A regression analysis revealed activity in SI, the posterior parietal cortex, the premotor cortex and the midcingulate cortex (see figure 4.6). No areas significantly increased with time.

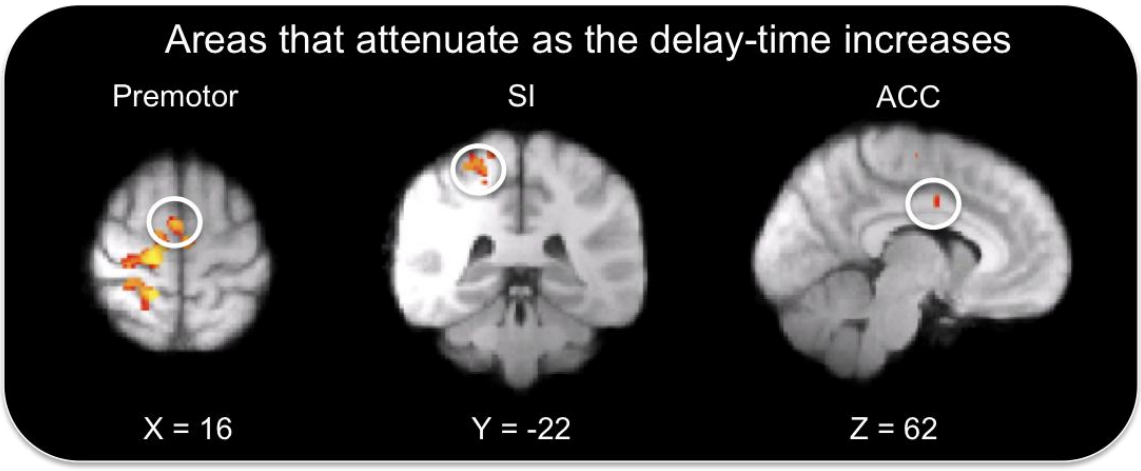


Figure 4.6: Activation that attenuates as the delay increases before pain recall, using Randomise and threshold-free cluster enhancement, corrected $p<0.05$. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates.

To further explore the mental representation of pain and distinguish between a representation that remains active following a noxious stimulus, and that which is actively recalled, the timeseries of the average activation intensity prior to, during and after the physical pain stimulus, the delay and the recall event was plotted (figure 4.7, 4.8, 4.9).

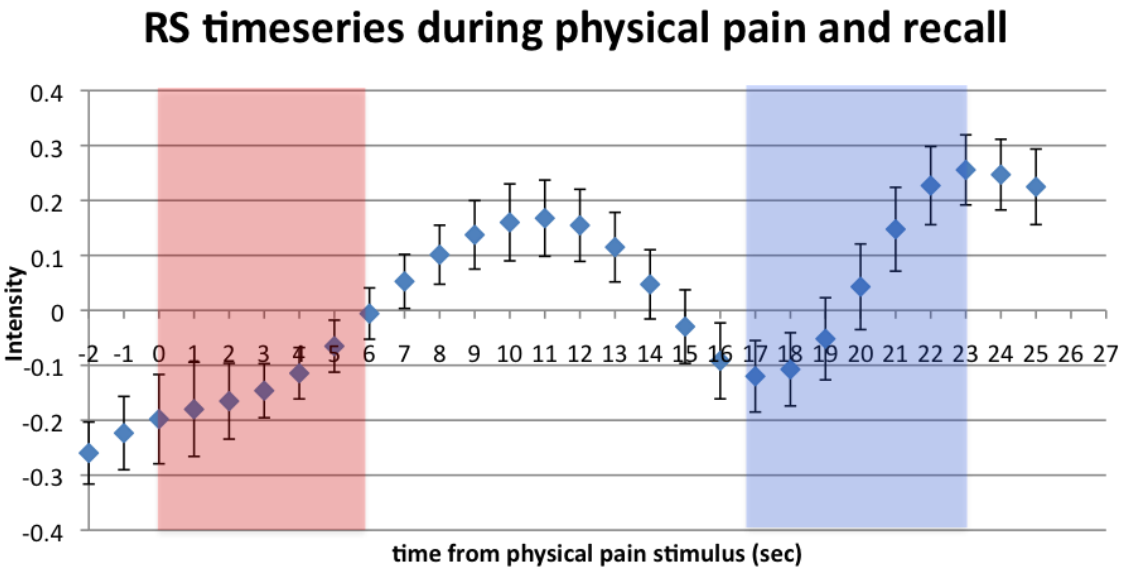


Figure 4.7: RS timeseries: Average Intensity of activation for all subjects within a mask, which includes all activation present during all recall conditions from 2 seconds before the physical pain events (red), the delay (11 seconds) between physical pain and recalled pain, the recalled pain event (blue) and 2 seconds following the recalled event.

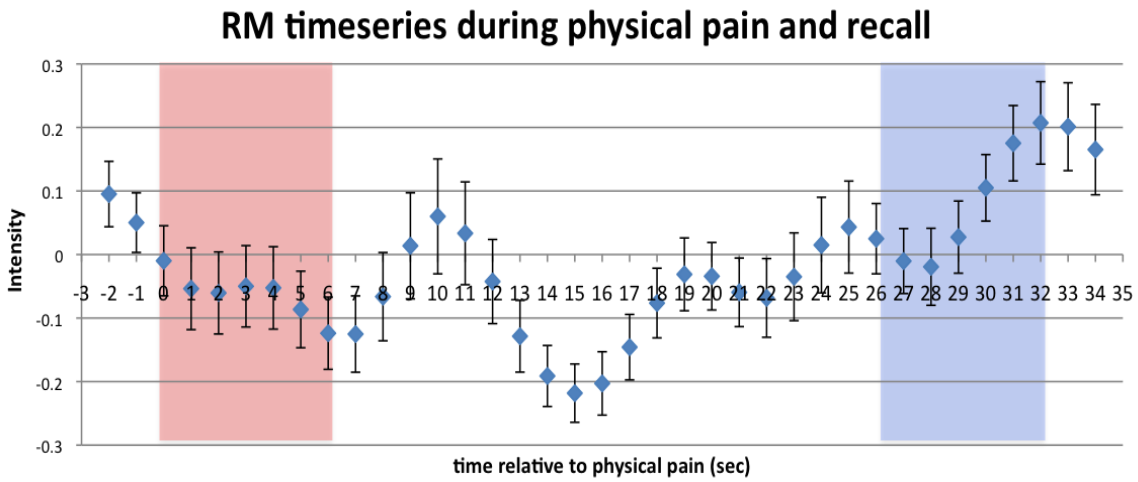


Figure 4.8: RM timeseries: Average Intensity of activation for all subjects within a mask, which includes all activation present during all recall conditions from 2 seconds before the physical pain events (red), the delay (20 seconds) between physical pain and recalled pain, the recalled pain event (blue) and 2 seconds following the recalled event.

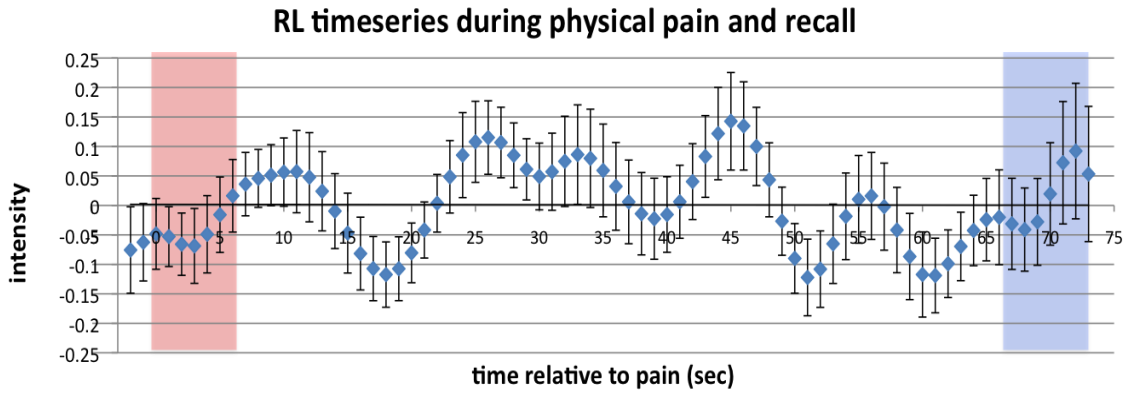


Figure 4.9: RL timeseries: Average Intensity of activation for all subjects within a mask, which includes all activation present during all recall conditions from 2 seconds before the physical pain events (red), the delay (59 seconds) between physical pain and recalled pain, the recalled pain event (blue) and 2 seconds following the recalled event.

Recall correlated with behavioural scores

The intensity and vividness ratings were incorporated into separate explanatory variable (EV) files for all three imagined events, per subject, to explore encoding of these separable components of the recalled pain experience. Incorporating the intensity ratings of RS revealed

bilateral activation in the anterior insula, the ACC, the anterior part of the midcingulate cortex, the primary motor cortex, and the supplementary motor area (SMA). Ipsilateral activity included the precuneus, the cuneal cortex, lateral occipital cortex, the temporal pole, caudate and the left putamen. The same analysis during RM revealed activation only in the premotor cortex and the SMA. The analysis including the intensity ratings for RL revealed bilateral anterior insula, SMA, anterior-MCC, premotor cortex, left cuneal cortex and right precuneus (Figure 4.10, 4.11; see table of activation 4.10, 4.11).

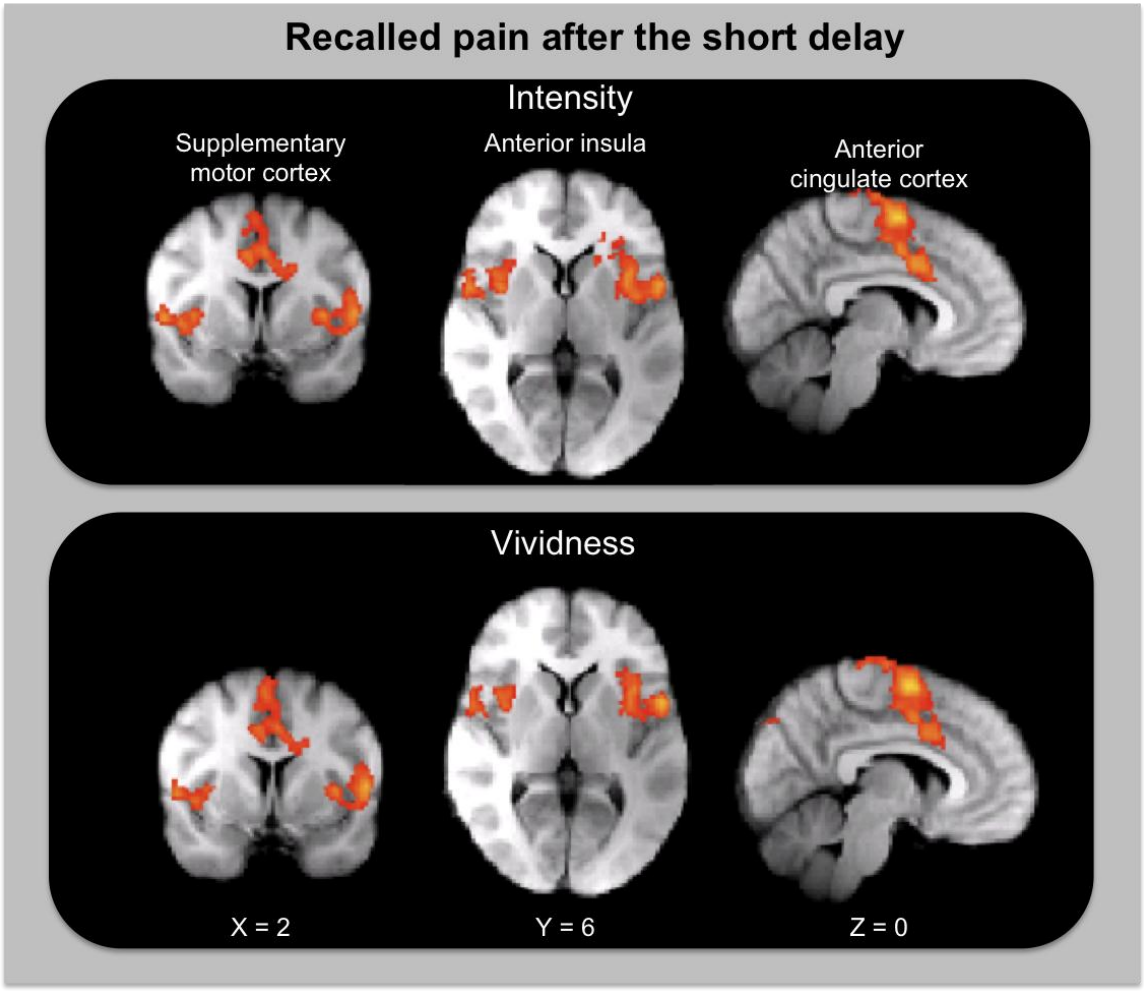


Figure 4.10: Mixed effects group contrast using behavioural data as a regressor (Z = 2.3; p = 0.01) depicting recall after the short delay (RS) condition for the intensity and vividness condition in three views. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates, Table 4.10 and 4.11.

Vividness ratings for recalled pain after the short delay revealed the same areas present in the intensity analysis, with the exception of the left caudate and the left putamen. As with intensity ratings, activation modulated by vividness ratings in RM revealed only the premotor cortex. For pain recall after the long delay, incorporating vividness ratings revealed the premotor cortex and ipsilateral anterior insula. Interestingly, activation was not observed in the SMA, ACC, MCC, cuneal cortex or precuneus that were all present in the intensity analysis (Figure 4.12; see table of activation 4.10, 4.11).

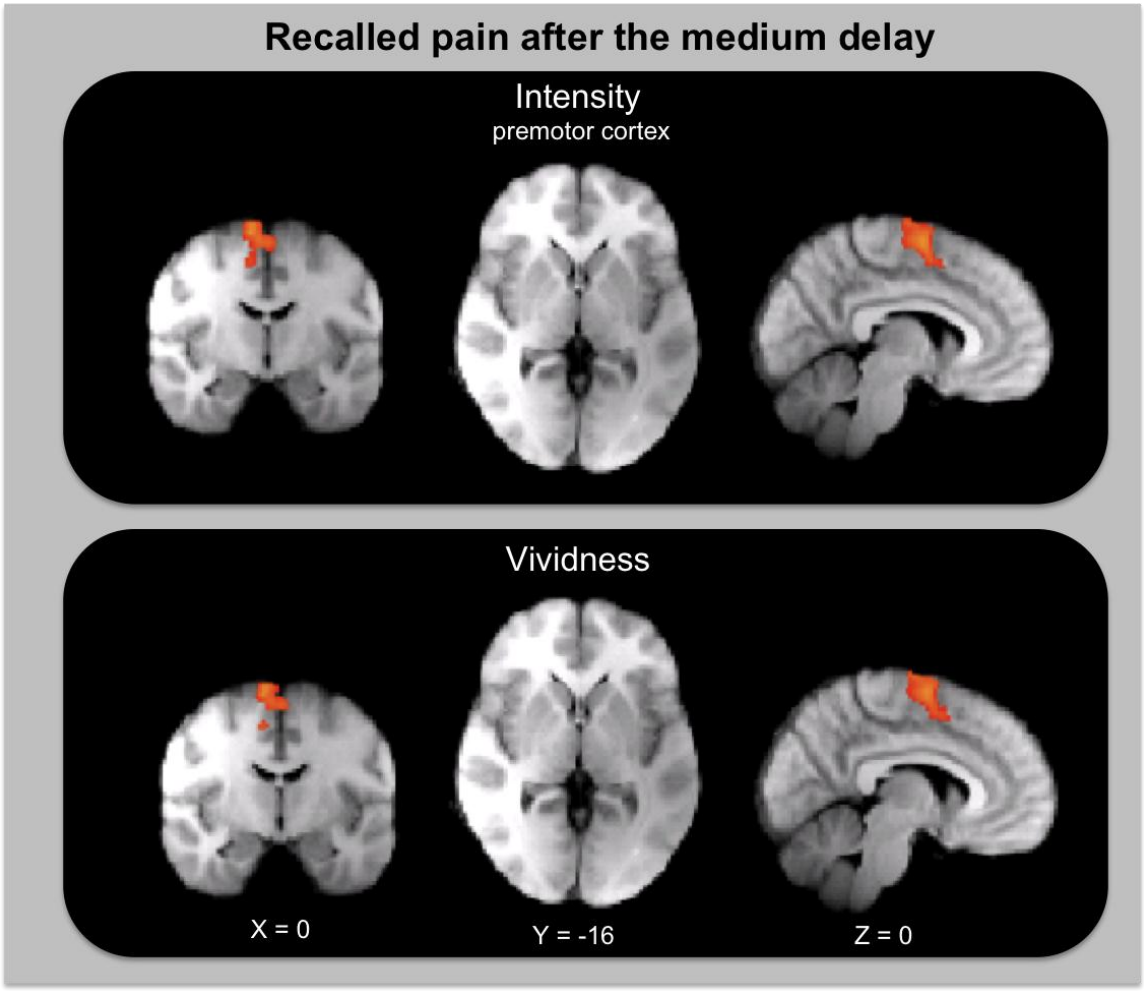


Figure 4.11 Mixed effects group contrast using behavioural data as a regressor (Z = 2.3; p = 0.01) depicting only the premotor cortex present in both analyses in the recall after medium delay (RM) in three views. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates, see table of activations 4.10, 4.11.

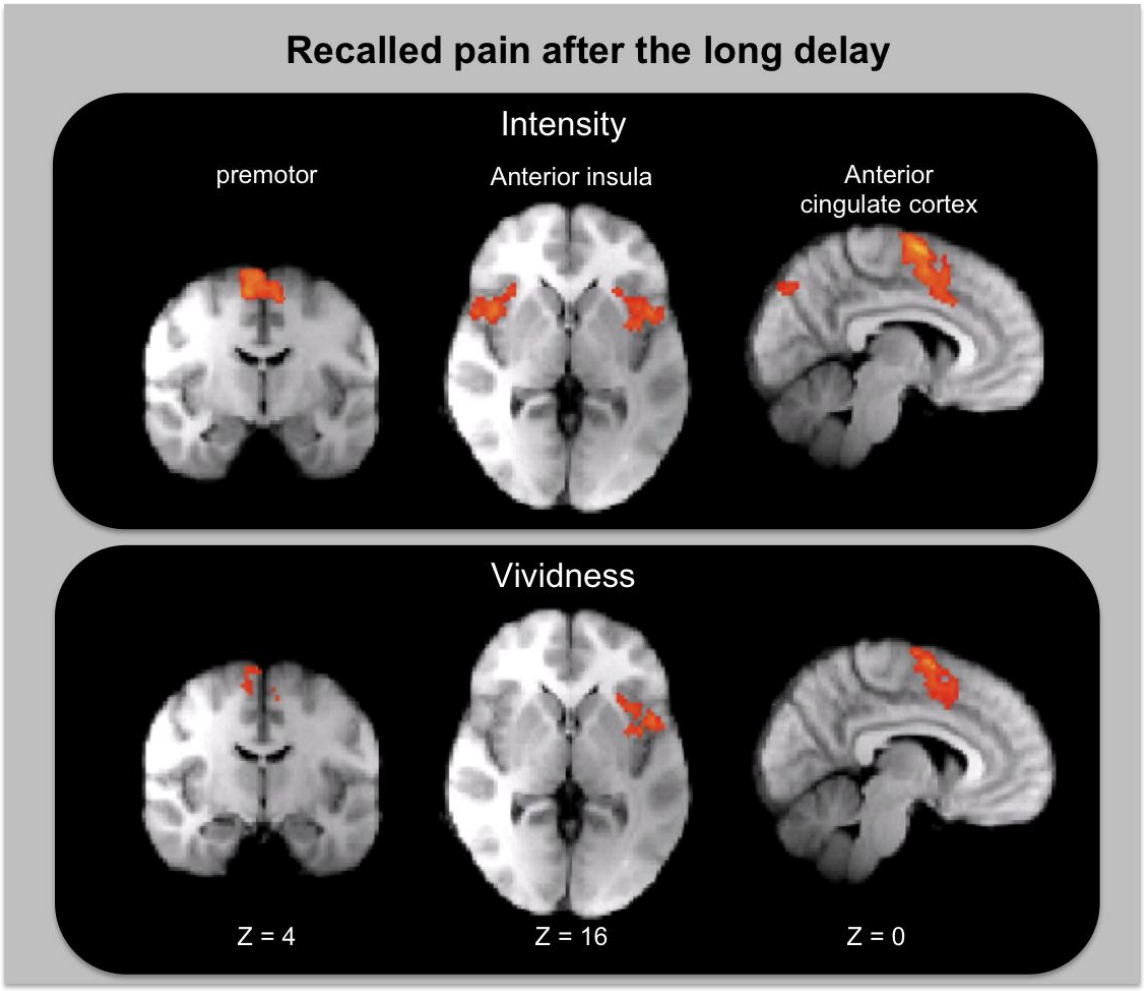


Figure 4.12: Mixed effects group contrast using behavioural data as a regressor (Z = 2.3; p = 0.01) depicting recall after long delay (RL) condition for the intensity and vividness condition, revealing regions involved in memory retrieval and high cognitive load in three views. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates, see table of activation 4.10, 4.11.

Pain activity increasing over time

To explore whether repeated rehearsal of pain recall had an effect on the neural correlates of physical pain, we incorporated the time of the pain stimulus as a weighting for each pain stimulus. In this way we were able to isolate areas that demonstrate a significant increase in BOLD activation as time increases. These areas included sensory and affective areas, such as

bilateral posterior and anterior insula, central opercular cortex, visual cortex, SII, the amygdale, and contra lateral putamen. This result represents a large proportion of all areas active during pain (figure 4.13; see table of activation 4.12).

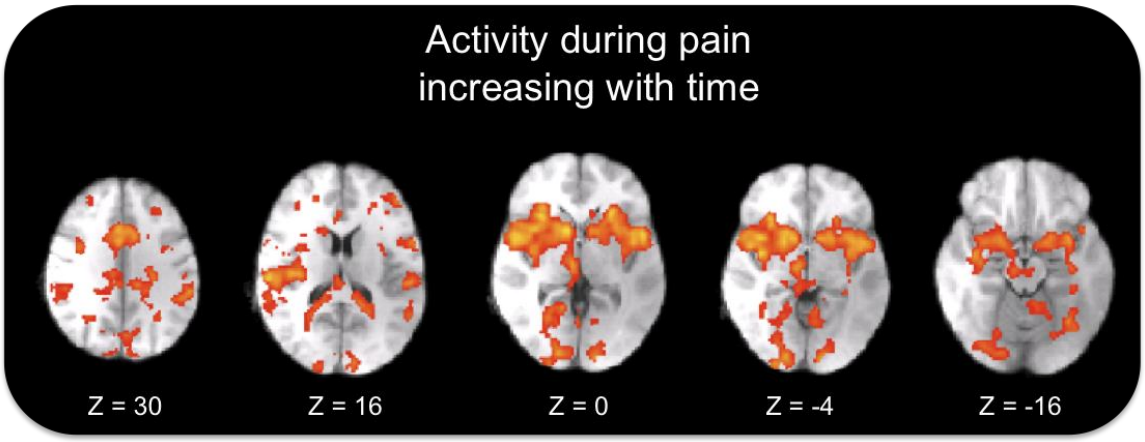


Figure 4.13: Mixed effects group contrast using time of event as a weighting per stimulus to find areas that significantly increase with time (Z = 2.3; p = 0.01). An extensive network of areas active during physical pain show increased BOLD activation over time. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates, see table of activations table 4.12.

4.4 Discussion

4.4.1 Summary

Previous studies have proposed that memory for noxious pain exists as a readily retrievable mental template, following an appropriate physiological or psychological cue. Furthermore, it has been put forward that a detailed but transient analogue representation becomes a catalogue representation, which is stored in long-term memory. Just as sensory and affective aspects of noxious painful stimuli are processed differently, so too are they separately encoded for in distinct brain areas. Based on our behavioural findings showing a significant decrease in intensity and vividness ratings over time, we demonstrate a diminished ability to accurately and completely re-experience the initial noxious stimulus as the time-to-test delay increases beyond the limits of short-term recall.

During recall events, we reveal a consistent neural signature that we posit is a mental representation of pain, which is predicted by active areas during the initial pain event. While many regions remain active after a minute, we are able to isolate areas specific to short-term recall that significantly attenuate with time. Specifically, activity within the primary somatosensory cortex and the posterior parietal cortex are consistent with results from previous research suggesting these regions encode sensory aspects of pain in the short-term memory. We also find activation in the primary motor cortex and the ACC demonstrating recall of pain affect, unique to the sensory re-experiencing involved in this paradigm. We further explore areas responsible for intensity and vividness of recalled pain at each of the three stages from short-term retrieval to long-term storage. Finally, we demonstrate that repeated recall affects neural activation during physical pain.

Studies in the past have mainly employed sensory-discrimination paradigms to explore time-dependent memory processing for pain. In our recall task, subjects are not asked simply to match the intensity aspects of two painful stimuli. Instead they are instructed to endeavour to recreate the full pain experience in terms of intensity, location and related emotions. Therefore, we are able to explore a more complete memory of the pain experience.

4.4.1 Subjective ratings decrease in intensity and vividness over time

Reported behavioural results confirm our hypothesis that increasing the time-to-test delay will affect the ability to recall the thermal qualities of pain. Averages of the behavioural ratings show a significant decrease between the two shorter delays and the long delay (figure 4.2). As the difference between the three delay times did not increase in a linear fashion it is not unexpected that there should be no significant difference between the short and the medium delays, which are only separated temporally by 9 seconds. What was perhaps surprising was the degree to which subjects were able to re-experience the painful stimulus and therefore rate their perceptions after a minute of delay between the stimulus and the recalled event.

4.4.2 Neural activity for pain predicts recall

To demonstrate the relationship between the physical pain events and subsequent recall, the individual behavioural ratings were incorporated as a weighting for each pain stimulus. Results from this analysis revealed activation during the pain stimulus that predicted how successfully subjects were able to re-experience the initial pain stimulus. Our results reveal that an extensive neural network activated during pain determines future recall (Figure 4.5). This may serve as assurance of the validity of our paradigm, while also providing new insight into the memory template of pain. While it has been established that pain perception depends on previous pain

experience and history, here we demonstrate that the memory template of pain may be manipulated by each individual pain event (Dannecker et al., 2003, Gedney and Logan, 2006, Jantsch et al., 2009b, Rhudy and Meagher, 2000, Terry et al., 2008b, Wiech et al., 2008).

4.4.3 Evidence for the decay of a memory template of pain over time

Activation maps during recalled pain relative to baseline demonstrate that a template of pain (i.e. activity in classical pain processing structures) can be recalled after a short delay (RS), but that this representation of pain degrades as the time-to-test delay increases (figure 4.6). Fewer structures are active during pain recall after a long delay than the other recalled conditions. In none of the recalled pain events was the posterior insula activated, confirming our previous result (Brooks and Tracey). Recalled pain > physical pain showed no significant activation specific to recall pain. This result is consistent with the hypothesis that pain memory exists as a template of the original painful stimulus (Byrne et al., 2007, Szpunar et al., 2007, Addis et al., 2007b).

We were able to replicate the conditions of our previous experiment exploring areas specific to physical pain relative to recalled pain after an eleven second delay. Here, we revealed activation in the bilateral posterior insula and other key pain areas such as bilateral SII, thalamus, PAG and RVM. Although more areas were active in this contrast than revealed in our previous experiment, the larger cohort in this study may have increased the statistical power of these additional areas. More areas were significantly more active in contrasts of physical pain versus imagined pain as the delay increased, further demonstrating the greater difference between the real and recalled events and thus the decay over time of the memory template.

4.4.4 Regions that characterise short-term storage of the sensory aspects of pain

We used a regression analysis to isolate areas specific to short-term memory for pain. Activation that significantly decreased as time increased included only the primary somatosensory cortex, the posterior parietal cortex, the premotor cortex and the midcingulate (figure 4.6). The attenuation of these structures when the time-to-test delay extends beyond the limit of short-term recall may account for loss of accuracy in sensory-discrimination paradigms, and a decreased ability to re-experience sensory information. These results confirm the theory that SI and the posterior parietal cortex characterise the short-term retention of noxious stimuli (Albanese et al., 2007a). The ability to re-experience pain may also be dependent on the role of the posterior parietal cortex and the premotor area in imitation (Molenberghs et al., 2009). A recent meta-analysis has also shown the posterior parietal area and the premotor cortex as the two most commonly activated in memory tasks involved in recall of context associated information (Kim, 2010). Losing the ability to activate these regions at longer delay times might further contribute to this loss of sensory information (Valentini, 2010). The midcingulate involved in motor-preparation in reaction to painful stimuli has been shown to significantly attenuate with time, as the vividness and therefore threat value of the recalled stimulus decreases (Morrison et al., 2007, Wiech et al., 2010). Although after a long time-to-test interval many regions within the mental representation of pain are still active, these few regions characterise those lost in the temporal gap between short-term accurate recall and long-term memory retention of pain (Albanese et al., 2007a, Jantsch et al., 2009a, Rainville et al., 2004a).

4.4.5 Separable components of the recalled pain experience

The regression analyses of our two behavioural ratings identify areas that correlate with the quality of the re-experiencing of pain at each of the three stages of memory explored in this study. As in our previous study, the correlation maps in this analysis, for both intensity and vividness ratings, show overlapping regions of activation, with more regions associated with intensity reports than those for vividness reports. Structures identified included those thought to be involved in sensory memory storage, affective pain processing, imitation and learning (figures 4.10, 4.11, 4.12). Despite no significant difference in the behavioural ratings between the RS and the RM conditions, once incorporated, maps of both intensity and vividness encoding reveal premotor cortex activation in the RM condition (figure 4.10, figure 4.11). The RM delay time at twenty seconds was chosen to represent a time-step beyond those tested by past sensory discrimination studies. Based on the present results, it is assumed that subjects lose the ability to accurately discriminate between the intensities of two painful stimuli separated by a delay longer than the limits of short-term memory. This could perhaps be explained by the attenuation of neural activation from the RS to the RM condition in areas responsible for intensity. BOLD activation corresponding to intensity and vividness ratings show more extensive activation after the longer delay than the RM condition. While this may seem counter-intuitive at first, the regions identified after this delay may be accounted for by the increase in difficulty of the task, and therefore cognitive load.

4.4.6 Short-term memory recall

In the RS condition, activation that correlated with intensity ratings included structures commonly associated with processing of affective qualities of pain and those involved in memory retrieval. Due to the nature of the sensory discrimination task, the paradigm employed by Albanese and colleagues did not result in activation of these areas commonly associated with affective components of pain. Additionally or alternatively, activation of the ACC during short-term pain recall might demonstrate the success with which subjects were able to re-experience the previous pain event. The activation in the anterior part of the midcingulate cortex revealed in this analysis has been associated with maintaining expected outcomes after a delay and cognitive processing of adaptive body changes and prospective perceptual biasing (Critchley et al., 2001, Walsh and Phillips, 2010, Wiech et al., 2010). The anterior insula, while also known for this same role, characterises interoceptive awareness and may also imply non-specific threat and harm detection in peri-personal space (Cohen et al., 1999, Craig, 2009, Critchley et al., 2004, Gu et al., 2010, Valentini, 2010).

Other areas present in RS for both the intensity and vividness analyses included the opercular cortex, cuneal cortex, the premotor cortex and the primary motor cortex. Each of these regions has been implicated in short-term recall execution. The opercular cortex has been associated with memory retrieval and the cuneal cortex is involved with working memory maintenance (Lepage et al., 2000, Michels et al., 2008). The primary motor cortex is said to be involved in memory consolidation of movement-based components (Robertson, 2009). Despite overlap between intensity and vividness encoding in the RS condition, activation in the basal ganglia was specific to the intensity analysis. One possible explanation for this might be the suggested role of the basal ganglia in learning, specifically procedural learning of sensory stimuli associated with motor responses (Bar-Gad et al., 2003, Wickens et al., 2003, Menon et al., 2000,

Hu et al., 2009), as well as imagery tasks (Li, 2000). These areas are commonly reported in pain experiments and are related specifically to the motor and cognitive components of pain (Borsook et al., 2010).

Recalled pain after a medium delay shows only the premotor cortex

The contralateral premotor cortex, active in the RS condition, was the only region active at each stage of recall for both intensity and vividness ratings and was the only region identified in the RM condition for both intensity and vividness ratings. This region is usually associated with motor recall or prediction of action but has also been implicated in perceptual attention, memory retention for offline learning, spatial encoding and tasks involving actions being turned into perceptual information. Processing in the premotor cortex extends beyond motor tasks (Kim, 2010, Wolfensteller et al., 2007). It has been shown to be active during pain perception in the upper limbs, as well as imagined pain in others (Costantini et al., 2008, Farrell et al., 2005). While the precise role of the premotor cortex extends beyond the scope of this study, each of these known functions may be relevant to the present recall task.

Activation during recalled pain after the long condition demonstrates increased cognitive load

Intensity encoding during the RL condition reveals activation in the anterior insula, premotor cortex and anterior midcingulate cortex. Activation of these structures in both the RS and RL condition could be due to the role of this area in both trying to maintain expected outcomes in the RS condition and increasing activity as cognitive load increases in the RL condition (Albanese et al., 2007a, Gray and Braver, 2002, Gu et al., 2010, Walsh and Phillips, 2010). This hypothesis is further supported by the presence of the precuneus in the intensity analysis. The precuneus has been shown to increase in activity as work-load increases (Michels et al., 2008). Interestingly, observed activation in the RL condition does not include anterior midcingulate when

vividness ratings were incorporated. Possible explanations may be either that intensity aspects of pain recall processed by the anterior midcingulate cortex do not apply to the vividness of the experience, or that a lighter cognitive work load associated with vividness ratings relative to intensity matching. The latter rationale is supported by the absence of activation in the cuneal cortex and the precuneus.

4.4.7 Pain template "learns" over time

The primary focus of this study has been to demonstrate how pain recall is predicted and determined by the qualities of and the temporal proximity to the noxious stimulus. However, as memory involves both recall of the past as well as learning for the future, we investigated the effect of rehearsal of recalled pain on neural activation during the physical pain stimulus. We demonstrate an expansive network of areas active during pain that increase significantly with each successive epoch (figure 4.9). This result is consistent with the literature on motor rehearsal. Practice has been shown to affect neural activation in motor memory (Meister et al., 2004, Stewart, 2008) and more pertinently, subsequent pain perception (Flor, 2008). As the limitations of the study design prevented us from collecting pain scores after each physical pain stimulus, we were unable to demonstrate conclusively that no sensitisation occurred over the course of the experiment. Subjects were asked to give an average pain rating at the conclusion of the experiment, which was not significantly different from the verbal rating given at the start. However, another experiment exploring the subjective experience of physical pain within a recalled-pain paradigm would be necessary to demonstrate whether no sensitisation is demonstrated. Studies using hypnosis and mental rehearsal to boost performance suggest that substantial mental training, beyond the limitations and repetition in this study must be performed

to increase performance of a motor task (Allami et al., 2008, Gentili et al., 2006, Louis et al., 2008, Wymbs and Grafton, 2009).

4.4.8 Conclusions

The neural underpinnings of pain memory may be crucial for understanding many aspects of the pain experience. Every pain experience must manifest itself in perception. This perception relies on expectation, which in turn is determined by pain memory. It is during short-term memory that this information may be manipulated and is finalised for future retrieval. It is therefore important to disentangle different aspects of the pain memory, in terms of temporal characteristics, as well as over which aspect of the pain experience they hold influence. Results reported here once again show widespread activation of both pain and working memory areas during pain recall and thus a neural representation of the previous pain. Furthermore, we have been able to paint a more complete picture of the temporal aspects associated with this memory template and explore the neural correlates associated with separate aspects of pain memory as short-term memory is transferred to long-term storage. While many areas are surprisingly still active during recall a minute after the initial noxious stimulus, areas that significantly decrease with time are those associated with noxious pain memory, imitation, and those responsible for recall of contextually associated information. These may be the crucial areas necessary for accurate recall of thermal pain. Areas that are correlated with ratings of intensity and vividness allow us to observe and dissociate both sensory and affective components of recall. Finally, we show that it is not only previous pain that determines activity during subsequent recall, but that rehearsal of recalled pain over the length of the experiment potentially affects activity during physical pain. Additional work would need to explore subjective perception of physical pain immediately following pain-recall.

4.5 Tables of activation

RS > Baseline

		voxelwise extent	Z-score	X	Y	Z
Juxtapositional cortex	(right)	4782	5.59	4	-2	64
Juxtapositional cortex	(left)		4.54	-2	-2	66
ACC	(right)		4.09	4	12	38
premotor	(right)		3.56	22	-26	66
SI	(right		3.83	24	-42	66
thalamus	(right)		3.42	10	0	2
thalamus	(left)		2.47	-4	-2	4
precentral	(left)	2034	4.54	-54	8	2
precentral	(right)		4.04	58	8	2
anterior insula	(right)		4.13	46	12	-8
anterior insula	(left)		4.12	-38	0	2
pallidum	(right)		2.36	16	4	4
pallidum	(left)		2.35	-14	2	4
cuneal cortex	(left)	1089	4.05	-6	-84	36
cuneal cortex	(right)		2.83	10	-84	36
precuneus	(left)		3.51	-2	-80	44
IFG	(right)	1795	4.5	56	14	-2
caudate	(right)		2.56	14	22	4
caudate	(left)		2.54	-18	18	4
posterior supramarginal gyrus	(left)	488	4.14	-56	-40	30

Table 4.1: Group contrast (mixed effects) recalled pain after the short delay condition (RS) > baseline. This analysis revealed an extensive network of areas associated with pain activation and short-term working memory. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

RM > Baseline						
		voxelwise extent	Z - score	X	Y	Z
juxtapositional cortex	(right)	3274	5.05	6	-2	64
ACC	(right)		3.51	4	4	42
IFG	(right)		3.89	54	10	2
paracingulate	(right)		3.99	58	8	2
precentral	(right)		4.4	8	-8	74
SII	(right)		3.12	50	-2	2
juxtapositional cortex	(left)		4.77	-4	2	52
ACC	(left)		3.15	-6	2	42
IFG	(left)		3.4	-52	10	4
paracingulate	(left)		3.68	-2	12	42
precentral	(left)		3.96	-52	8	4
SII	(left)		2.36	-54	0	2
anterior insula	(left)	658	3.99	-40	4	-4
premotor	(left)		2.89	-4	-4	70

Table 4.2: Group contrast (mixed effects) Recalled pain after the medium delay condition (RM) > baseline. After a time-to-test delay after the proposed limit of accurate pain recall, fewer structures are active yet a robust network of areas remain. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

RL > Baseline						
		voxelwise extent	Z - score	X	Y	Z
premotor	(right)	2383	4.9	4	0	64
anterior insula	(right)		3.83	34	10	6
frontal operculum	(right)		2.45	56	10	6
temporal pole	(right)		3.69	2	16	34
frontal operculum	(left)		4.09	46	6	-4
temporal pole	(left)		3.64	-54	10	-8
anterior insula	(left)	997	4.68	-42	4	-4
ACC	(left)		4.64	0	18	34
IFG	(left)		3.66	-48	8	6
IFG	(right)	989	4.62	50	14	-6

Table 4.3: Group contrast (mixed effects) Recalled pain after the long delay condition (RL) > baseline. This analysis reveals areas still active after a time-to-test delay of a minute. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

RS-RM						
		Voxelwise extent	Z-score	X	Y	Z
dlPFC	right	754	3.42	34	-2	-22
paracingulate	right		3.21	36	-6	-12
RS-RL						
		Voxelwise extent	Z-score	X	Y	Z
ACC	right	608	3.22	-8	-2	34
dlPFC	right		3.42	-22	34	-2
IFG	right		2.85	-34	32	16
middle frontal	right		2.91	-24	22	30
inferior parietal	right		3.07	-42	-42	30
posterior cingulate	right	519	3.09	-18	-48	22
precuneus	right		3.07	-18	-56	36

Table 4.4: Group contrast (mixed effects) Recalled pain after the short delay condition > Recalled pain after the medium delay(RS > RM), and recalled pain after the short delay condition > recalled pain after long delay condition (RS > RL). Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Physical pain > RS

		voxelwise extent	Z-score	X	Y	Z
SII	(right)	2714	4.35	54	-26	16
posterior insula	(right)		3.7	34	-20	18
thalamus	(right)		3.15	8	-12	6
anterior insula	(right)		3.89	34	24	8
IFG	(right)		2.35	50	18	16
PAG	(right)		2.97	4	-28	-4
putamen	(right)		3.6	26	0	-4
posterior insula	(left)	1146	3.92	-50	-4	2
SII	(left)		3.48	-58	-26	16
thalamus	(left)		3.4	-10	-22	6
PAG	(left)		2.77	-6	-28	-4
putamen	(left)		2.55	-22	4	-8
pallidum	(left)		3	-16	0	-6
VTA	(right)	748	4.16	10	-20	-8

Table 4.5: Group contrast (mixed effects) Physical pain > Recalled pain after the short delay condition (RS) > baseline. This analysis reveals areas specific to nociception relative to the mental representation of pain after a short delay. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Physical pain > RM

		voxelwise extent	Z-score	X	Y	Z
SII	(right)	5250	4.41	54	-22	16
anterior insula	(right)		4.01	34	0	8
posterior insula	(right)		3.44	36	-4	-6
caudate	(right)		3.27	10	6	8
pallidum	(right)		3.12	22	0	-4
PAG	(right)		3.15	6	-28	-6
hippcampus	(right)		2.76	26	-16	-20
inferior parietal	(right)		2.81	52	-46	22
angular gyrus	(right)		2.44	56	-56	22
putamen	(right)		3.6	24	0	-4
temporal fusiform gyrus	(right)		2.57	22	-32	-22
SII	(left)	2821	4.75	-52	-4	16
posterior insula	(left)		4.27	-34	-18	10
thalamus	(left)		3.8	-10	-18	6
precuneus	(left)		4.3	-6	-60	12
anterior insula	(left)		3.48	-34	-2	8
pallidum	(left)		2.82	-16	0	-4
temporal fusiform gyrus	(left)		2.8	-28	-32	-24

putamen	(left)		3.67	-24	0	-4
PAG	(left)		3.5	-2	-28	-4
thalamus	(right)	2005	4.02	4	-20	2
DlPFC	(right)		2.78	40	50	2
vta	(right)		3.09	4	-30	-18
occipital fusiform gyrus	(right)	1588	3.93	16	-92	-10
occipital fusiform gyrus	(left)		3.22	-34	-72	-10
cerebellum VI	(left)	1540	3.97	-24	-58	-24
cerebellum VI	(right)		3.35	28	-54	-22
cerebellum I-Vi	(right)		2.87	4	-54	-14

Table 4.6: Group contrast (mixed effects) Physical pain > Recalled pain after the medium delay condition. This analysis reveals areas specific to nociception relative to the mental representation of pain after a medium delay. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Physical Pain > RL

		voxelwise extent	Z-score	X	Y	Z
SII	(left)	8633	4.75	-40	-6	-12
posterior insula	(left)		3.99	-36	22	10
anterior insula	(left)		3.2	-30	14	12
caudate	(left)		2.5	-8	6	8
thalamus	(left)		3.2	-4	-16	4
ACC	(left)		2.45	-8	26	24
paracingulate	(left)		2.95	-12	48	0
putamen	(left)		2.7	-16	8	-12
occipital fusiform gyrus	(left)		3.2	-40	-66	-6
posterior cingulate	(left)		3.3	-6	-44	26
cerebellum IV	(left)		2.51	-8	-50	-16
cerebellum VI	(left)		3.93	-32	-50	-24
PAG	(left)		3.07	-4	-30	-2
VTA	(left)		2.89	-6	-30	-20
posterior insula	(right)	5371	4.76	36	-14	8
SII	(right)		4.1	56	-26	18
anterior insula	(right)		3.98	38	2	10
caudate	(right)		4.23	8	6	8
thalamus	(right)		3.94	10	-16	12
Prefrontal cortex: dmPFC	(right)	1430	3.66	-2	64	10
prefrontal cortex: dlPFC	(right)		2.93	26	64	2
prefrontal cortex: vmPFC	(right)		3.46	6	58	-2
ACC	(right)		2.8	2	26	20
putamen	(right)		2.45	16	14	-10
pallidum	(right)		2.75	14	2	-2
PAG	(right)		3.09	6	-30	-4
VTA	(right)		3.59	6	-30	-16
amygdala	(right)		2.79	30	0	-26
occipital fusiform gyrus	(right)	1098	4.23	22	-88	-10
hippocampus	(right)		2.75	28	-34	-4
visual cortex	(right)		3.82	14	-92	2
cerebellum IV	(right)		3.05	6	-50	-14
posterior cingulate	(right)	708	3.48	-8	-44	28

Table 4.7: Group contrast (mixed effects) Physical pain > Recalled pain after the long delay condition. This analysis reveals areas specific to nociception relative to the mental representation of pain after a medium delay. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Physical pain with intensity ratings						
		voxelwise extent	Z-score	X	Y	Z
posterior insula	(left)	14722	5.39	-38	0	-10
ACC	(left)		3.2	-6	16	30
amygdala	(left)		2.92	-28	2	-22
anterior insula	(left)		5.16	-30	16	8
caudate	(left)		3.14	-10	6	4
IFG	(left)		2.59	-28	40	24
IFG	(left)		3.84	-56	12	14
pallidum	(left)		2.61	-16	-2	-2
posterior cingulate	(left)		3.81	-2	-34	24
precentral	(left)		5.12	-54	4	10
premotor	(left)		2.51	-8	-12	60
putamen	(left)		2.65	-22	4	6
SII	(left)		3.37	-54	-28	18
thalamus	(left)		3.71	-12	-16	6
posterior cingulate	(right)	3086	3.97	2	-30	30
ACC	(right)		3.83	6	18	30
amygdala	(right)		2.33	26	2	-22
anterior insula	(right)		5.1	32	14	4
caudate	(right)		4.03	8	4	6
DLPFC	(right)		2.69	32	38	26
pallidum	(right)		2.53	14	-2	-2
posterior insula	(right)		5.07	40	10	-6
precentral	(right)		4.12	56	4	10
premotor	(right)		3.72	10	2	48
putamen	(right)		3.06	28	4	2
SII	(right)		4.12	56	4	10
thalamus	(right)		3.81	6	-16	0
visual cortex	(left)	1720	4.09	24	-102	-4
occipital fusiform	(left)		3.76	-30	-76	-10
cerebellum VI	(left)		3.63	-26	-58	-24
visual cortex	(right)	1412	4.04	-14	-94	-2
occipital fusiform	(right)		3.7	26	-84	-18
cerebellum VI	(right)		3.49	30	-66	-26

Table 4.8: Group contrast (mixed effects) Areas active during pain activation that correlate with recalled pain intensity ratings of the subsequent recalled pain event. This extended network of activation demonstrates a strong relationship between initial painful stimulus and subsequent recalled pain ratings. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Physical pain with vividness ratings						
		voxelwise extent	Z - score	X	Y	Z
precentral	(right)	13750	5.17	-54	4	10
ACC	(right)		3.91	4	20	22
amygdala	(right)		2.89	28	4	-14
anterior insula	(right)		5.14	32	14	4
caudate	(right)		3.49	10	8	4
cerebellum VI	(right)		3.39	30	-66	-26
middle frontal	(right)		2.71	38	22	26
occipital fusiform	(right)		3.59	26	-84	-18
pallidum	(right)		2.79	16	4	-2
posterior insula	(right)		3.52	34	-18	10
prefrontal : dlPFC	(right)		3.53	38	42	6
premotor	(right)		3.41	6	8	48
putamen	(right)		2.91	18	8	-4
SII	(right)		3.97	52	-28	16
thalamus	(right)		3.71	14	-14	8
posterior insula	(left)	2275	3.9	-38	-20	6
ACC	(left)		2.91	-4	20	28
anterior insula	(left)		5.01	-38	0	-10
caudate	(left)		2.71	-8	8	2
cerebellum VI	(left)		3.46	-26	-58	-24
occipital fusiform	(left)		3.77	-30	-76	-10
pallidum	(left)		3.12	-14	0	-4
prefrontal : dlPFC	(left)		4.25	-42	28	20
prefrontal: vlPFC	(left)		3.54	-44	42	12
premotor	(left)		2.66	-4	8	46
putamen	(left)		3.33	-14	6	-10
SII	(left)		2.96	-52	-28	14
temporal occipital	(left)		3.84	-36	-52	-20
thalamus	(left)		3.53	-12	-16	6
visual cortex	(right)	1551	4.16	24	-102	-4
visual cortex	(left)	1262	4.05	-12	-94	-2

Table 4.9: Group contrast (mixed effects) Areas active during pain activation that correlate with recalled pain vividness ratings of the subsequent recalled pain event. This extended network of activation demonstrates a strong relationship between initial painful stimulus and subsequent recalled pain ratings. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Intensity ratings

RS		voxelwise extent	Z - score	X	Y	Z
cuneal cortex	(right)	2668	4.54	4	0	62
anterior insula	(right)		3.87	42	12	0
precuneus	(right)		3.51	20	-28	62
temporal pole	(right)		2.98	2	12	38
precentral	(left)	898	3.76	20	-28	62
ACC	(left)		4.07	0	12	34
anterior insula	(left)		3.64	-38	4	2
Juxtopositional lobule	(left)		3.9	-6	-4	66
premotor	(left)		3.45	16	-22	70
temporal pole	(left)		3.28	-50	10	-6
lateral occipital	(left)		3.54	-6	-84	44
precuneus	(left)	567	3.58	-2	-80	42
cuneal cortex	(left)		3.56	-6	-84	36

RM		voxelwise extent	Z - score	X	Y	Z
Juxtopositional positionl lobule	(right)	835	3.76	4	-2	62
Premotor cortex	(right)		3.6	10	-2	68

RL		voxelwise extent	Z - score	X	Y	Z
Juxtapositional	(left)	1611	4.26	-6	-4	66
acc	(left)		4.17	-4	14	36
acc	(right)		3.93	10	-6	62
anterior insula	(right)		3.26	42	16	-4
anterior insula	(left)		3.74	-40	14	-4
precuneus	(right)		3.75	6	12	38
premotor	(left)		3.45	-4	-2	56
Juxtapositional	(right)		3.12	8	-90	38
occipital pole	(right)		3.28	8	-76	40
frontal operculum	(left)	529	4.18	-46	10	-4
frontal operculum	(right)		3.28	4	-2	62
occipital pole	(left)		2.89	-4	-90	32
cuneal	(left)	367	2.98	-4	-84	42

Table 4.10: Group contrast (mixed effects) Areas during RS, RM and RL that correlate with recalled pain intensity ratings of each respective recalled pain events. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Vividness rating

RS		voxelwise extent	Z - score	X	Y	Z
precuneus	(left)	2838	4.62	4	0	62
ACC	(left)		3.45	-4	4	40
anterior insula	(left)		3.55	-38	14	2
premotor	(left)		4.48	6	-2	62
superior parietal	(left)		3.25	-10	-80	46
temporal pole	(left)		3.45	-50	10	-6
visual cortex	(left)		3.45	-6	-92	26
Precentral	(left)	718	4.07	-54	6	4
SMA	(left)		3.63	-4	0	62
ACC	(right)	624	3.95	0	12	36
anterior insula	(right)		3.75	42	12	0
premotor	(right)		4.63	56	10	0
Precentral	(right)		3.48	-2	-82	42

RM		voxelwise extent	Z - score	X	Y	Z
premotor	(right)	736	3.72	4	-2	62
premotor	(left)		4.25	-4	0	58

RL		voxelwise extent	Z - score	X	Y	Z
anterior insula	(left)	1061	4.27	-44	8	-6
premotor	(right)		2.99	4	-2	62
premotor	(left)	451	3.6	-4	0	58

Table 4.11: Group contrast (mixed effects) Areas during RS, RM and RL that correlate with recalled pain vividness ratings of each respective recalled pain events. Coordinates in MNI space and associated peak voxel z-scores. p < 0.05 corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Physical Pain increasing with time					
		Z - score	X	Y	Z
central opercular	(left)	4.77	-52	4	4
ACC	(right)	4.07	6	18	26
ACC	(left)	3.75	-2	20	26
accumbens	(right)	3.34	10	8	6
accumbens	(left)	3.18	-10	8	-6
amygdala	(left)	3.15	-28	2	-22
amygdala	(right)	4.32	38	8	-6
anterior insula	(left)	4.27	-40	8	-8
anterior insula	(right)	4.45	10	8	-2
caudate	(left)	3.86	-12	8	-4
caudate	(right)	4.32	54	4	0
central opercular	(right)	3.02	30	40	22
DLPFC	(left)	3.08	-28	46	22
DLPFC	(right)	3.41	-34	-24	-12
Hippocampus	(left)	3.37	-36	-20	-14
Hippocampus	(right)	4.25	56	-26	20
parietal opercular	(left)	3.83	-58	-26	18
parietal opercular	(right)	2.85	10	-30	38
posterior cingulate	(left)	3.05	-8	-28	28
posterior cingulate	(right)	3.35	38	4	30
precentral	(left)	4.49	-54	8	4
precentral	(right)	3.04	6	-74	36
precuneus	(left)	3.07	-2	-74	36
precuneus	(right)	4.65	22	8	-12
putamen	(left)	4.02	-20	8	-12

putamen	(right)	4.26	56	-26	20
SII	(left)	4.07	-52	-30	20
SII	(right)	3.04	6	-74	36
superior parietal	(left)	3.46	-2	-76	32
superior parietal	(right)	3.28	28	-68	-22
Visual cortex	(left)	3.7	-12	-94	0
Visual cortex	(right)	3.85	18	-92	0
IFG	(left)	2.7	-38	18	24
IFG	(right)	2.5	40	16	24
posterior insula	(right)	4.3	40	-6	-8
primary motor cortex	(right)	3.42	28	-26	56

Table 4.12: Group contrast (mixed effects) Areas during physical pain that correlate with the increase in time. Coordinates in MNI space and associated peak voxel z-scores. $p < 0.05$ corrected for multiple comparisons. Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels. In this case the cluster extent was 27330 voxels.

Chapter 5

The effect of pain recall on subsequent pain perception

5.1 Introduction

In the preceding chapter, we were unable to acquire a pain rating for the physical pain stimulus. As such, we were unable to discount the possibility that sensitisation as a result of repeating nociceptive stimulation occurred and the possible effect this may have had on recalled pain scores. The aim of this experiment was to test for possible sensitisation with repeated stimulation and explore the effect of recalling pain on subsequent physical pain perception, relative to a control trial, which presented repeated physical pain stimuli with no recall task. Previously, we demonstrated that recall is dependent on both the quality of the initial stimulus and the time-to-test delay. In terms of our theory of a memory template for pain, we expect not only that this template will be utilised in recall, but that it can be updated with each new pain event.

The following experiment therefore seeks to explore the effect of pain recall on the perception of subsequent noxious events. Other studies in motor and visual memory have shown that mental rehearsal can affect future performance (Avanzino et al., 2009, Gentili et al., 2006, Gustin et al., 2010, Meister et al., 2004, Morrison et al., 2007, Moseley, 2007, Moseley and Arntz, 2007, Ramachandran and Altschuler, 2009, Wymbs and Grafton, 2009). Specifically, neuroimaging studies have shown that associated brain-activation can change after a motor imagery task (Meister et al., 2004, Morrison et al., 2007, Wymbs and Grafton, 2009). Behaviourally, motor imagery training has been shown to increase the speed with which subjects are able to carry out movements and improve efficacy, specifically with highly complex tasks relative to control tasks (Allami et al., 2008, Avanzino et al., 2009, Louis et al., 2008, Rodriguez et al., 2008, Rodriguez and Llanos…, 2009). In the previous chapter we show that an extensive network of brain regions

activated during pain processing increase significantly over time. To investigate these increases, we test the effect of repeated pain recall on subsequent pain perception over time.

5.1.2 Theory of internal models

Cognitive processing of a sensory event depends on previous learning and experience (Fernandez and Turk, 1989, Kim, 2010, Koyama et al., 2005b, Lewandowski et al., 2005, Marty et al., 2009, McCracken and Gauntlett-Gilbert…, 2007, McCracken, 2007, Sarinopoulos et al., 2010, Sawamoto et al., 2000, Tracey, 2010, Van Damme et al., 2010, Wiech et al., 2008, Wolpert and Kawato, 1998). In this way, with each new event we have the capability to change future sensory processing. Manipulating individual factors such as attention, expectation, and specific cognitive strategies experimentally has resulted in lower subjective ratings for pain in both patients and healthy subjects (Fernandez and Turk, 1989, Kim, 2010, Koyama et al., 2005b, McCracken, 2007, Sawamoto et al., 2000, Tracey, 2010, Wiech et al., 2008). As cognitive strategies are rehearsed, associated responses to stimuli can change over time. This phenomenon is well explored in motor imagery and learning.

The theory of internal models has been put forward to explain the tested effect of rehearsal on performance. (Gentili et al., 2006, Wolpert and Ghahramani, 2000, Wolpert and Miall, 1996) This includes both an inverse model, which generates the command necessary to execute the desired motor response and a forward model, which combines the forward dynamics model and the forward sensory model. The forward dynamics model predicts the future state of the active body part, while the forward sensory model predicts the sensory consequences. Improvements in motor performance following imagery training are attributed to the reinforcement of the forward internal model, as the inverse model is absent in motor imagery (as no physical command is carried out).

Rehearsal is said to enforce the functional linkage between the inverse and the forward model as the forward model teaches the inverse model through self-supervising learning; this results in better motor performance. Many have shown that the forward model precedes that of the inverse model. (Avanzino et al., 2009, Flanagan and Johansson, 2003, Wolpert and Kawato, 1998) In other words, the future prediction based on the memory of previous motor action must be formed before the generation of necessary action commands. Therefore, by rehearsing an action by way of the forward model, we change the way we process relevant motor commands.

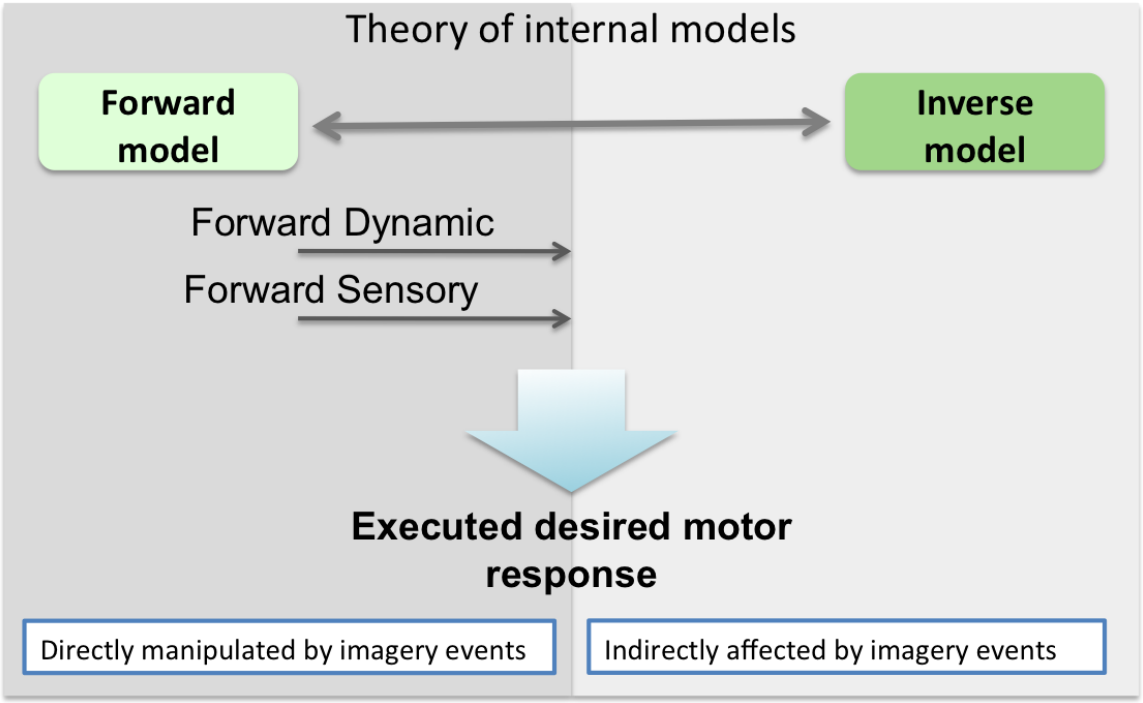


Figure 5.1 Illustrating the theory of internal models. The forward model, comprising the forward dynamic model and the forward sensory model, is directly manipulated by imagery events. Imagery events activate areas associated with the forward model, which affect the inverse model when engaging in a physical motor action. The forward model always precedes the inverse model, and both influence the other resulting in an increase in performance.

While we cannot assume general similarities between motor memory and pain memory, the role of the forward sensory model could be analogous to future prediction in the form of expectation and cognitive appraisal; crucial to subjective pain perception (Fairhurst et al., 2007,

Gray et al., 2007, Moseley and Arntz, 2007, Ploghaus et al., 2003, Ploghaus et al., 1999, Ploner et al., 2010, Sarinopoulos et al., 2010, Sawamoto et al., 2000, Wiech et al., 2010, Wiech et al., 2008). Future predictions based on past experience might be an essential key to understanding individual differences in pain reporting (Koyama et al., 2005a). Previous ratings and the memory of previous painful events affect subsequent perception (Fairhurst et al., 2007, Gray et al., 2007, Moseley and Arntz, 2007, Wiech et al., 2008).

Expectation in particular has been shown to be a powerful modulator of subsequent pain. The threat of an increase in pain severity can change the perception of a mild pain to a high pain, or even a non-noxious stimulus, to being perceived as being painful (Dannecker et al., 2003, Koyama et al., 2005a, Price, 2000, Robinson and Clore, 2002, Sawamoto et al., 2000, Wiech et al., 2010). Furthermore, it has been demonstrated that the level of certainty to which individuals can predict the sensory outcome can determine whether perceived pain is reduced or amplified. Uncertainty has been shown to increase pain perception, while certainty can have the opposite effect (Critchley et al., 2001, Ploghaus et al., 2003, Porro et al., 2002, Sarinopoulos et al., 2010). In a study analogous to our own, prior to receiving a noxious stimulus, an active mental representation of pain was induced. However, this representation referred to the future pain event not a previous painful stimulus. The results of this study demonstrated areas active during physical pain overlapped those areas activated during expectation, consistent with our result in previous chapters. Expectation of lower pain ratings resulted in lower subjective ratings for the physical pain that followed, demonstrating the effect changed the learned context associated with pain (Koyama et al., 2005a). As experiential context can influence pain perception, we hypothesise that repeated rehearsal of pain-specific imagery should also have an effect on pain perception over time.

5.2 Materials and methods

5.2.1 Subjects

Two groups of 15 healthy volunteers (8 females, and 7 males in each group; age range: mean age, trial A: 32 $\pm$ 5.1 (SD) years, trial B: 29 $\pm$ 7.4 (SD) years) were recruited after screening for previous history of pain, neurological or psychiatric disorders. Eight of the 15 subjects completed both trials, while 7 completed only on trial due to drop-out and access. Written consent was obtained for all subjects. The study was approved by the Milton Keynes Research Ethics Committee.

5.2.2 Study Design

This study was composed of two trials (figure 5.2). The first of these consisted of a thermal pain stimulus followed by an imagined pain event. The imagined pain event was rated using a VAS according to imagined pain intensity and imagined pain vividness, as described in previous chapters. This event was followed by a second noxious stimulus identical in objective intensity to the first, after which subjects were asked to rate it in terms of pain intensity and pain unpleasantness. The second trial was used as a control trial, which identically matched the first, but excluded the imagined pain event. Trial A always preceded trial B. Both trials were administered on different days. Each trial consisted of 12 identical blocks. Each thermal pain stimulus lasted six seconds and was applied to the dorsum of the subject's left hand.

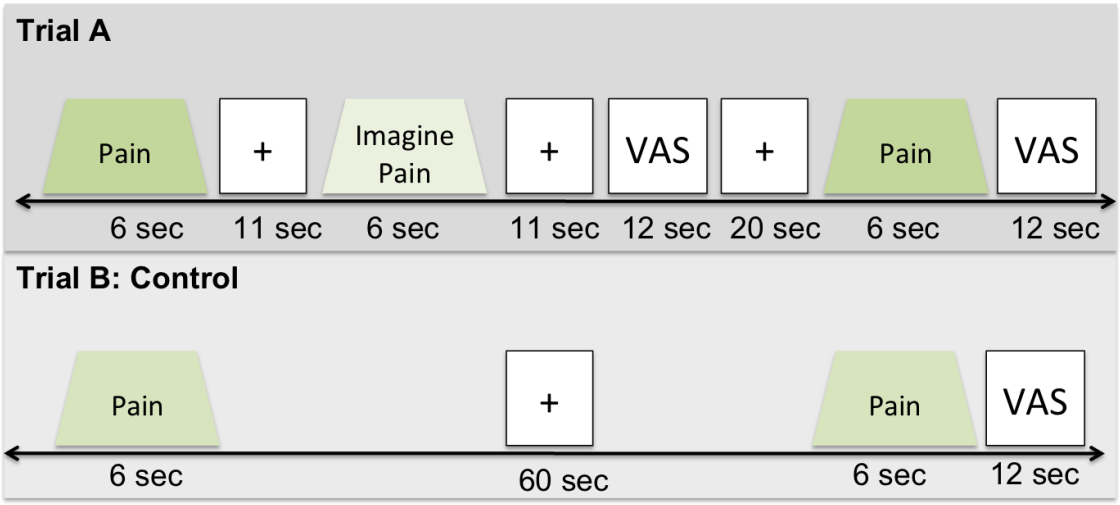


Figure 5.2: Study Design. Trial A: Visual stimuli indicating a noxious thermal event followed by the imagined pain cue and VAS ratings for both intensity and vividness of imagined pain. This is then followed by an identical thermal stimulus and rating scales of pain intensity and unpleasantness for the physical pain event; Trial B: the control trial, replicated the first, but excluded the "Imagine pain" event and vividness rating scale. VAS: visual analogue scale.

5.2.3 Thermal noxious stimuli

A thermal resistor developed in-house and controlled by in-house written software was used to increase skin temperature. Before the experiment, all subjects were thresholded using a randomised staircase method to find subjective ratings of 6/10 (high pain). A one-minute interval was allowed between each stimulus to insure the safety of the skin, during which the subjects gave a verbal rating for the previous stimulus. Temperatures applied across subjects ranged from 46.5ºC - 53ºC in the first trial (mean ±SD = 49.5 ºC±2.6) and 43ºC - 54ºC in the second trial (mean ±SD = 49.6 ºC±3.7).

5.2.4 Visual stimuli

Visual stimuli consisted of six-second prompts of: "Feeling pain," and "Imagine feeling pain". The "Feeling pain" visual prompt was always concurrent with a thermal noxious stimulus.

The VASs were presented to obtain subjective ratings for intensity of imagined pain and vividness. Each scale was presented for six seconds. The “Pain intensity” and “Imagined pain intensity” scale were anchored with no pain at the minimum and extremely painful at the maximum end. “Pain unpleasantness” was anchored with not unpleasant, and extremely unpleasant. “Vividness” was anchored with not vivid and extremely vivid. Between events, a fixation-cross was displayed, during which subjects were instructed not to perform any task. Visual stimulation was continuous throughout the experiment.

5.2.5 Psychophysical data

Mean ratings were taken across subjects for each block, and grouped according to type (For the Trial A: physical pain intensity and unpleasantness; Imagined recalled pain: intensity and vividness. For the control trial, trial B, physical pain intensity and unpleasantness). Mean scores were also calculated for each subject for each rating type across all blocks. Two-tailed t-tests were used to check for significant differences between the ratings of pain intensity and unpleasantness for the imagined trial and the ratings for the control trial. Pearson’s product-moment coefficient was calculated to assess the relationship between the subjective ratings for physical pain intensity, physical pain unpleasantness, imagined pain intensity and imagined pain vividness with time. A repeated-measures ANOVA was run to compare the effects of both conditions versus time, and separately for each condition relative to time.

5.3 Results

To check whether averages across subjects for each trial changed over time, a correlation of physical pain ratings intensity and unpleasantness with time for trial A was calculated using a two-tailed Pearson product moment correlation coefficient for an N of 12 blocks, r= 0.854 for pain

intensity versus time; r = 0.76 for pain unpleasantness; both measures were significantly correlated with time; $p < 0.01$ for both physical pain scores. This was repeated for trial B. Neither physical pain nor unpleasantness was shown to be significantly correlated with time for trial B; r = 0.567 for physical pain intensity mean ± SE = 6.04 ± 0.45; r = 0.207, mean ± SE = 4.97 ± 0.38 for pain unpleasantness (figures 5.3, and 5.4). Standard error was calculated for each average time point, for all average ratings to illustrate the variance within subjects. An f-test between the standard errors from physical pain intensity scores and pain unpleasantness scores between trial A and trial B found significant differences in the variances across subjects for each epoch $p < 0.01$ for both physical pain intensity and physical pain unpleasantness.

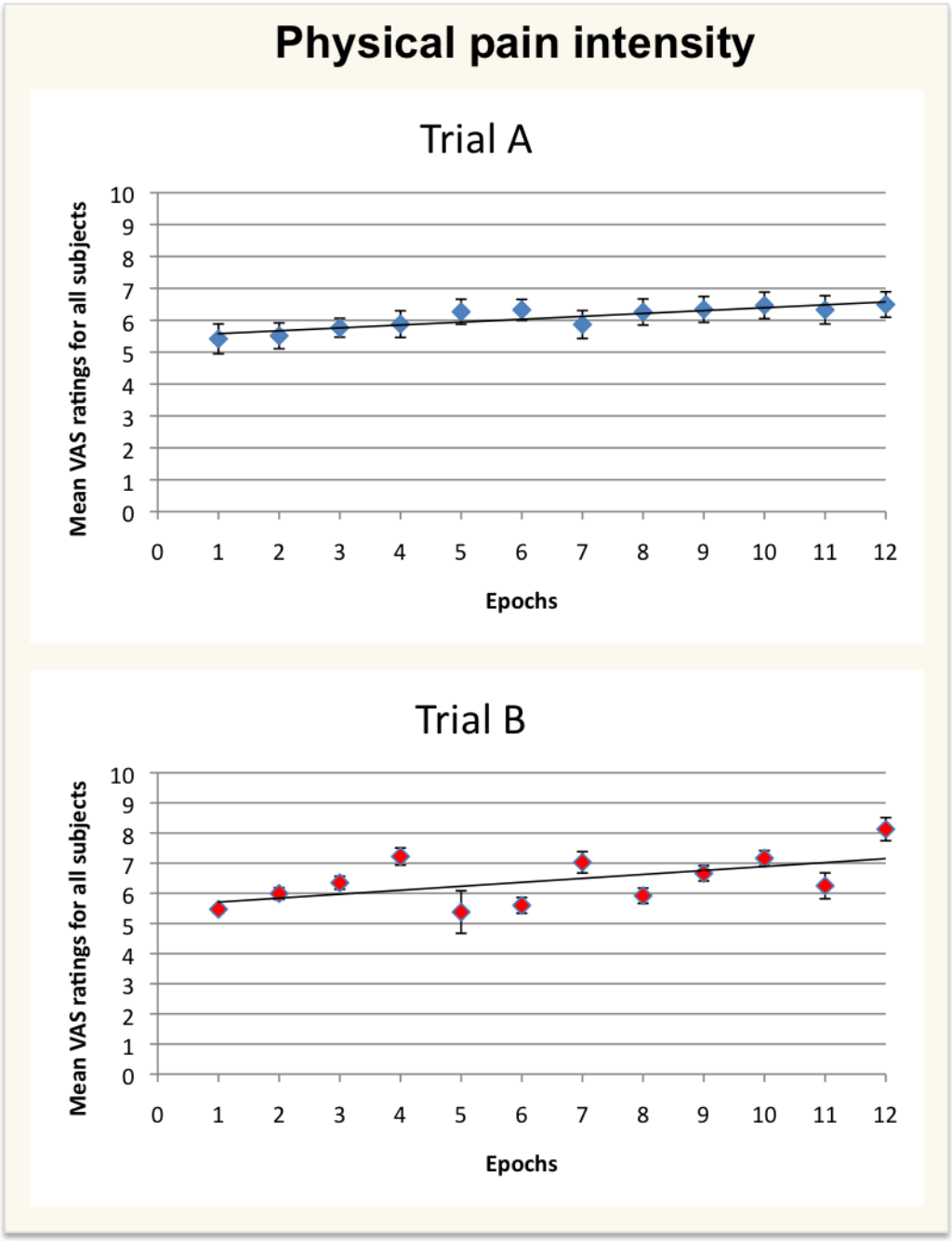


Figure 5.3: Subjective ratings of physical pain intensity for trial A and the control trial B averaged across subjects for each epoch. Trial A demonstrates a closer correlation, with less fluctuation between time points. Trial B shows less consistent ratings across time. Variance in trial A is significantly greater than in Trial B. Mean physical pain intensity for trial A 6.08, STD $\pm$ 0.44, r2= .854 p< 0.01; mean physical pain intensity trial B 6.43, STD $\pm$ 0.84, r2= .567 p> 0.05.

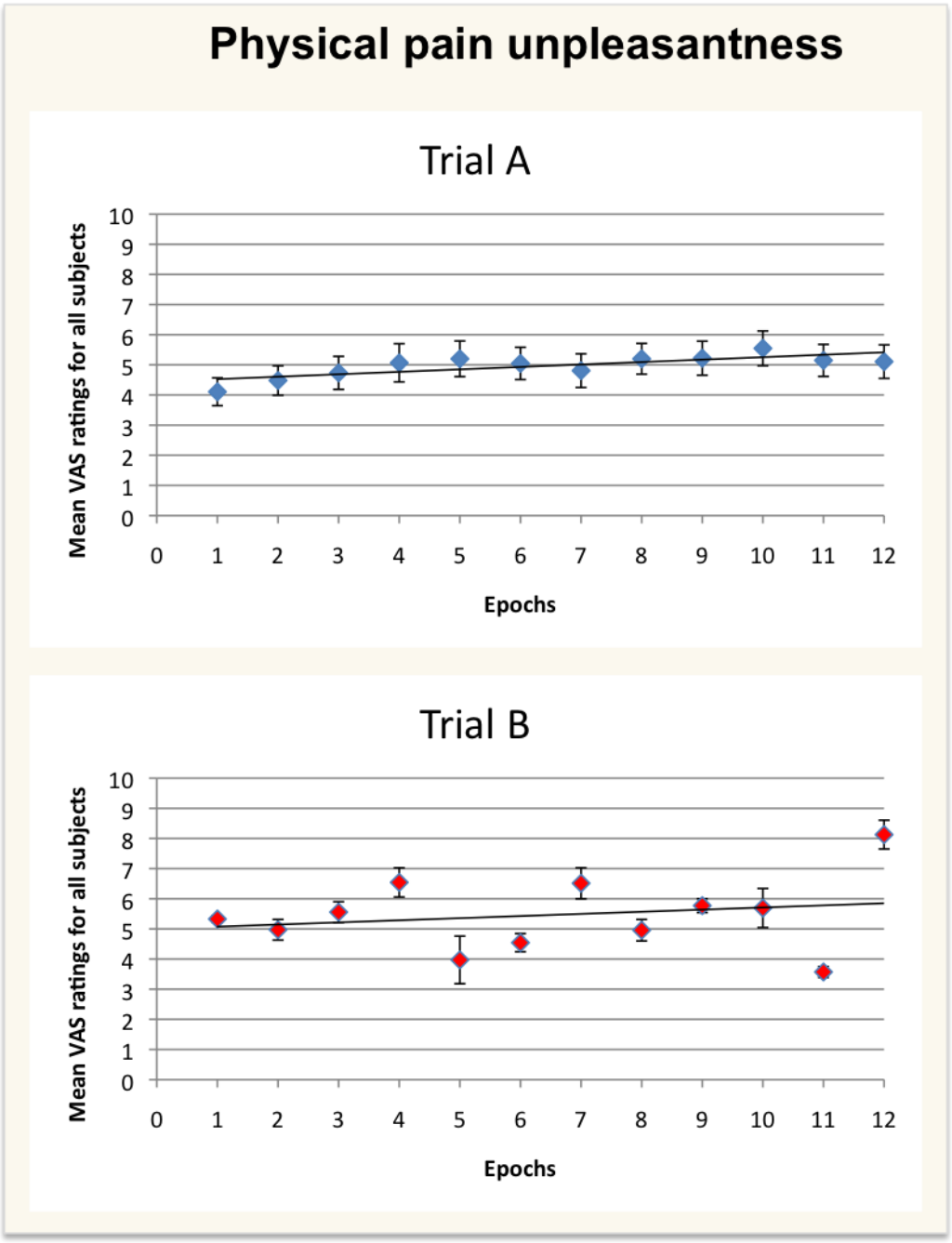


Figure 5.4: Subjective ratings of physical pain unpleasantness for trial A and the control trial B averaged across subjects for each epoch. Similar to ratings for physical pain intensity, Trial A demonstrates less fluctuation between time points. Trial B shows less consistent ratings across time. Variance in trial A is significantly larger than trial B. Mean physical pain unpleasantness for trial A 4.97 STD $\pm$ 0.39, r2= 0.76 $p<0.05$; mean physical pain unpleasantness for trial B 5.46, STD $\pm$ 1.23 r2=0.207 $p < 0.05$

After demonstrating a significant effect of time in trial A, a repeated-measures ANOVA tested whether the interaction between the trial and the effect of time was significantly different for physical pain intensity and physical pain unpleasantness. The interaction effect of physical pain ratings and time was found to be significantly different between both trials. Mauchly's test indicated that the assumption of sphericity had been violated; therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\boldsymbol{\varepsilon}$ = 0.41). The results show that physical pain intensity between trials over time differed significantly, $F(4.4, 62.3) = 4.4$, $p < 0.05$. For physical pain unpleasantness, Mauchly's test indicated that the assumption of sphericity had been violated; therefore degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\boldsymbol{\varepsilon}$= 0.83) The results show that the pain unpleasantness between trials over time differed significantly, $F(14.99, 4.05) = 7.3$, $p < 0.05$.

A two-tailed t-test was performed to establish whether averages across epochs for all subjects differed significantly between trial A and trial B for physical pain intensity and physical pain unpleasantness. Neither condition was shown to be significantly different between trials. Mean ratings for physical pain intensity for trial A ± SD = 5.79 ± 0.31, mean physical pain intensity trial B ± SD = 5.97 ± 0.188. Mean ± SD trial A physical pain unpleasantness = 4.77 ±0.44, trial B pain unpleasantness mean ± SD = 5.12 ± 0.21 (figure 5.5).

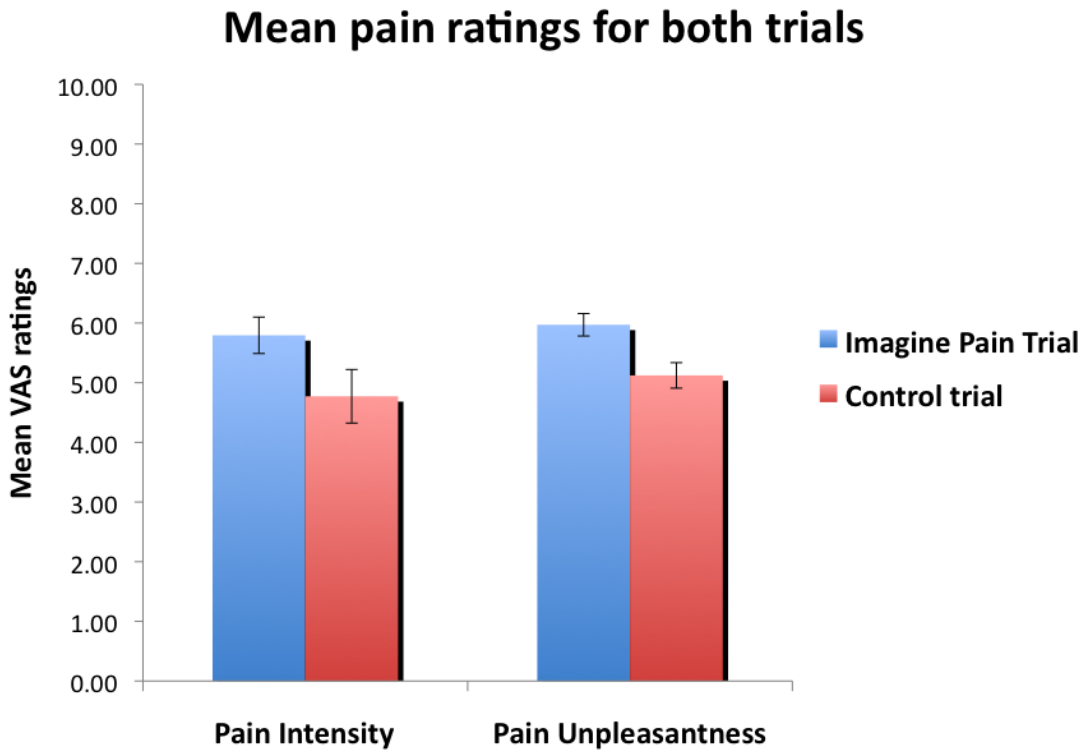


Figure 5.5: Subjective ratings of pain intensity and pain unpleasantness for the imagined pain trial and the control trial averaged across individuals across conditions. Mean pain intensity trial A ± SE 6.43 ± 0.24, physical pain unpleasantness trial A ± SE 5.46 ± 0.35, Mean pain intensity trial B ± SE 6.08 ± 0.11, physical pain unpleasantness trial B ± SE 4.97 ± 0.11

For trial A, ratings for recalled pain intensity and vividness demonstrated a significant positive linear increase, similar to the physical pain ratings. The two-tailed Pearson product-moment correlation coefficient was r = 0.769 mean ± SD = 6.43 ± 0.83 mean ± SD = 5.46 ± 1.23 for recalled pain intensity, and r = 0.775 for imagined vividness; $p < 0.01$ for both imagined pain scores.

When the relationship between imagined pain intensity and physical pain intensity over time was compared, no significant difference was found. Mauchly's test indicated that the

assumption of sphericity had been violated therefore degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (**ε** = 0.322), F(49.52, 3.54) = 0.895.

5.4 Discussion

In this study we sought to establish whether rehearsal of a recalled pain task affects subsequent pain perception. We demonstrate that no sensitisation or significant increase in physical pain intensity or physical pain unpleasantness occurs with repeated noxious stimulus in the absence of a recalled pain. We find a significant increase over time in pain intensity and unpleasantness ratings of physical pain that follows a recalled-pain event, in trial A. This same correlation between physical pain ratings and time is not shown in the control trial B. Using a repeated-measures ANOVA we find the interaction between the trial and effect over time is significantly different between trials. When exploring any significant difference between the averages for all time points across subjects we find no significant difference between physical pain ratings between both trials. We show a significant increase in recalled pain ratings for recalled pain intensity and vividness in trial A over time. Using a repeated-measures ANOVA we show no significant difference between physical pain intensity ratings to recalled pain intensity ratings over time.

5.4.1 The control trial

In each of the preceding experimental chapters, we utilised a thermal pain stimulus applied to the back of the left hand. In Chapter 3, we varied the stimulus intensity, and in Chapter 4 we varied the delay time between the stimulus and the recalled event. The limitations of these paradigms, specifically exploring the capacity to recall a physical pain event, prevented the acquisition of any behavioural measure for physical pain. As such we were unable to show that no

pain sensitisation occurred as a result of repeated noxious stimulation. Inferences from the behavioural and imaging results were attributed solely to the manipulated variables. Each condition was measured relative to the other conditions with no "control" condition, to establish whether the presence or absence of a recalled event affected subsequent events. In this study we demonstrate that repeated exposure to the same thermal stimulus does not change significantly over time. Therefore, no effects of sensitisation were evident in trial B. We compare this to trial A to show that, keeping the intensity of the pain stimulus constant at a "high pain" level, and the time-to-test delay constant at a "short delay" of 11 seconds, pain recall has a significant effect over time.

However, limitations of this study prevent definite conclusions from being drawn. One such limitation is due to the considerable length of time between events to which it was necessary for the subject to attend. As such, it is possible that the attention to which subjects devoted to the physical pain stimulus in both trials were disproportionate, and therefore not comparable. Furthermore, Trial A was consistently presented before Trial B. As the effect of interest explored specifically how participants were able to learn over time, order effects are particularly relevant.

5.4.2 The effect of pain recall over time

We hypothesised that pain recall would significantly affect subsequent pain perception. As subjects repeatedly mentally rehearse the pain stimulus, the effect on subsequent pain increases. When subjects are instructed to recall a physical pain stimulus, subsequent pain ratings for both pain intensity and unpleasantness show a significant positive linear correlation over time. This is further demonstrated in the repeated measures ANOVA, which shows that the relationship between pain ratings over time significantly differs when subjects recall pain before receiving a painful stimulus compared to when they do not. Comparing the means for all subjects at each time point, for both trials, we show higher standard deviation for trial B than trial A, which goes

further to describe the significant positive correlation over time for trial A. After pain recall, subjects show a clear increase over time, whereas in the control trial pain ratings for each time point fluctuate. As trial B involved only one event, physical pain repeated twice for each epoch, and each epoch repeated 12 times, it is possible that the subjects were not able to devote the same attention to the stimulus, and thus account for the wide variation across time. When looking at the within subjects variability using an f-test, we notice that there is significantly increased variance in physical pain ratings in trial A relative to trial B. This could be due to the subtlety of the effect in trial A, which may be stronger in some individuals and less so in others. As trial B has no manipulation, it would be reasonable to expect there would be little within-subject variation.

Perhaps the most plausible explanation is to consider the pain-recall event as creating a mental representation to which individuals may refer to when evaluating physical pain. Providing a neutral contextual association may explain the lower variability across time points for Trial A relative to Trial B. Using this mental representation, subjects may increase their level of certainty to which they are able to predict the intensity or unpleasantness of the subsequent pain stimulus. This effect would be contrasted by Trial B, in which long delays between events may increase uncertainty, and therefore increase variability in pain ratings over time.

Worth considering is a confound of possible order effects, as both trial A always preceded trial B. As we suggest that repeated rehearsal of recalled pain can potentiate learning, if rehearsal of recall pain in trial A were to make long lasting changes to pain perception, these effects would carry over into subjective ratings of physical pain in trial B. However, as both trials were presented on different days, with at least two weeks between administering each trial, it is unlikely that "training" during trial A, would substantially affect pain scores in trial B. Despite showing a trend of pain scores increasing over time, t-tests between ratings did not show a significant difference in ratings for pain for either pain intensity or pain unpleasantness between the two trials. In our

previous chapters we collected average pain ratings between trial blocks: three measures for physical pain in Chapter 3 in total, and two measures in Chapter 4.

In these chapters we did not find any significant difference between pain ratings collected before, during and after the experiment. In this experiment we optimised the study design to remain as faithful to the previous design as possible, but maximising the potential for better rehearsal and as a result greater effect of rehearsal. This was done by using a “high pain” stimulus, short delay time between the stimulus and the recall event, and increasing the number of repeats to twelve. Despite observing a significant effect of pain recall over time, physical pain intensity ratings across time for each subject did not significantly differ from the control trial, supporting our previous findings.

There may be several explanations for observing no significant differences in the mean ratings for physical pain intensity and unpleasantness between the two trials. The first to consider is that apart from a gradual increase over time observed in Trial A, the effect of recall on subsequent perception may be too subtle to detect, or has no effect on subsequent perception. In the first case it is possible that despite the efforts taken to maximise the effect of rehearsal; participants were not given any prior training, which may be essential to observe the desired effect (Grant and Rainville, 2009, Perlman et al., 2010, Zeidan et al., 2010). It may also be possible that recalling a pain event does not affect subsequent pain perception. This may be that the short-term representation of pain degrades before the onset of the physical pain stimulus, and 12 repeats is not sufficient to have long-term memory effects.

The motivation behind this study was founded on increased activation observed in the Chapter Four as a result of increasing rehearsal as well as general concepts related to recall and expectation. We demonstrated a significant increase of pain ratings over time, consistent with this neural activation. We also excluded the possibility that this may be due to pain sensitisation due

simply to repeating a physical pain stimulus. In the subsequent chapter we replicate aspects of this experiment to further explore the effect of pain recall on subsequent pain perception, under more controlled scanning conditions; as cognitive effects observed behaviourally may differ in and out of the scanner (Boyle et al., 2006, Tomasi et al., 2005, Youell et al., 2004).

5.4.3 The problem of causality

The main result of this experiment was to find a significant positive linear increase with time for both physical pain and recalled pain ratings in trial A. No significant difference is shown between the physical and the recalled pain event using a repeated-measures ANOVA, supporting the strong relationship between physical pain events and recalled pain scores demonstrated in previous chapters. Although we demonstrate that repeated rehearsal of recalled pain increased subsequent pain ratings, relative to a control trial, we cannot clearly demonstrate whether it is the increase in the ability to recall a pain event which affects the subsequent physical pain perception, or whether the increase in pain perception affects the ability to recall.

Despite this problem of causality, it provides a good illustration of how the memory template of pain may affect each physical pain event, and each physical pain event can alter the memory template of pain. Although this cycle could potentially be damaging, reinforcing negative affective qualities of the pain experience, it also provides the potential of being able to change the memory template with every new pain event. This demonstrates that false beliefs about pain may be replaced by positive coping strategies; possibly improving the management of pain as this mental imagery is rehearsed.

This concept is demonstrated neatly in other fields, where mental rehearsal of motor tasks has been shown to increase physical motor performance (Avanzino et al., 2009, Gentili et al., 2006, Meister et al., 2004, Morrison et al., 2007). In the field of pain research, the study of the mechanisms and effects of mental rehearsal is still in its nascent stage. Some studies have

employed mental rehearsal of motor and visual tasks and explored the effects on pain perception in patients suffering neuropathic pain (Gustin et al., 2010, Moseley, 2007). Although results of these studies are inconclusive as to whether mental rehearsal increases or decreases pain intensity, each of these studies demonstrates that mental rehearsal can significantly modulate pain perception. The two cited experiments using imagery have only been carried out in a cohort of patients with a history of pain symptoms, who received prior training. An explanation as to why, in the present study, no significant differences across time per subject in physical pain ratings were found between trials may be attributed to the use of a cohort of naïve, healthy volunteers, who received no previous training. As pain perception depends on previous experience, perhaps a longer training period might have produced a stronger effect.

As we have demonstrated in chapters 3 and 4, pain-related recall relies on the previous pain stimulus. In this paradigm by varying only whether or not the recalled condition preceded the physical pain, we can demonstrate a significant effect of pain recall on subsequent perception of noxious events. As forward sensory models affect motor performance, so too could pre-stimulus "priming" change individual pain perception (Bushnell et al., 1985, Fernandez and Turk, 1989, Posner et al., 1980, Wiech et al., 2010). Indeed, many recent studies have shown specific brain areas activated before the painful stimulus which predict whether the individual will perceive a particular stimulus as painful (Fairhurst et al., 2007, Ploner et al., 2010, Wiech and Tracey, 2009); therefore exploring how imagery tasks tap into these mechanisms might someday prove beneficial in a clinical setting.

Imagery tasks such as the guided imagery technique, visual illusions and attention management techniques such as mindfulness meditation involve cognitive rehearsal, while simply observing or perceiving the mental or perceptual representation with no additional emotional or cognitive biasing (Buhle and Wager, 2010, Elomaa et al., 2009, Fernandez and Turk, 1989, Grant et

al., 2011, McCracken, 2007, McCracken et al., 2007a, Moseley, 2007, Ramachandran and Altschuler, 2009). A wide range of experiments exploring these techniques have shown promise, as results report less negative appraisal of pain as well as significant reductions in pain intensity in patient cohorts suffering from chronic pain, (Elomaa et al., 2009, Grant et al., 2011, McCracken, 2007, McCracken et al., 2007a, Moseley, 2007, Ramachandran and Altschuler, 2009). However, more research is needed to refine these techniques (Elomaa et al., 2009). This study, in conjunction with the experiments presented in previous chapters and Chapter Six, may contribute to this aim by furthering our understanding of the underlying memory processes involved.

5.4.4 Conclusions

As other studies have demonstrated the effect of visual and motor imagery on physical pain reporting in patients, we demonstrate a significant change in the relationship of pain ratings over time between the trial A that included a pain recall task prior to the physical pain stimulus and the control task B that did not contain a recall component. Pain intensity and unpleasantness in trial A are highly correlated with time, while the control task pain ratings are not, demonstrating the effect of each rehearsal task on subsequent pain ratings. However, we may not assume that pain recall specifically is responsible for this effect, as the effect may be present after recall not specific to pain. As this study is the first to look at pain imagery, not linked to other visual or motor imagery in healthy controls, future studies may look at the effect of increasing the training period, as well as looking at the specificity of pain-related recall on future pain perception.

Chapter 6

The effect of pain and visual recall on subsequent physical pain perception using FMRI

Chapter 6:
The effect of pain and visual recall on subsequent physical pain perception

6.1 Introduction

In the preceding chapters we have discussed the existence of a memory trace of a previous pain stimulus, which exists in short-term memory containing analogue information before being converted into long-term storage. Cued sensory re-experiencing has been shown to affect subsequent pain ratings with repeated rehearsal. In this chapter, we explore the effect of pain-related recall versus pain-unrelated recall on subsequent ratings of pain. Comparing imagery tasks in different sensory modalities, we hypothesise that certain regions will be common to imagery, but pain-recall will activate distinct regions specific to pain. We expect pain-specific recall will significantly affect pain unpleasantness ratings, consistent with results from analogous experiments using mindfulness meditation (Brown and Jones, 2010, Grant and Rainville, 2009)

In Chapter Five, we discussed the theoretical role of the forward sensory learning model, which describes the effect of a relevant stimulus acting as a primer on subsequent perception. Previous research has concentrated on applying this theory to motor and visual learning (Avanzino et al., 2009, Gentili et al., 2006, Gustin et al., 2010, Meister et al., 2004, Morrison et al., 2007, Moseley, 2007, Moseley and Arntz, 2007, Ramachandran and Altschuler, 2009, Wymbs and Grafton, 2009). In previous chapters, we put forward evidence for the existence of a neural memory trace of pain and investigated its dependence on both the intensity of the initial stimulus and the time-to-test delay. Behaviourally, we have demonstrated that recalling a pain event has a significant effect on pain ratings over time. Applying the forward sensory learning model, we suggest that attending to the painful experience through rehearsal modulated the physiological response to pain stimuli. Our results in the previous chapter demonstrate how recall can aid in

contextualising pain ratings of subsequent pain perception. This is supported by studies manipulating attention and expectation, shown to reduce subjective pain ratings.

The paradigm employed here and in Chapter Five builds on studies involving visual and motor imagery, creating a mental representation of future pain and mindfulness meditation practices. Both visual and motor imagery related to pain can produce significant changes in pain perception. Many studies have demonstrated the clinical usefulness of guided imagery, motor imagery and mirror visual feedback in many chronic pain conditions (Moseley and Arntz, 2007, Ramachandran and Altschuler, 2009). However, there remains some controversy as to how these techniques affect pain processing in certain patient populations (Gustin et al., 2008). In a cohort of patients suffering from below-level neuropathic pain following spinal cord imagery, motor imagery was shown to increase ongoing pain ratings, when the individual imagined movement in the area of the body affected by pain (Gustin et al., 2008). These results conflicted with results from another group in neuropathic pain following at-level neuropathic pain after spinal cord injury (Moseley, 2007).

The two important differences between these studies included the type of neuropathic pain as well as the kind of imagery used. Structural changes associated with the different pain condition may explain difference in results. Perhaps more compelling might be the alternative explanation, which considers the nature of the imagery employed. In the first study, subjects were instructed to imagine right ankle plantar flexion, as if “pushing down the accelerator pedal in a car”. Participants were given an audio recording of a car accelerating and decelerating to aid imagery. Motor imagery training was performed at home using this technique before performing the same in an experimental context (Gustin et al., 2008). In the second study, participants were given no previous training, but performed a motor task in conjunction with visual tasks, which gave the illusion of the patient walking, pain-free (Moseley, 2007). The most striking difference

between these imagery techniques is that of context. Imagery in the first study involved imagining a context familiar to the patient, in familiar home surroundings, and easily associated with motor tasks, which have otherwise caused them pain in their affected area in the past. However, in the second study, the context of the imagery was entirely unfamiliar, being conducted in an experimental setting, with an added visual illusion perhaps replacing negative associations of pain during motor tasks, with neutral, pain-free experience. In this study, we predict that the "imagine pain" task will change the affective quality of subsequent acute pain stimuli, in a similar manner.

In a similar vein, new studies exploring the effect of practicing the technique of mindfulness meditation have been shown to reduce the affective qualities of pain perception. Mindfulness meditation is an acceptance-based attention management technique, which encourages attention to be drawn toward not away from painful stimuli (McCracken et al., 2007a). In so doing, practitioners of this technique aim to change the negative affective bias of pain to a neutral bias (Baer, 2003, Grant et al., 2011, Hayes…, 2004, McCracken et al., 2007a, McCracken et al., 2007b). Although the recall-pain paradigm does not involve meditation nor previous experience or training, similar strategies related to attention-management are inherent to the design. These include specifically drawing attention toward the painful stimulus within a defined time frame, in the absence of threat or negative bias, intrinsic to a physical stimulus.

Attention management is included in the practice of cognitive behavioural therapy. A recent paper exploring different approaches included in the program included both mindfulness meditation as well as "pain imagery" as strategies that produced significant decreases in ratings of ongoing pain. This study highlighted the need to further refine and explore the therapeutic potential of these pain management strategies (Elomaa et al., 2009). Mindfulness meditation practice seems to produce long-term changes in grey matter plasticity with prolonged training (Hölzel et al., 2008, Lazar et al., 2005, Pagnoni and Cekic, 2007, Vestergaard-Poulsen et al., 2009).

In this study, individuals received no training prior to participation. However, we hypothesise that "imagining" pain can achieve similar objectives, as subjects are instructed to attend to aspects of the physical pain intensity for recall but as they are aware no painful stimulus will be administered, the threat value is diminished, and therefore the affective bias will be neutralised. This in turn will show similar decreases in pain unpleasantness ratings.

The majority of studies exploring this technique have found a significant effect only on affective qualities of pain perception (Brown and Jones, 2010, Grant et al., 2011, Grossman et al., 2007, McCracken and Gauntlett-Gilbert…, 2007, Tang et al., 2007, Vestergaard-Poulsen et al., 2009). In Chapter Three, we demonstrate that different components of the pain experience are encoded in different regions of the brain. Furthermore, in Chapter Four, we show that only some aspects of the pain memory survive after the transition into long-term storage. The separable encoding of sensory and affective qualities of pain may explain the specificity with which the majority of hypnosis and meditation studies modulate only pain unpleasantness ratings (Grant et al., 2011, Miron et al., 1989, Rainville et al., 1999a). In these studies, as well as our own, the context of the pain is being specifically manipulated by replacing a negative cognitive bias with neutral appraisal. So, although the intensity of the painful stimulus is being attended to, and therefore readily retrievable, the affective quality of the pain can be reduced.

Many studies have now demonstrated the power of imagery in reducing subjective pain ratings; visual, motor and attention strategies focus on visual, or motor aspects of affective body part or pain-related behaviour (Elomaa et al., 2009, Fernandez and Turk, 1989, Moseley, 2007, Ramachandran and Altschuler, 2009). However, methodology varies and as yet the importance of relating imagery to pain remains unexplored (Elomaa et al., 2009). In order to isolate the specific effect of pain-specific imagery from possibly overlapping effects of different but related sensory stimuli, we used a visual stimuli wholly unrelated to pain, the individual or the body. In this way,

we hope to separate possible effects on physical pain perception specific to recalling a pain-related stimulus, from those associated with a demanding sensory recall task unrelated to pain, as well as establishing possible regions common to both.

6.2 Materials and methods

6.2.1 Subjects

Fifteen right-handed healthy volunteers (eight female, seven male; age range: 20-35 years, mean age: 27.2, Std $\pm$ 4.3 years) were recruited for a pain study using functional magnetic resonance imaging (FMRI). All subjects were screened for an absence of any prior history of pain, neurological or psychiatric disorders, and did not meet any of the exclusion criteria for MR experimentation. After obtaining written informed consent, subjects were scanned. This study has been approved by the Milton Keynes Research Ethics Committee.

6.2.2 Study Design

Before the start of the experiment the thermal pain stimulus was defined by subjective thresholding in the scanner as identified by a 6/10 pain verbal intensity rating, where 0 is not painful and 10 is extremely painful. Following this there were two training sessions during which subjects viewed the visual stimuli of houses, which would later be included in the experiment. The first training session displayed each house image for one second followed by a one second break between visual stimuli. The second trial presented six blocks of six images each lasting 800ms with a 200ms gap between images, to match stimulus presentation during the experiment, with a six-second gap between stimuli.

The experimental paradigm consisted of two trials, differing in the instruction to either “imagine pain” or “imagine house”. Each of these trials consisted of a high pain stimulus, followed by the trail-specific imagined event, and finally receiving a pain stimulus identical to the first. Both trials began with a physical pain stimulus (p1), followed by the presentation of one block of six images of houses. An eleven second gap, marked by a fixation cross, separated the physical pain

stimulus from the recalled condition specific to the trial. After recall subjects were asked to rate the imagined pain in terms of intensity of the imagined pain. For recall of the visual stimulus, subjects were asked to decide between two choices pertaining to the image, for example “how many doors”. The degree to which subjects moved the scalar gave an indication of how certain they were of each answer. In this way accuracy of the imagined visual stimulus was recorded. For both imagined pain and house stimuli, subjects were asked to give a rating for vividness. Following a delay, subjects received the second physical pain stimulus (Malhotra-Kumar et al., 2010), which they were asked to rate in terms of intensity and unpleasantness. The two trials were pseudo-randomised across the trial with seven repeats per condition. The painful stimulus presented during physical pain events was kept at the same temperature throughout both trials after thresholding. The duration of each fixation cross within each epoch was 11 seconds. Between each epoch a fixation cross was presented for approximately 34 seconds, but was jittered throughout the experiment. A one-minute interval was allowed between each six-second pain stimulus to ensure the safety of the skin, after which the subjects gave a verbal rating for the previous stimulus.

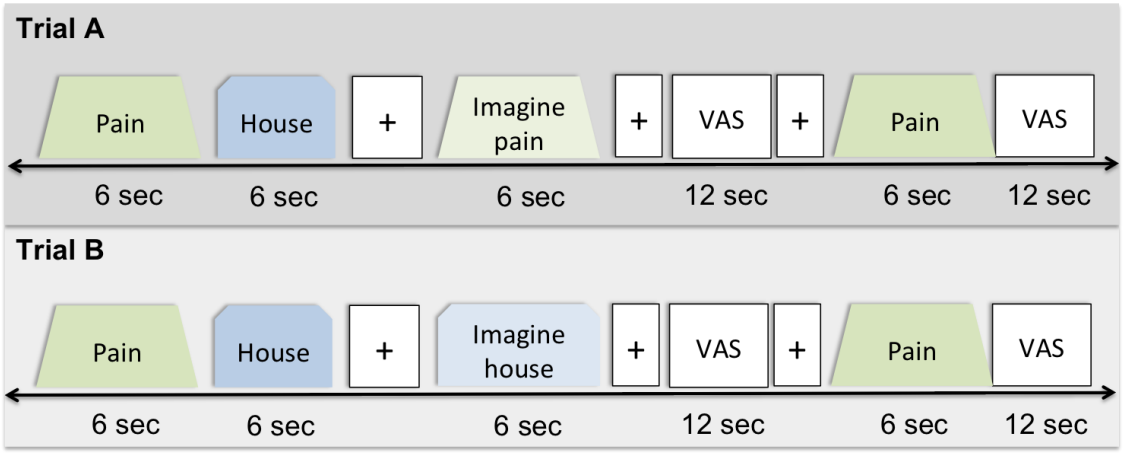


Figure 6.1: Study Design: Two trials presented pseudo-randomly across subjects, differing only in the nature of the imagined task between two physical pain stimuli. Following the imagined event, visual analogue scales (VAS) prompted ratings for imagined accuracy and vividness.

6.2.3 Thermal stimuli

An in-house built thermal pain device was used to deliver noxious stimuli. This device has been reliably used within several previous studies published by the PaIN Group (Bantick et al., 2002b, Ploghaus et al., 2001b). All subjects were thresholded using a randomised staircase approach to find a temperature at which the desired subjective rating is consistently obtained. This temperature was then delivered by the thermode, controlled via the in-house developed software, Paingain. This software ran both the visual and sensory stimuli for the experiment, including presentation of behavioural rating scales and recording of subjective ratings. Temperatures applied across subjects ranged from 46.5ºC-56ºC (mean ±SD = 50.75ºC±2.9).

6.2.4 Visual stimuli

In both trials, physical pain was marked with a six second prompt showing “Feeling pain” presented concurrently with the painful stimulus and “Imagine feeling pain” or “imagine house” during which there was no thermal stimulus. Following the physical pain events, a 6 second block consisting of 6 images of houses was presented. Each image was presented for 800ms, with a gap between images marked by a fixation cross lasting 200ms. Each block consisted of 6 different images. No images were repeated within or between trials. Visual analogue scales (VAS) were presented to obtain online ratings for intensity of imagined pain and vividness. Each scale was presented for six seconds. Between events and epochs a fixation cross was presented.

Trial A

The “Imagined pain intensity” scale was presented following the recalled pain event, anchored with “no pain” at the minimum, and “extremely painful” at the maximum end. Similarly, the “Vividness” scale was anchored with “not vivid” and “extremely vivid”.

Trial B

The first ratings scale following an “imagine house” event presented one of four questions pertaining to the recalled visual stimulus, all presented pseudo-randomly within the trial: “how many windows”, “how many pillars”, “how many doors”, or “how many turrets”. All, save the question “how many turrets”, were presented twice. Subjects were shown each of these screens before beginning the experiment, and any clarifications necessary for answering the question were made. For this rating scale anchors on both sides of the scale represented a possible answer to the question in numerical form. Answers for each question varied, but the left anchor always represented the smaller number and the right anchor always represented the larger of the two numbers. After this rating scale, subjects were asked to rate the vividness of the recalled visual

stimulus. The same ratings scale used for vividness in trial A was used for trial B, anchored with "not vivid" and "extremely vivid". All visual stimuli were projected onto a screen visible to the subject via prism glasses. Visual stimulation was continuous throughout the experiment.

6.2.5 MRI Data acquisition

Functional imaging was conducted using a 3 Tesla Siemens/Varian MRI system with a bird-cage radio frequency coil and four channel phased-array receiver coil. A gradient echo-planar imaging (EPI) sequence was used with a TR = 3 s; matrix = 64 x 64; TE =30ms; 41 x 3 mm axial oblique slices; volumes = 537; FOV=192 x 192; voxel size = 3 x 3 x 3 mm^3. Scans were acquired continuously throughout the experiment. Signal dropout due to susceptibility-induced field inhomogeneities was minimized for orbitofrontal cortex (Deichmann, 2005). High resolution, T1-weighted, structural scans (64 slices at 1 x 1 x 1 mm^3 voxel size) were obtained for each individual for anatomical overlay of brain activation. Fieldmap B0 phase and magnitude images were also acquired to correct for possible distortion.

6.2.6 Data Analysis

Psychophysical Data

Pain intensity and unpleasantness ratings for both trials were grouped according to trials and averaged across subjects. Two-tailed t-tests were carried out testing significant differences between trials. A repeated-measures ANOVA was carried out to test whether differences between pain intensity and unpleasantness scores were due to an interaction effect of vividness scores. A two-tailed Pearson product-moment correlation coefficient was calculated for all physical pain intensity and physical pain unpleasantness ratings over time. Following this, these behavioural scores including physical pain intensity and physical pain unpleasantness, vividness ratings for both recall tasks and recalled pain intensity ratings, were divided into two groups according to the

order in which participants received either trial A or trial B. A two-tailed Pearson product-moment correlation coefficient was calculated for physical pain intensity and pain unpleasantness scores according to group of participants (group one who received trial A first, and group two who received trial B first) over time. Correlation tests were then run between corresponding vividness ratings for the preceding recall pain scores with the physical pain scores for intensity and vividness for both groups. Finally, correlation tests were run between the recalled pain scores for the recall task and the subsequent physical pain scores for group one and group two. Each of these statistical analyses was carried out using PASW statistics 18.0.

Imaging Data

Analysis of all neuroimaging data sets was performed using FEAT (FMRIB Expert Analysis Tool) Version 5.63, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Statistic processing included: motion correction using MCFLIRT (Motion Correction FMRIB's Linear Image Registration tool, (Jenkinson, 2001 #107)), non-brain removal using BET (Smith et al., 2002), B0 fieldmaps for unwarping distortion in the images (Jenkinson, 2003), spatial smoothing using a Gaussian Kernel of 5 mm full width at half-maximum and non-linear high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=40.0 s). Registration included co-registration of the functional scan onto the individual T1 high-resolution structural image and then registration onto a standard brain (Montreal Neurological Institute MNI 152 brain) using FNIRT (FMRIB's Non-linear Image Registration Tool), (Jenkinson and Smith, 2001), Statistical analysis at the first, individual subject level was carried out using a general linear modelling (GLM) approach (Friston et al., 1993). Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al., 2001c). Second level analysis grouped the data of all subjects using the data from the first level of analysis. For group statistics, analysis was carried out using FEAT (FMRI Expert Analysis Tool) with higher-level analysis carried

out using FLAME 1 (FMRIB's Local Analysis of Mixed Effects). This analysis method allows for incorporation of variance within session and across time (fixed effects) and cross session variances (random effects). Cluster thresholding was performed with a Z-threshold of 2.3 and a corrected p-value of < 0.01 with a cluster-based correction for multiple comparisons using Gaussian Random Field Theory (Friston et al., 1993, Worsley et al., 1992). A conjunction analysis was carried out using inclusive masking. Using fslmaths, all voxels active during “imagine pain” surviving the Z-threshold of 3.1 was extracted and subsequently used as a mask to find voxels within this mask also activated during the “imagine house” condition.

2.3 Results

6.3.1 Behavioural data

Pain intensity and unpleasantness scores were compared between both trials with a two-tailed t-test (figure 6.2, and 6.3). While pain intensity was not significantly different between the two trials, pain unpleasantness was shown to be significantly lower after subjects imagined pain than after imagining the visual "house" stimulus ($t_{(14)} = 2.26$, $p < 0.04$, mean pain unpleasantness in imagine pain trial 59.03, mean pain unpleasantness after imagining the visual stimulus 64.7; see figure 6.2).

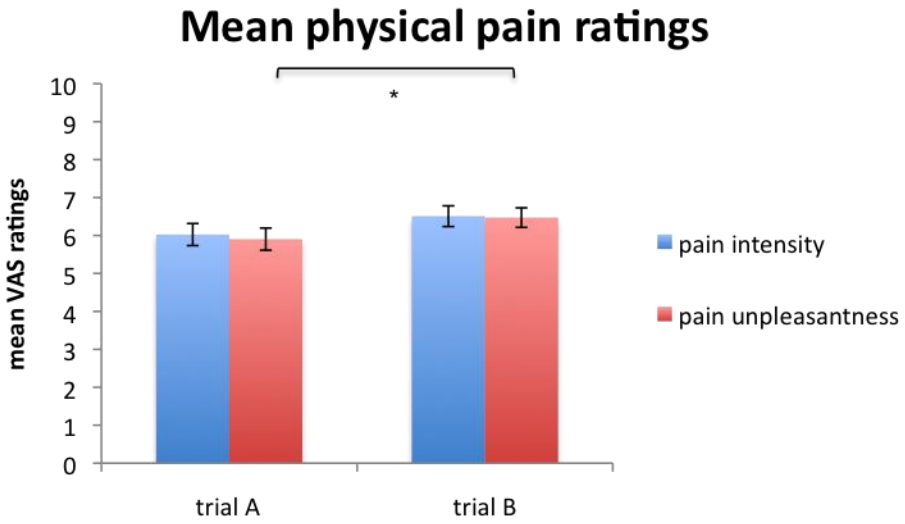


Figure 6.2: Subjective ratings of pain intensity and pain unpleasantness for trial A and trial B averaged across individuals for all time points. Mean pain intensity trial A ± SE 6.02 ± 0.29, physical pain unpleasantness trial A ± SE 5.9 ± 0.29, Mean pain intensity trial B ± SE 6.51 ± 0.27, physical pain unpleasantness trial B ± SE 6.47 ± 0.26. Mean physical pain intensity ratings were not significant between trials. Mean physical pain unpleasantness ratings were significant using a 2-tailed t-test, $p < 0.05$, indicated by *.

Vividness between the two imagined conditions was shown to be significantly different, as the imagined visual stimulus was shown to be significantly more vivid. ($t_{(14)} = 2.19$, $p < 0.046$, mean "imagine pain" vividness in trial A 56.1, mean "imagine house" vividness in trial B 65.7). Confirming our results in the previous chapter, both physical pain intensity and physical pain unpleasantness have a strong correlation; mean scores for all subjects across time demonstrated a gradual increase over time (see figure 6.3, and figure 6.4).

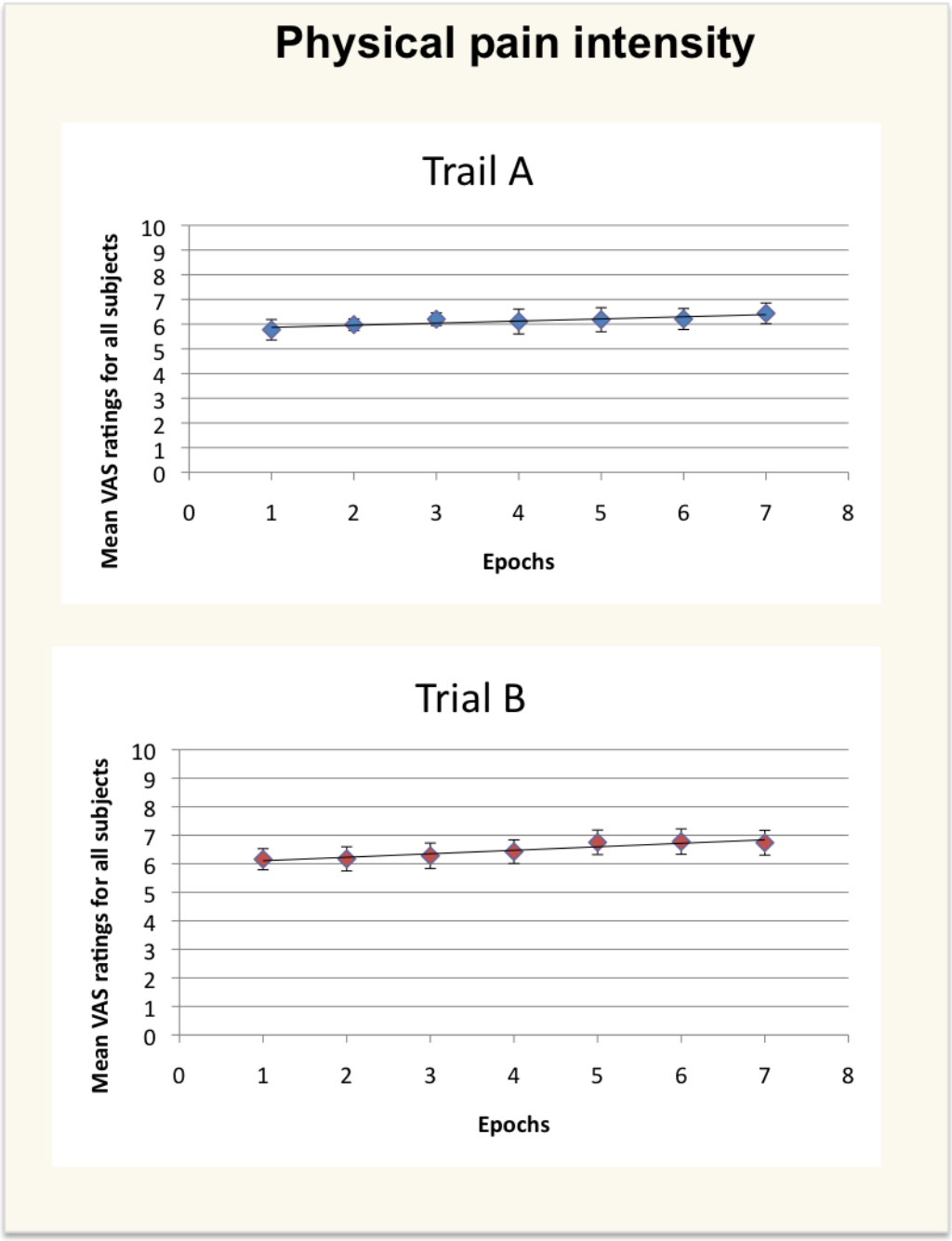


Figure 6.3: Subjective ratings of physical pain intensity for trial A and the control trial B averaged across subjects for each epoch. Mean physical pain intensity for trial A 6.02, STD ± 0.21, r2= 0.9 p< 0.01; mean physical pain intensity trial B 6.51, STD ± 0.3, r2= 0.8 p> 0.05.

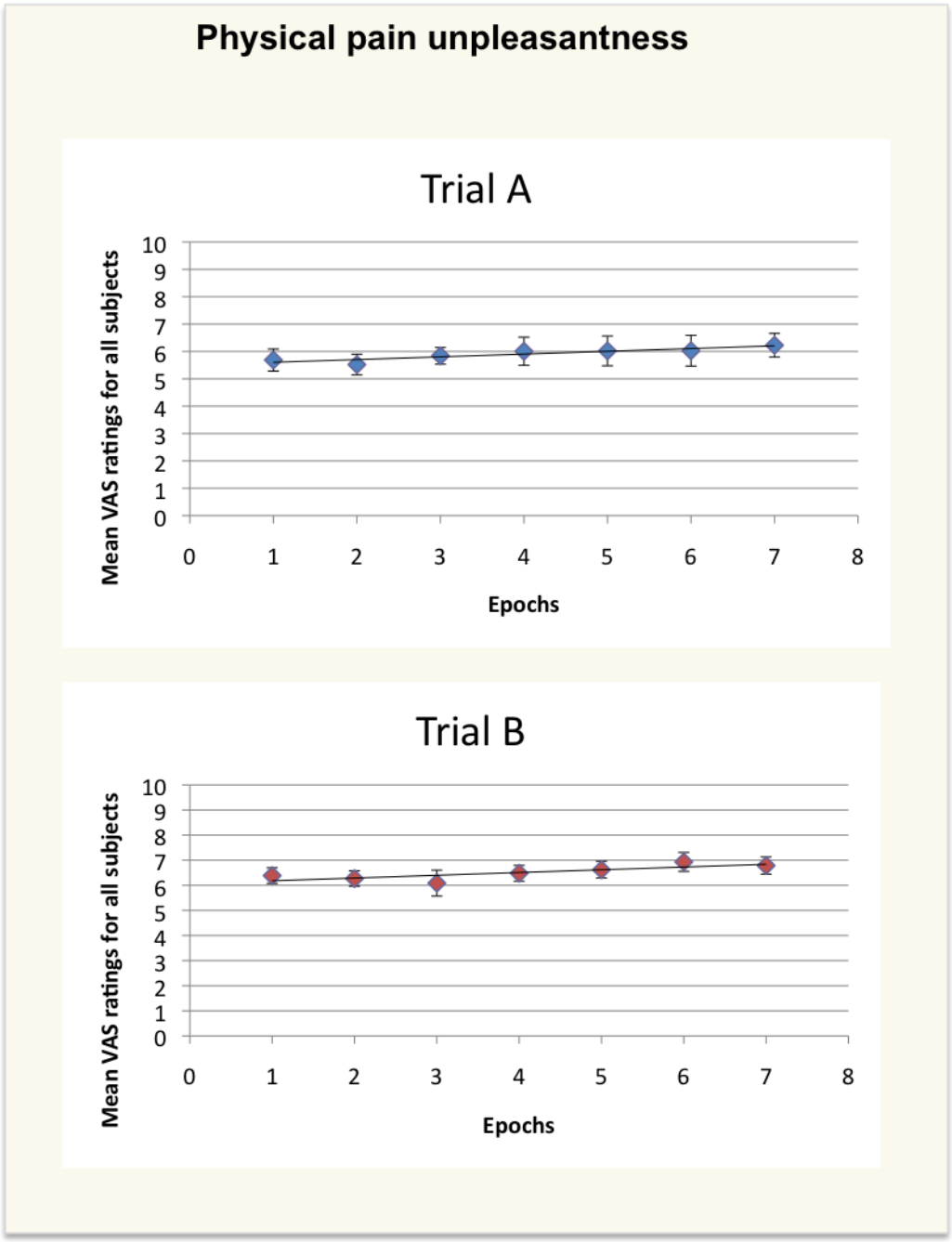


Figure 6.4: Subjective ratings of physical pain unpleasantness for trial A and trial B averaged across subjects for each epoch. Mean physical pain unpleasantness for trial A 5.9 STD ± 0.24, r2= 0.91 p<0.01; mean physical pain unpleasantness for trial B 6.47, STD ± 0.28 r2=0.94 p > 0.01.

A repeated-measures ANOVA was run to check whether there was a significant interaction effect of vividness on pain unpleasantness. No significant interaction was found, demonstrating that differences in pain unpleasantness could not be attributed to differences in vividness ratings. Mauchly's test indicated that the assumption of sphericity had been violated, therefore, degrees of freedom were corrected using Huynh-Feldt estimates of sphericity (epsilon = 1.0), $F(14, 1.0) = 0.895$ $p= 0.375$. This correction is performed for ANOVAs applied to longitudinal data when the epsilon value is greater than 0.75 and normal assumptions made about constant variance is untrue.

As the increase in pain scores over time was a surprising result, we investigated whether this could be attributed to sensitisation over time. We explored whether subjects receiving higher temperatures showed a greater incline in the slope of physical pain scores (both intensity and unpleasantness) relative to time. Two-tailed Pearson product moment corrolations were performed for both trials, for physical pain intensity and physical pain unpleasantness. For an N of 15 subjects for trial A $r= 0.45$ for slope of pain intensity versus time and temperature; $r = 0.422$ for pain unpleasantness; both measures were not significantly correlated with time; $p =0.107$, and $p= 0.133$ respectively; for trial B $r= -0.003$ for slope of pain intensity versus time and temperature; $r = 0.195$ for pain unpleasantness; both measures were not significantly correlated with time; $p =0.991$, and $p= 0.505$ respectively.

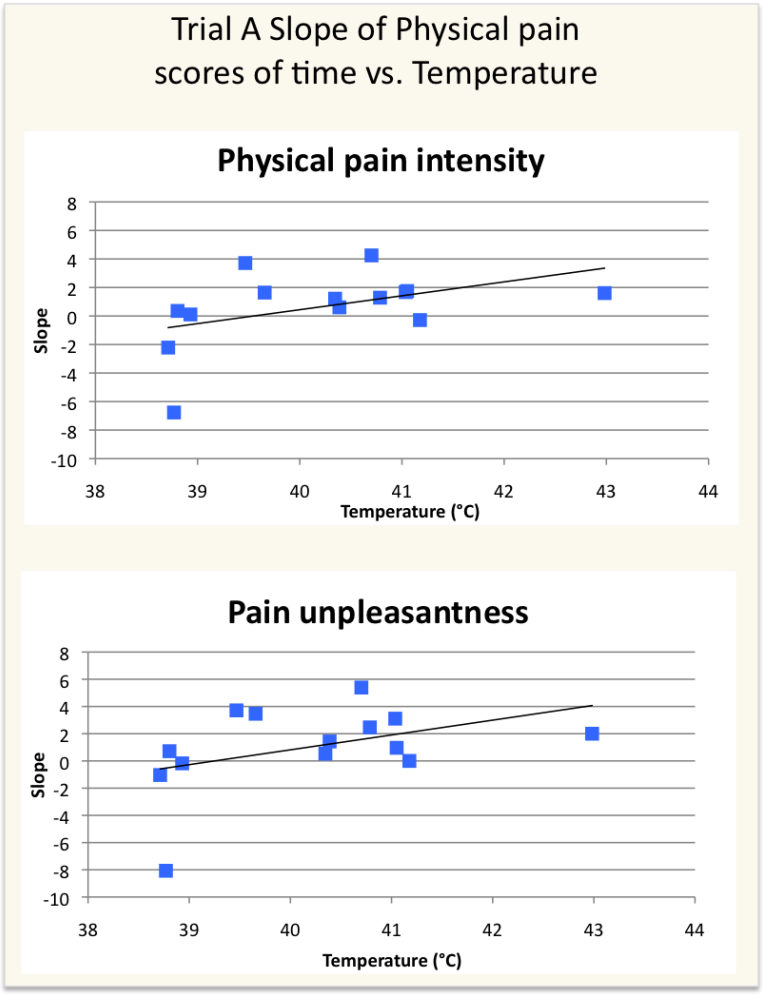


Figure 6.5: Slopes of subjective ratings of physical pain intensity and physical pain unpleasantness for trial A versus time. Mean slope for trial A physical pain intensity 2.56, std. ± 2.55, pain unpleasantness 1.04, std. ± 3.04; mean temperature 40.2, std. ± 1.18.

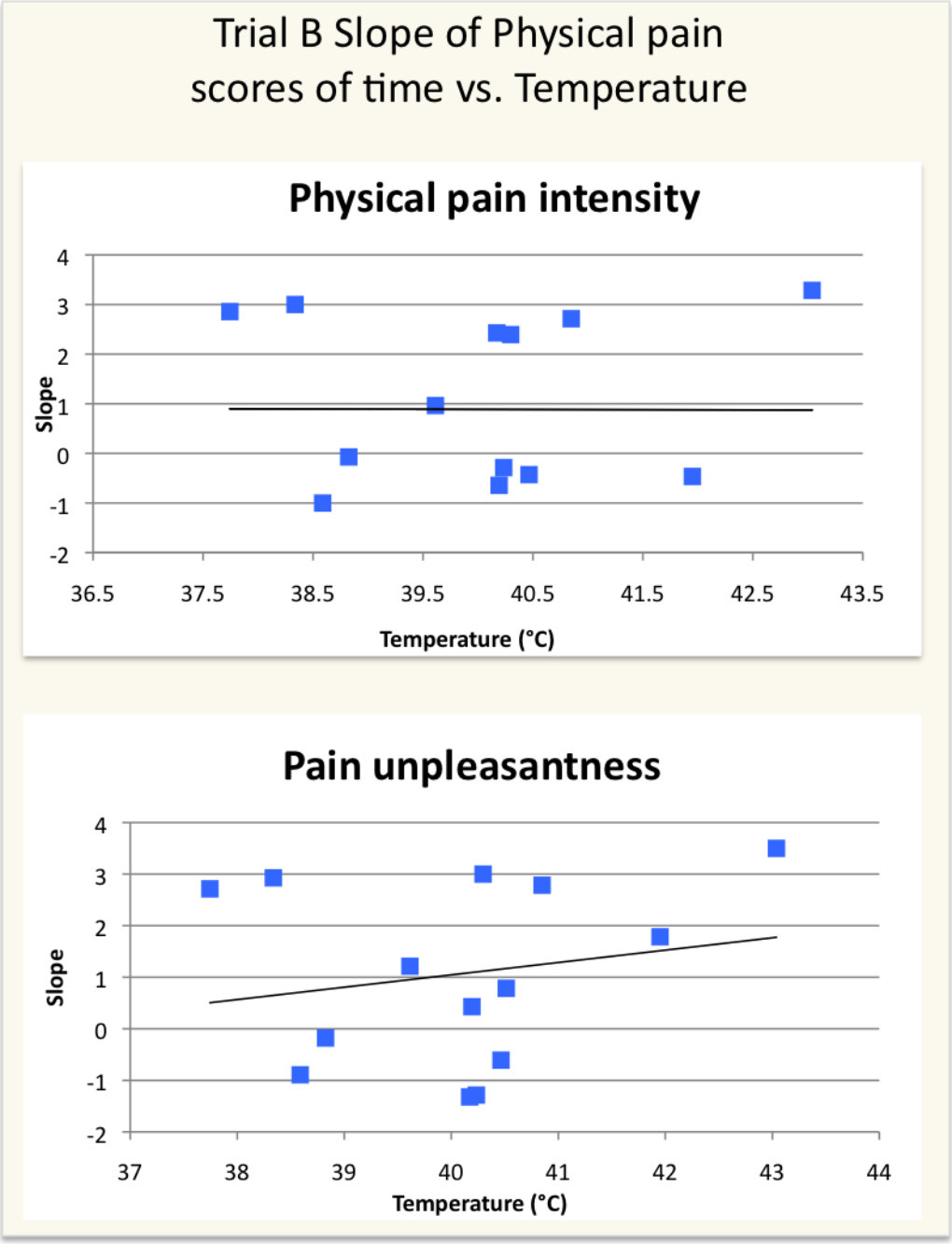


Figure 6.6: Slopes of subjective ratings of physical pain intensity and physical pain unpleasantness for trial B versus time. Mean slope for trial B physical pain intensity 0.88, std. ± 1.77, pain unpleasantness 1.06, std. ± 1.67; mean temperature 40.06, std. ± 1.36.

6.3.2 Order effects

Care was taken to ensure both trials were pseudo-randomised to prevent any effects caused by the order in which the trials were presented to the subjects. One limitation of the previous chapter was that the pain-recall trial was always presented before the control trial. As the results of the previous experiment have been attributed to learning over time, the order in which the trials are presented could determine the strength of the effect. In order to explore whether order affected pain ratings over time, individuals for whom trial A (group 1) and trial B (group 2) were presented first were analysed separately. The two-tailed Pearson product-moment correlation coefficient was calculated between average ratings for physical pain intensity over all subjects and all time-points. Results from this analysis showed that physical pain intensity and unpleasantness significantly increase with time whether preceded by a visual or a pain stimulus if presented in the first block. However, physical pain intensity and unpleasantness presented in the second trial did not have a significant correlation with time (figure 6.5-6.8).

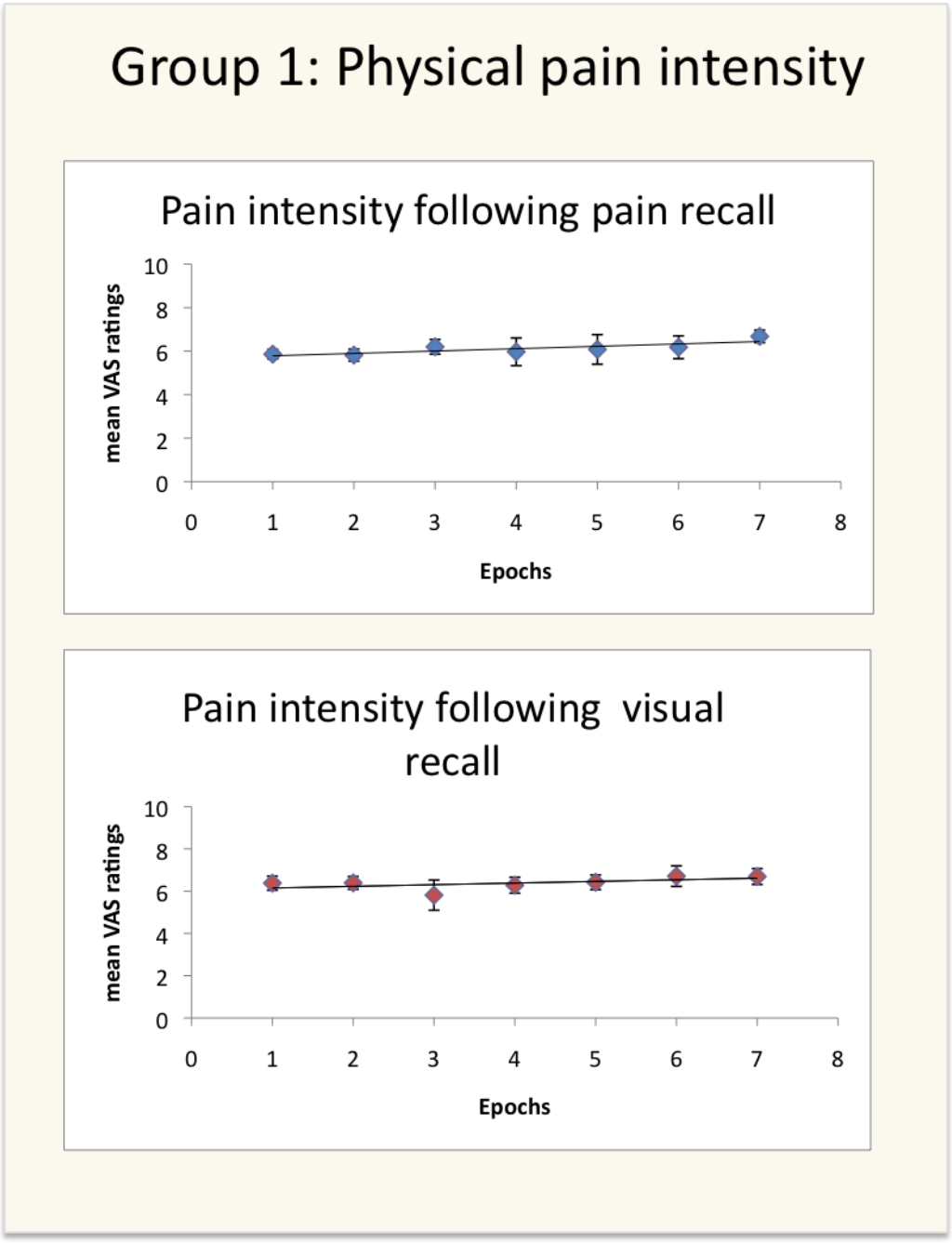


Figure 6.7: Subjective ratings of physical pain intensity for group one, in which subjects were presented first with trial A, recalling pain before trial B, recalling a visual stimulus. Physical pain intensity ratings were averaged across subjects for each epoch. Mean physical pain intensity ratings after recalling r2= 0.81 $p < 0.01$; mean physical pain intensity ratings after recalling a visual stimulus r 2=0.56 not significant, $p = 0.19$

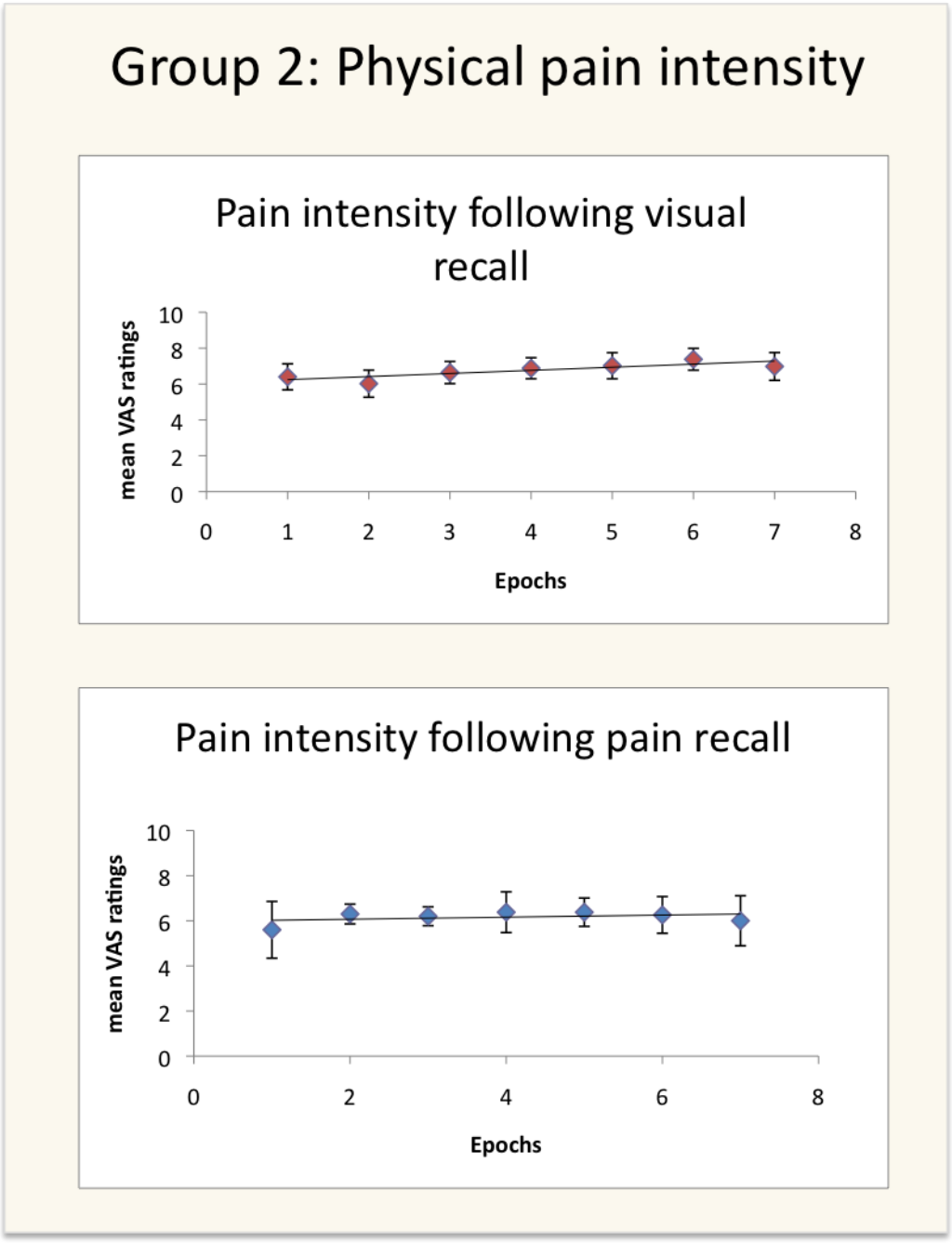


Figure 6.8: Subjective ratings of physical pain intensity for group two, in which subjects were presented first with trial B, recalling a visual stimulus before trial A, recalling a painful stimulus. Physical pain intensity ratings were averaged across subjects for each epoch. Mean physical pain intensity ratings after recalling r2= 0.83 p <0.05; mean physical pain intensity ratings after recalling a painful stimulus r2=0.36 not significant p= 0.43

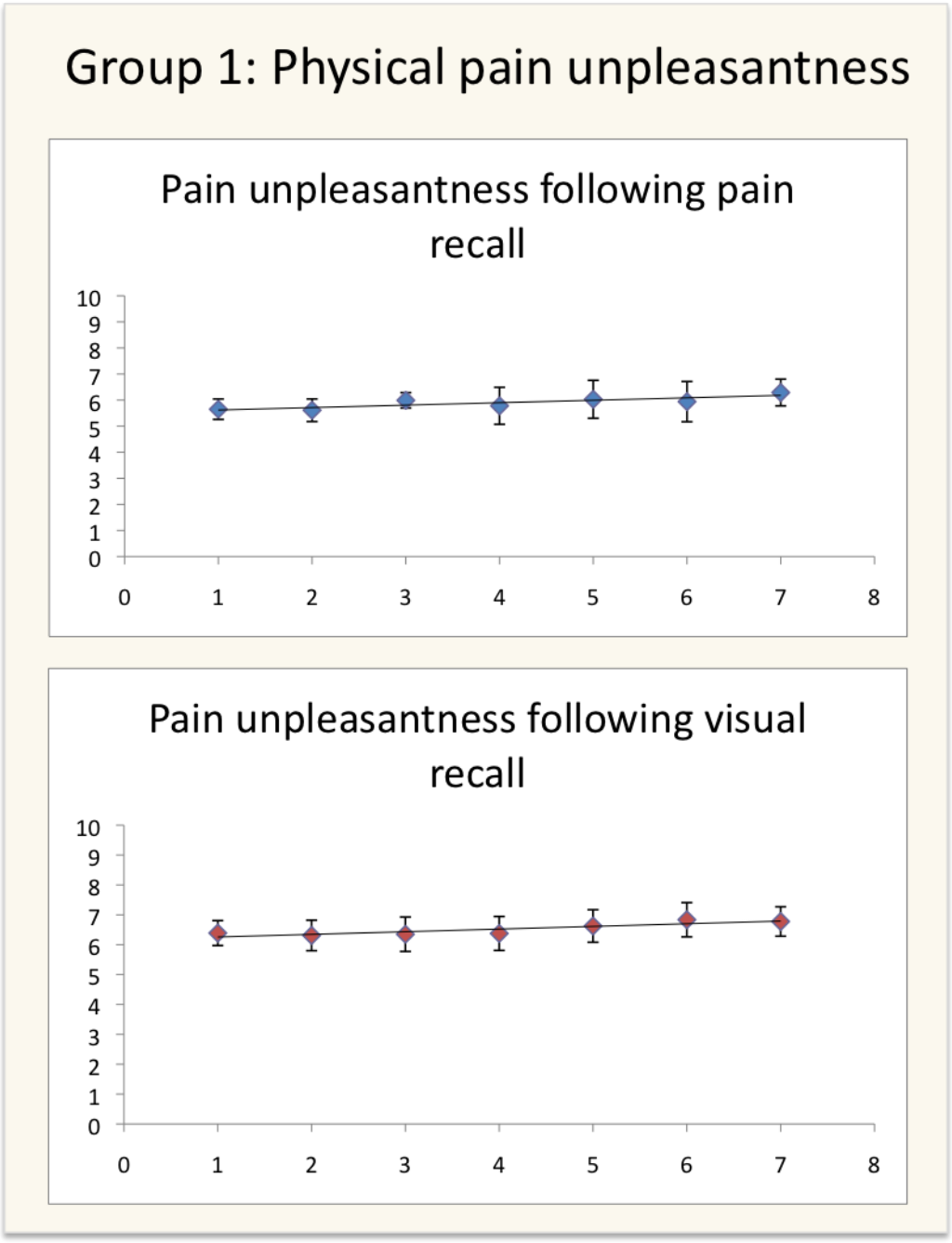


Figure 6.9: Subjective ratings of physical pain unpleasantness for group one, in which subjects were presented first with trial A, recalling pain before trial B, recalling a visual stimulus. Physical pain unpleasantness ratings were averaged across subjects for each epoch. Mean physical pain unpleasantness ratings after recalling, $r^2= 0.85$ $p<0.05$; mean physical pain unpleasantness ratings after recalling a visual stimulus $r^2=0.87$ $p > 0.05$

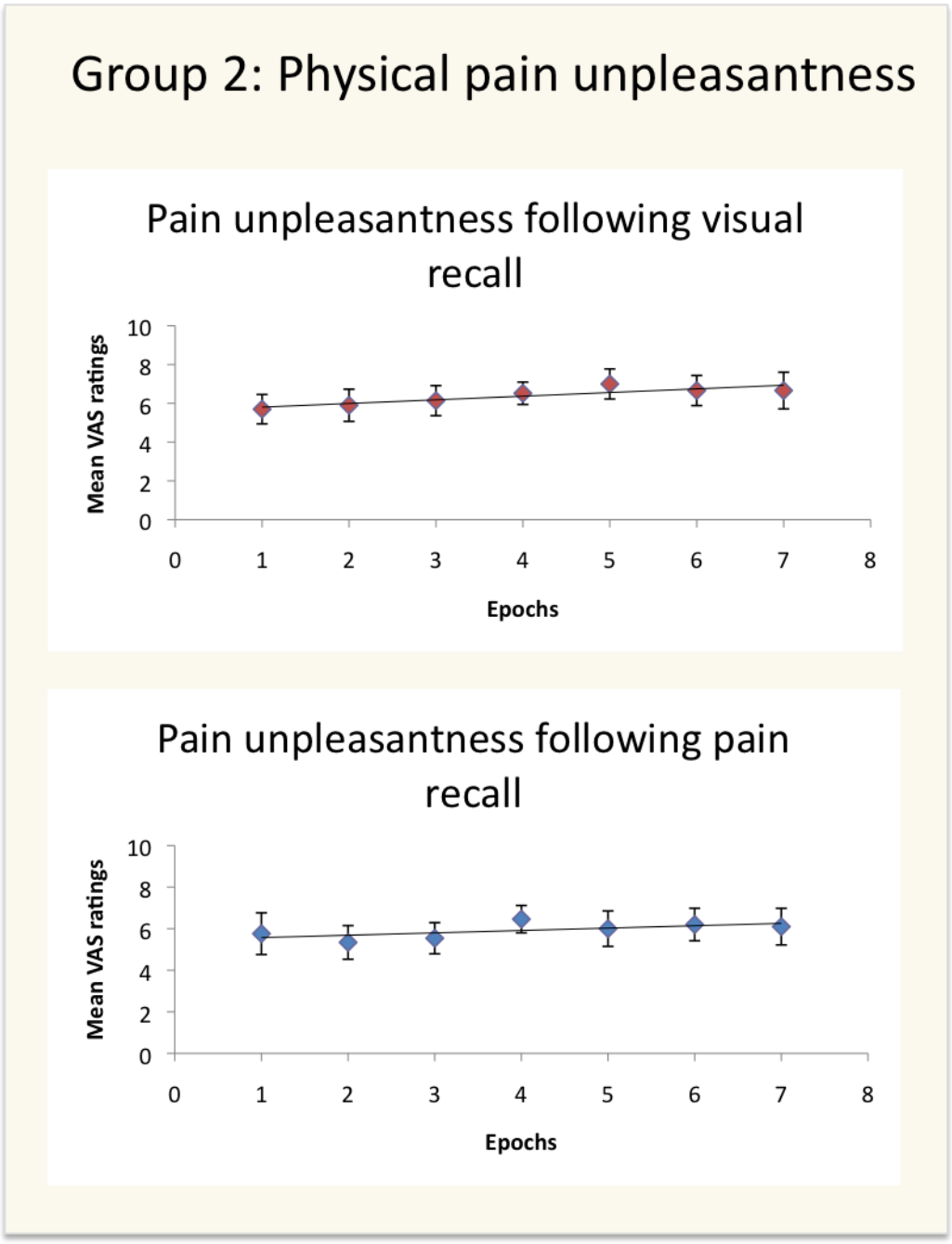


Figure 6.10: Subjective ratings of physical pain unpleasantness for group two, in which subjects were presented first with trial B, recalling a visual stimulus before trial A, recalling a painful stimulus. Physical pain unpleasantness ratings were averaged across subjects for each epoch. Mean physical pain unpleasantness ratings after recalling a visual stimulus, r^2= 0.87 $p<0.05$; mean physical pain unpleasantness ratings after recalling a painful stimulus r^2=0.63 not significant p = 0.13

6.3.3 Explanatory variables

In order to further describe the differences between group one and group two, scores for vividness for both trials, for both groups were correlated with scores for physical pain intensity and pain unpleasantness. However, vividness scores were not significantly correlated with either measure in either group (for group one physical pain intensity following a pain stimulus r^2 =0.38, p = 0.398; following a visual stimulus r^2 =0.19, p = 0.68; for group two following a pain stimulus r^2 =0.38, p = 0.398, and following a visual stimulus r^2 =0.56, p = 0.19; for group one physical pain unpleasantness following a pain stimulus r^2 =0.49, p = 0.26; following a visual stimulus r^2 =-0.1, p = 0.98; for group two following a pain stimulus r^2 =0.05, p = 0.92, following a visual stimulus r^2 =0.65, p = 0.11).

Physical pain intensity and unpleasantness scores that followed pain recall did show a significant correlation with recalled pain intensity scores for group one (figure 6.9 and 6.10), only (for group one, recalled pain intensity correlated with physical pain intensity scores r^2 =0.805, $p<0.05$, recalled pain intensity correlated with physical pain unpleasantness scores for group one r^2 =0.88, $p<0.01$; not significant correlation scores group two for recalled pain intensity and physical pain intensity r^2 =-0.44 p = 0.93, for physical pain unpleasantness r^2 =0.71, p=0.07).

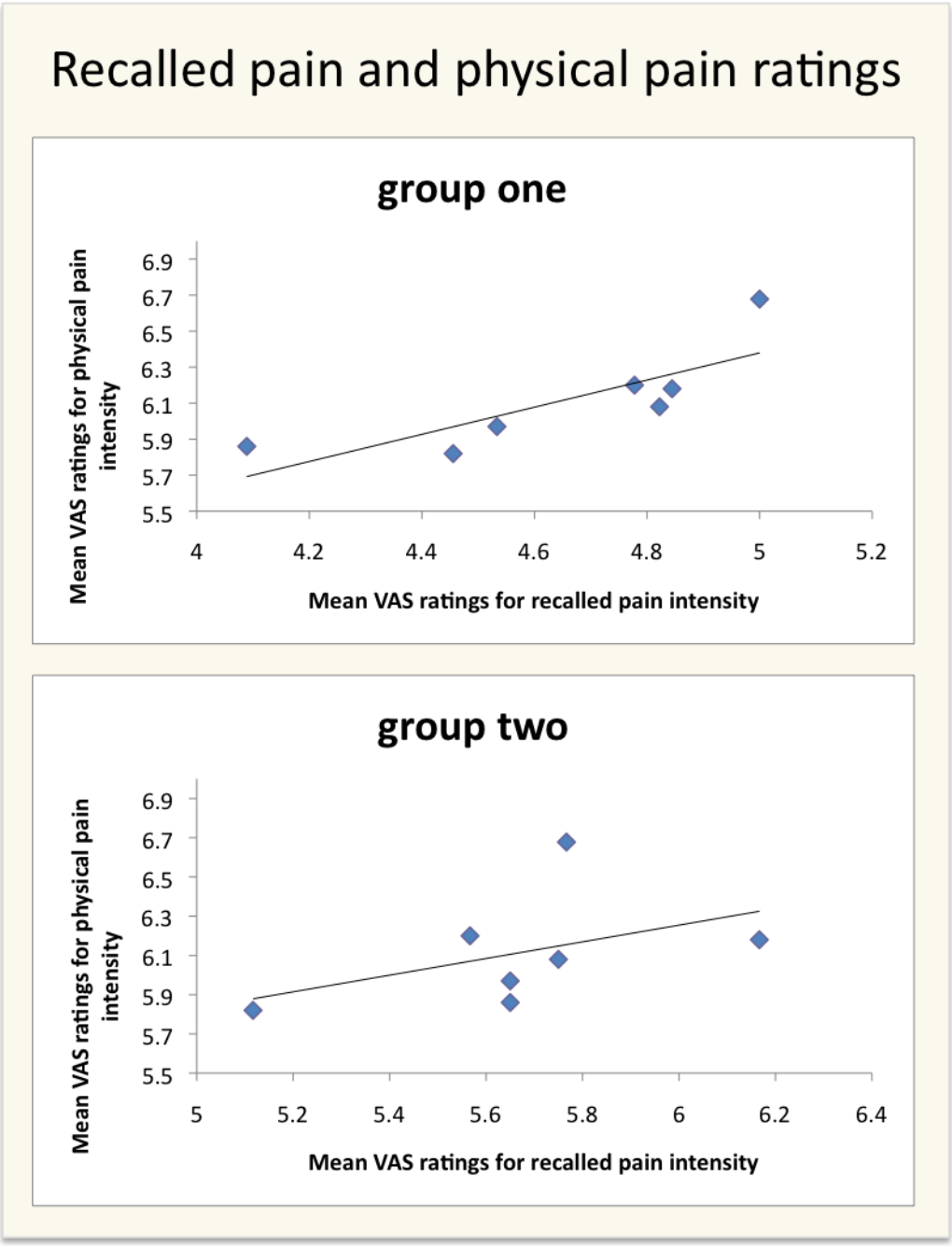


Figure 6.11 Subjective ratings for physical pain intensity and recalled pain intensity for group one, in which subjects were presented first with trial A, and group two, in which subjects were first presented with trial B. Physical pain unpleasantness ratings were averaged across subjects for each epoch. For group one, recalled pain intensity correlated with physical pain intensity scores $r2 = 0.805$, $p<0.05$, not significant correlation scores group two for recalled pain intensity and physical pain intensity $r2 = -0.44$ $p = 0.93$.

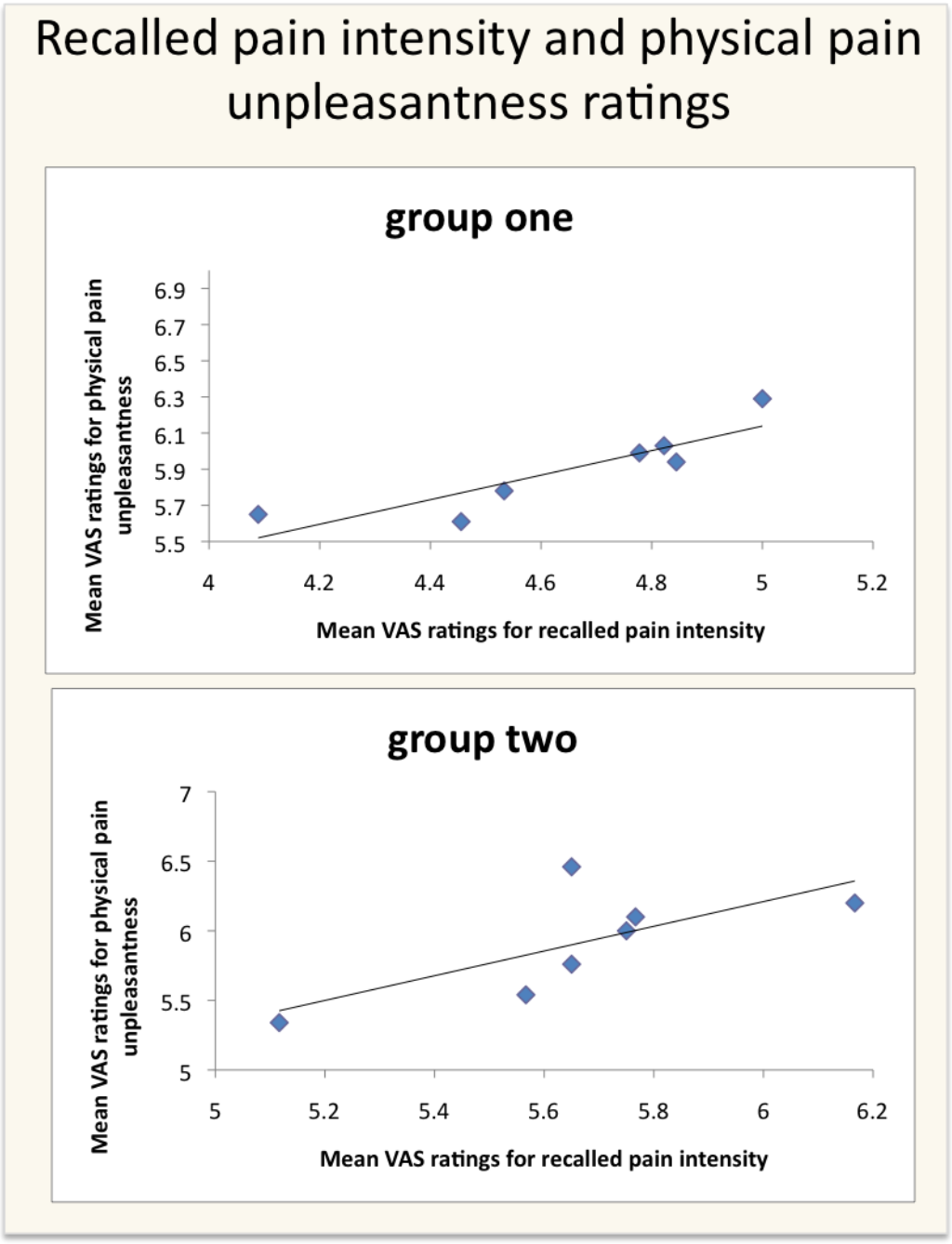


Figure 6.12 Subjective ratings for physical pain unpleasantness and recalled pain intensity for group one, in which subjects were presented first with trial A, and group two, in which subjects were first presented with trial. Physical pain unpleasantness ratings were averaged across subjects for each epoch. Recalled pain intensity correlated with physical pain unpleasantness scores for group one $r2 = 0.88$, $p<0.01$; however, this was not significant for group two $r2 = 0.71$, $p=0.07$.

6.3.4 Main effect of the manipulation

The order in which the trials were presented affected the correlation of physical pain intensity and unpleasantness over time. However, mean ratings of all subjects across epochs showed that despite the order of the trials, physical pain ratings that followed pain-related recall were consistently lower than ratings that followed visual recall (figure 6.11, and 6.12). A 2-tailed t-test of physical pain intensity scores for group one following a visual stimulus and ratings following a pain stimulus was not significant $t = 2.05$, where $p = 0.89$, however, physical pain intensity ratings for group two following a visual stimulus and ratings following a pain stimulus was shown to be significant, $t = 3.5$ $p < 0.05$. A 2-tailed t-test for ratings of physical pain unpleasantness following a visual stimulus and a pain stimulus for group one was shown to be significant $t = 9.5$ $p < 0.01$, and group two $t = 3.4$, $p < 0.05$.

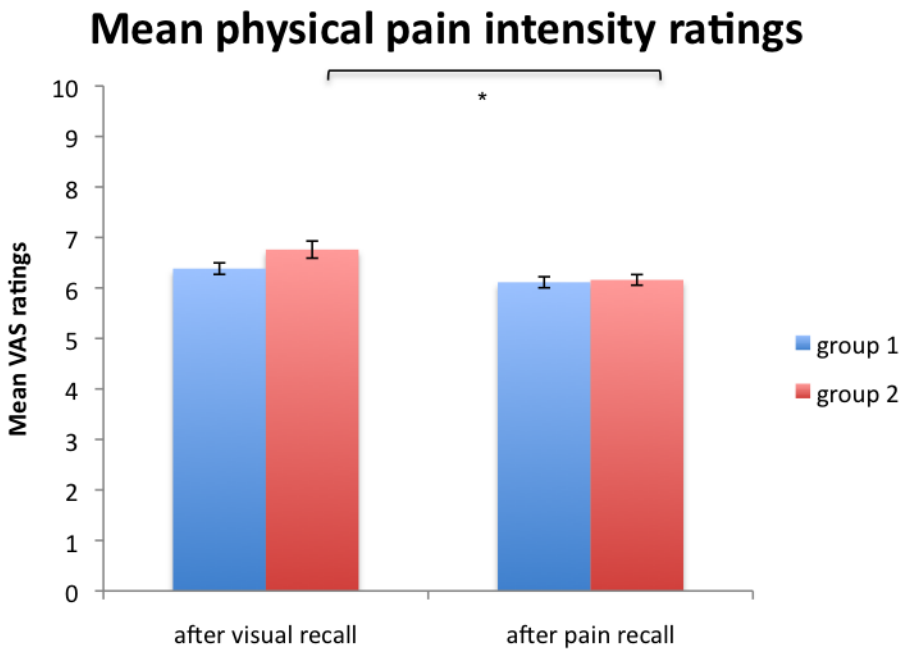


Figure 6.13: Subjective ratings of physical pain intensity for group 1 and group 2, after a visual and pain recall averaged across individuals for all time points. Mean physical pain intensity after visual recall for group one ± SE 6.4 ± 1.14, for group two ± SE 6.76 ± 1.69; mean physical pain intensity after pain recall for group one ± SE 6.11 ± 1.1, for group two SE 6.2 ± 1.05. Mean physical pain intensity ratings were significant for group 2 using a 2-tailed t-test, $p < 0.05$, indicated by *.

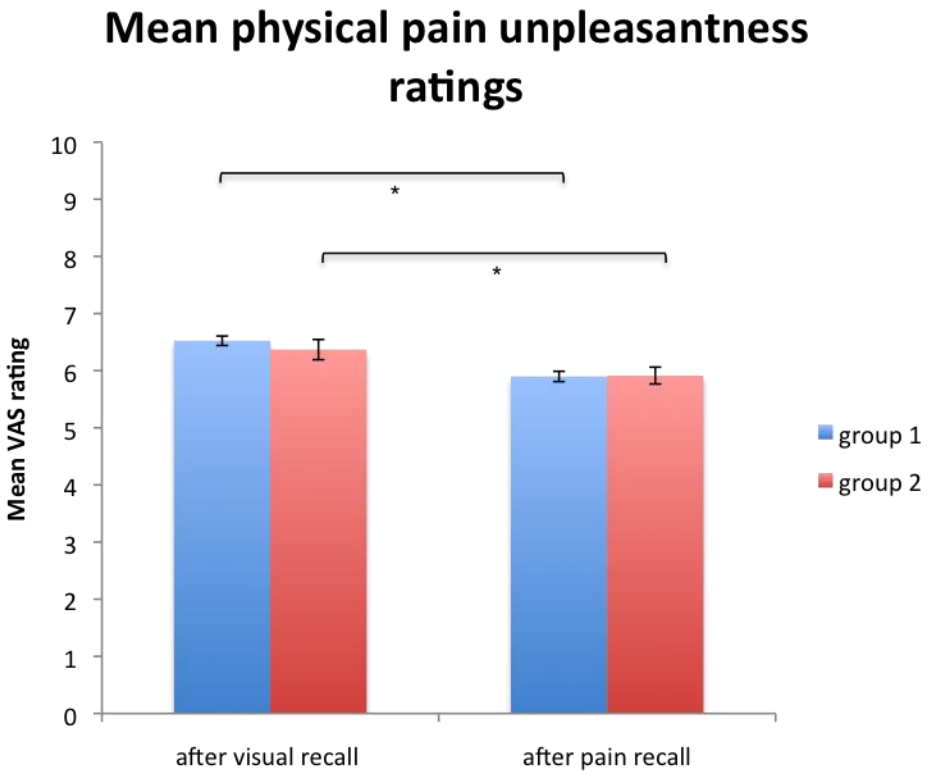


Figure 6.14: Subjective ratings of physical pain unpleasantness for group 1 and group 2, after a visual and pain recall averaged across individuals for all time points. Mean physical pain unpleasantness after visual recall for group one ± SE 6.5 ± 0.08, for group two ± SE 6.3 ± 0.18; mean physical pain unpleasantness after pain recall for group one ± SE 5.90 ± 0.09, for group two SE 5.91 ± 0.15. Mean physical pain unpleasantness ratings were significant for group 1 and 2 using a 2-tailed t-test, $p < 0.05$, indicated by *.

6.3.5 Imaging Data

A group analysis was run averaging data across all 15 subjects for both trials. Contrasting the activation during the first pain stimulus (P1) and the second pain stimulus (Malhotra-Kumar et al., 2010), the observed results support our hypothesis that an imagery task changes subsequent pain activation.

Significant effect of imagery

In Trial A, a more extended network of brain areas was shown to be active during P1 than in P2. Structures that were significantly more active in P1 relative to P2 included bilateral dlPFC, right superior frontal, bilateral superior parietal, bilateral intraparietal, bilateral inferior parietal cortex, bilateral lingual gyrus, bilateral lateral occipital cortex. The same was true for Trial B, where the same contrast revealed activation bilaterally in the anterior intraparietal cortex, dlPFC, IFG, temporal gyrus, intracalcarine sulcus, right middle temporal gyrus, middle frontal gyrus, paracingulate gyrus, superior lateral occipital gyrus, visual cortex, and ipsilateral superior frontal gyrus (figure 6.15, table 6.1, and 6.2).

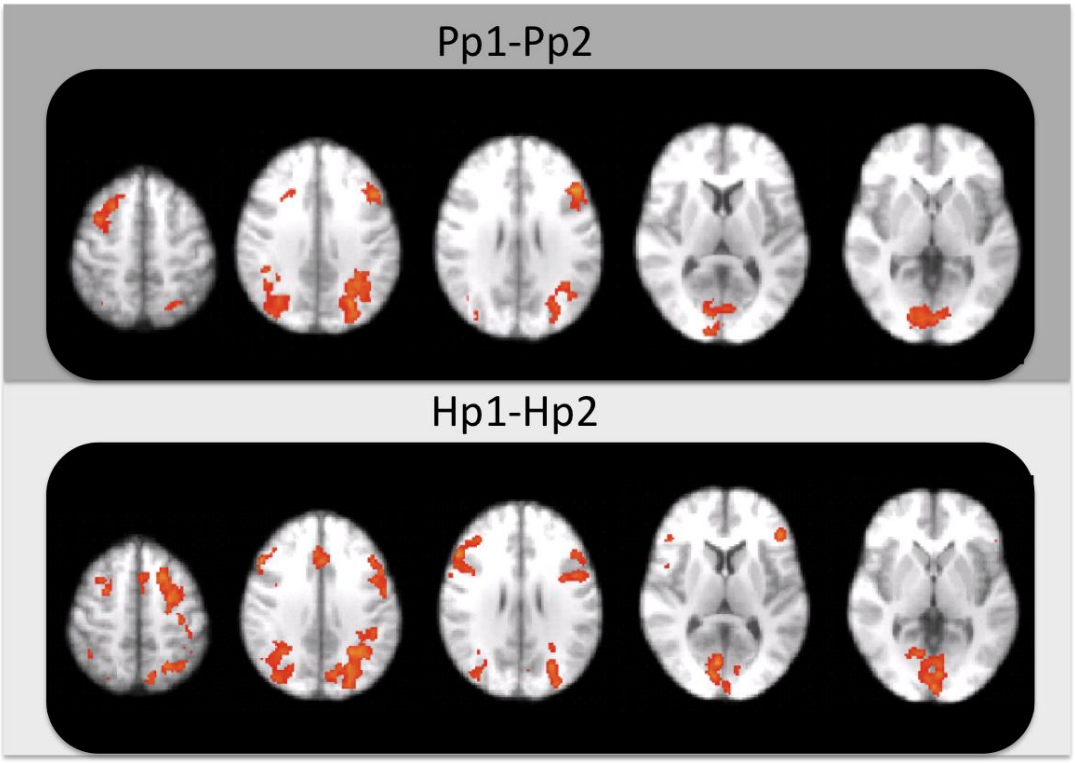


Figure 6.15: Mixed effects group contrast, comparing first and second physical pain events for the trial A (Pp1 and Pp2, respectively) and for trial B (Hp1 and Hp2). This analysis demonstrates significantly more extensive activation when individuals do not perform a recall task prior to receiving a painful stimulus, for both trials ($Z = 2.3$; $p = 0.05$). Regions active for both trials include prefrontal areas associated with negative appraisal. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates, Table 6.1, and 6.2

Significant difference between pain and house

Looking at significant differences between P1 and imagined pain we find bilateral activation in the anterior insula, posterior insula, and contralateral activation in the putamen, accumbens, ACC, posterior cingulate cortex, secondary somatosensory cortex, as well as the amygdala. As fewer areas are activated during P2, fewer regions are specific to physical pain; thus a comparison of P2 and recalled pain (P2 > imagined pain) include bilateral anterior insula, bilateral posterior insula, and bilateral SII (figure 6.16).

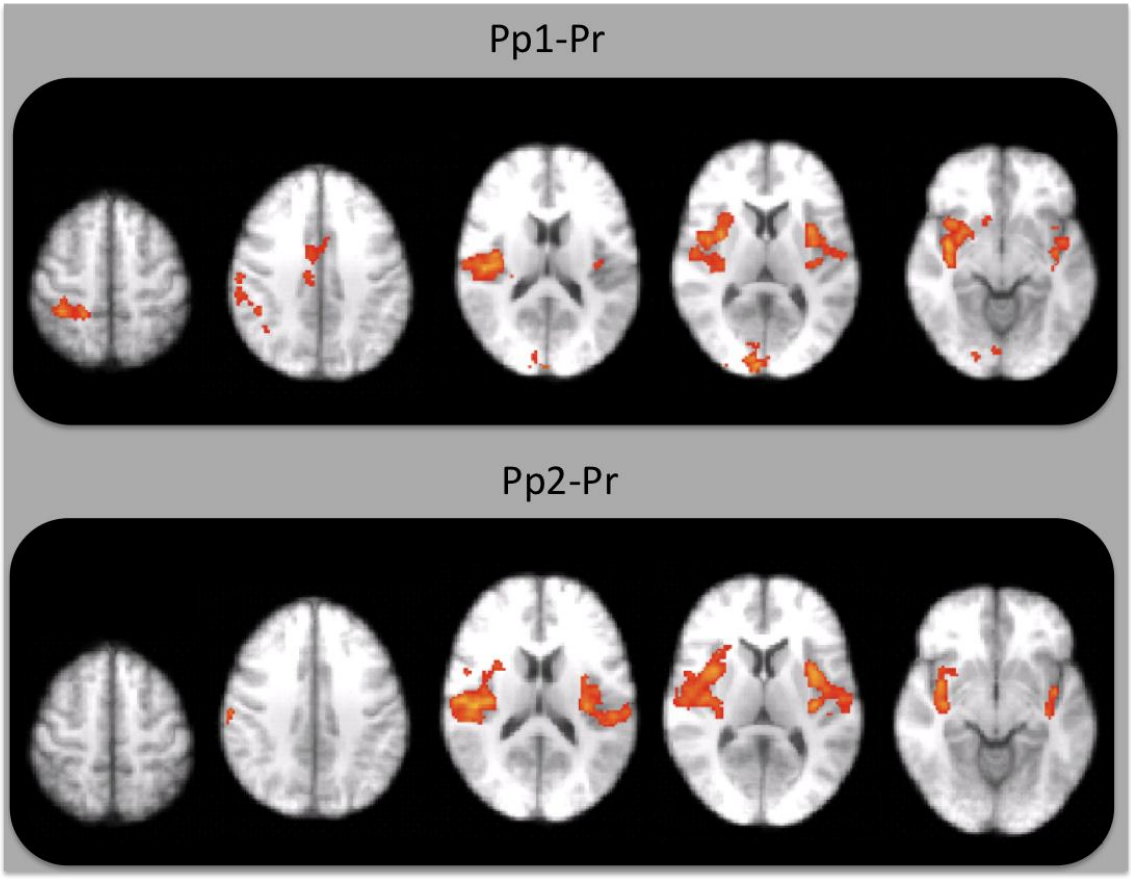


Figure 6.16: Mixed effects group contrast, comparing activation during physical pain for both pain events in trial A (Pp1 and Pp2) with activation during recalled pain (Pr) (Z = 2.3; p = 0.05). Relative to recalled pain, there seems less activation unique to physical pain in P2, after the recalled event. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis.

The reverse contrast looking at activation specific to recalled pain relative to P1 included ipsilateral SI, precentral gyrus, the paracingulate cortex, the superior frontal gyrus, and the ipsilateral middle frontal gyrus. More areas were significantly more active during recalled pain relative to P2 including bilateral middle frontal gyrus, superior frontal gyrus, superior part of the lateral occipital cortex, ipsilateral paracingulate, primary somatosensory cortex, left middle temporal gyrus, inferior frontal gyrus, and ipsilateral dlPFC (figure 6.17, tables 6.3 and 6.4).

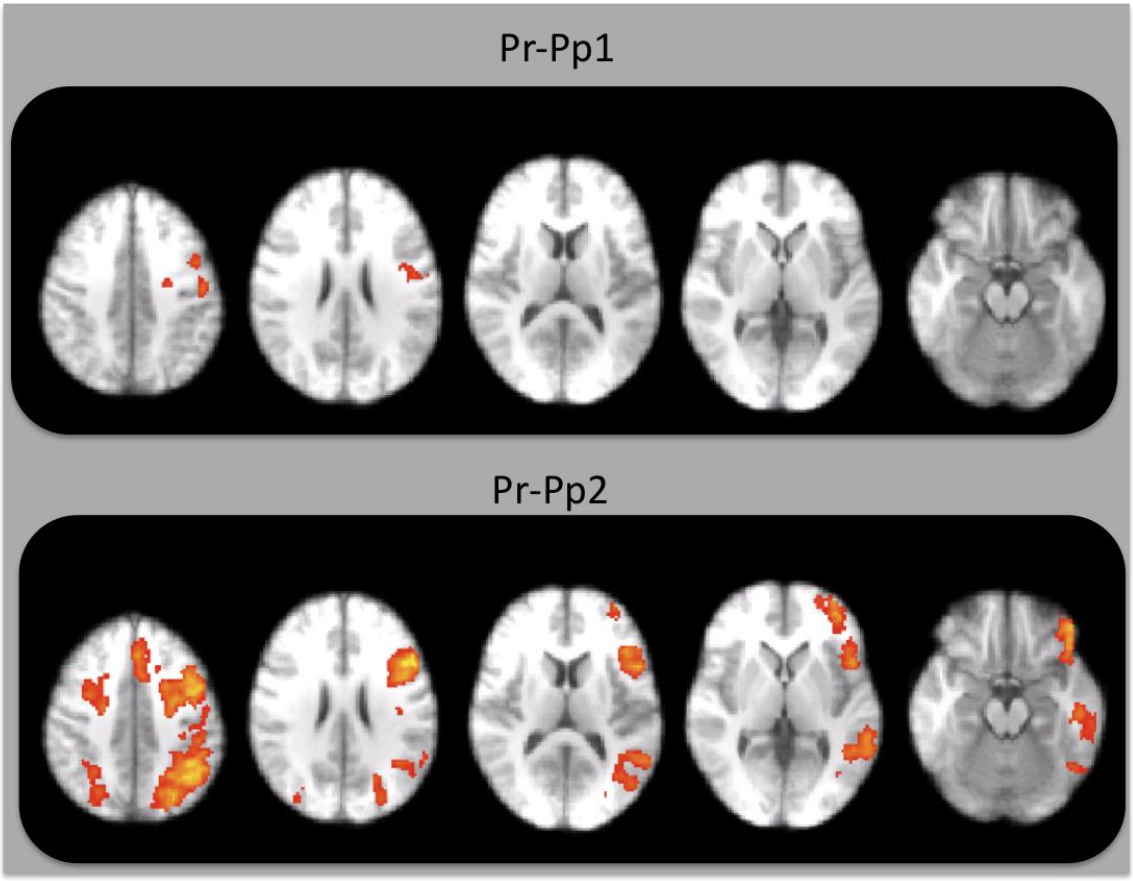


Figure 6.17: Mixed effects group contrast, comparing activation during recalled pain relative to the first and second physical pain events for trial A (Pp1 and Pp2, respectively) (Z = 2.3; p = 0.05). Again, more regions survive the subtraction as being more active during recalled pain than physical pain. These areas include an extensive network of areas associated with memory. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates, table 6.3 and 6.4

Subtraction imagined pain – house

By comparing activation during the imagery events, during which no physical pain stimulus was administered, where subjects were to respond simply to different visual cues ("imagine house" or "imagine pain"), we found significantly different patterns of activation. Subtractions comparing the imagined conditions only yielded significant differences in the recalled pain condition relative to the "imagine house" condition. These regions included many areas classically associated with pain, as well as memory areas: Bilateral anterior cingulate cortex, midcingulate,

bilateral anterior insula, bilateral dlPFC, dmPFC, vlPFC, left putamen, bilateral caudate, bilateral planum polare, bilateral IFG, bilateral paracingulate bilateral premotor cortex, bilateral pallidum, bilateral precentral gyrus, bilateral rostral acc, bilateral SII, bilateral SMA (figure 6.18, table 6.5). The reverse contrast ("imagine house" – "imagine pain") revealed nothing significantly more active in the imagined house contrast than in the imagined pain.

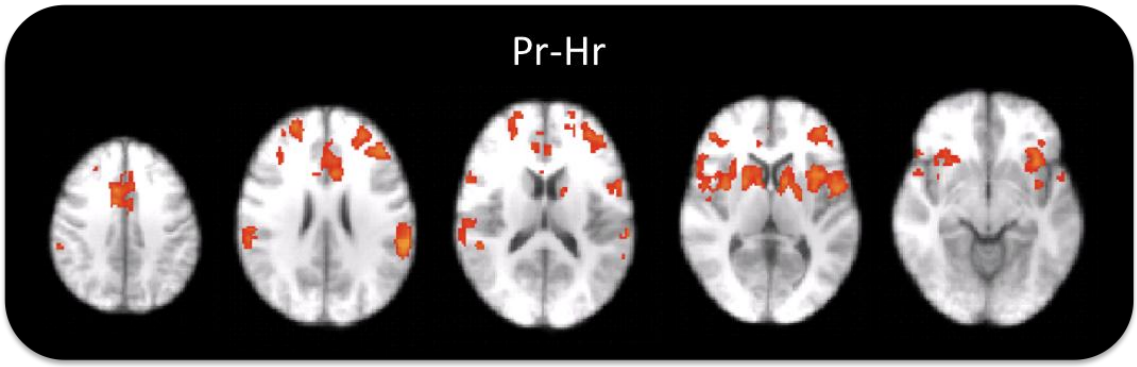


Figure 6.18: Mixed effects group contrast, exploring significant activation associated with recalling pain relative to recalling a visual scene (Pr and Hr, respectively) (Z = 2.3; p = 0.05). Regions shown to be active are all areas classically associated with pain and memory. No activation was found to be specifically more active in Hr >Pr. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates, Table 6.5.

Conjunction analysis

In order to explore areas activated during both imagery tasks, a conjunction analysis using inclusive masking was performed. Areas shown to be active during both imagined events included bilateral activation in the anterior insula, middle temporal gyrus, dlPFC, precentral gyrus paracingulate cortex, SMA, precuneus and the cerebellum. Ipsilateral activation included the IFG, superior parietal cortex, the superior part of the lateral occipital cortex, and the supramarginal gyrus (figure 6.19, table 6.6).

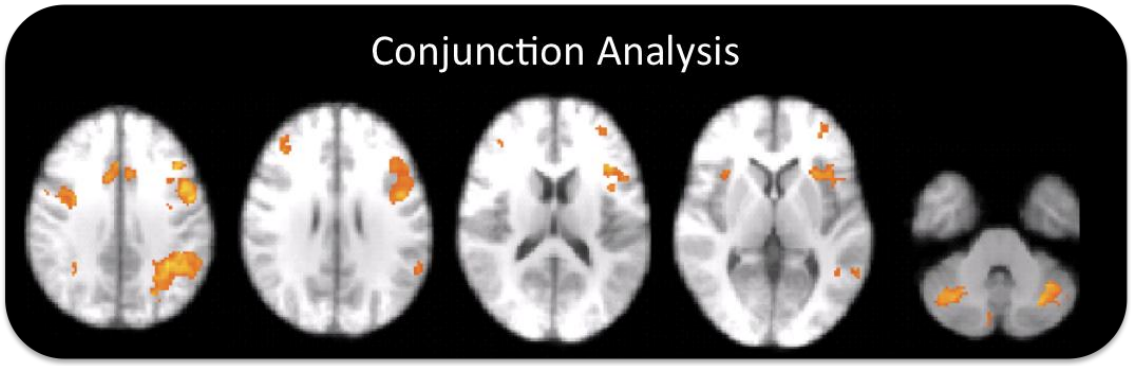


Figure 6.19: Conjunction analysis using inclusive masking of activation maps for Pr and Hr (Z = 3.0; p = 0.05), exploring activation common to both recalled conditions that survive a 3.0 threshold. Results from this contrast include areas involved in memory, imitation and self-monitoring. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates, Table 6.6

Unpleasantness in imagined scenarios

As our behavioural results demonstrated significantly lower unpleasantness scores in Trial A, after recalling pain, we explored activation during the recalled pain condition that correlated with subsequent unpleasantness scores. Results from this contrast were then compared between the trials. Areas that were observed to be significantly more active during the "imagine pain" event included bilateral anterior insula, the central opercular cortex, the caudate, the putamen, the precentral gyrus, the paracingulate cortex, the SMA, superior frontal gyrus, and the dlPFC. Ipsilateral activation was revealed in the ACC, secondary somatosensory cortex, the middle frontal gyrus, and contralateral IFG. Regions that were more active during "imagine house" relative to "imagine pain" included ipsilateral activation in the parahippocampus, the temporal fusiform gyrus, and the hippocampus. Contralateral activation was revealed in the inferior temporal gyrus, the superior parietal cortex, the superior part of the lateral occipital cortex, and the precuneus (figure 6.20, table 6.7).

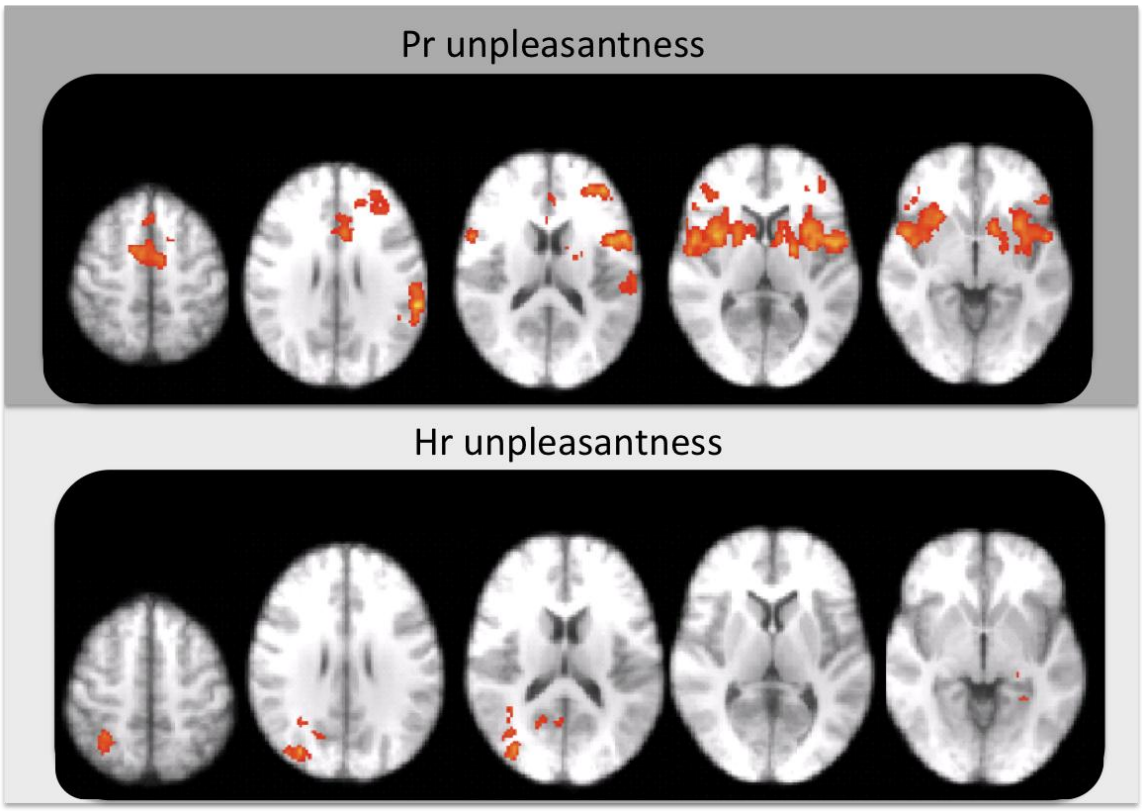


Figure 6.20: Mixed effects group contrast, using behavioural ratings for pain unpleasantness as a regressor and subtracting activation during recall in trial A and trial B (Pr > Hr and Hr > Pr) (Z = 2.3; p = 0.01). We identify regions that predict unpleasantness ratings in subsequent physical pain trials. Images are displayed in radiological convention (R – L). See Materials and methods for further details of this analysis and full tables of activation with MNI coordinates, Table 6.7.

6.4 Discussion

This study sought to establish whether recall specific to pain affected subsequent pain perception. By pairing a painful stimulus with a visual stimulus, we were able to show differential effects on pain perception between recalling a painful stimulus versus recalling a visual stimulus. Our behavioural results show both a significant manipulation effect as well as an effect over time. In Trial A, mean pain unpleasantness ratings for the physical pain after subjects recalled a painful stimulus across subjects were significantly lower in trial B after recalling a visual stimulus. We also show a significant effect of time, as physical pain intensity as well as physical pain unpleasantness ratings for both trial A and trial B are shown to increase over time. Analysing the order in which the trials were presented to subjects, we were able to demonstrate time effects from those caused by the manipulation.

Our imaging results show a significant difference in activation during physical pain without a prior recall event and after subsequent recall. This was true for both recalled conditions. A conjunction analysis established similarities between both recalled events to establish commonalities between recalling a painful event and recalling a visual stimulus. Exploring differences between recalled conditions, a subtraction analysis demonstrated significantly more activation during pain recall than visual recall. In order to explain the change in unpleasantness ratings, activity in the recalled conditions were explored to establish regions correlating with pain unpleasantness scores. These areas differed between pain recall and house recall confirming that pain-related recall affects activation during subsequent perception differently from an unrelated recall.

6.4.1 Behavioural results

Our study design allowed for the comparison of identical stimuli, which differed only in the cue that subjects were given prior to receiving the physical pain stimulus. Using a behavioural measure of this physical pain, we found that although pain intensity scores were not significantly different between trials, pain unpleasantness scores were significantly lower after subjects recalled pain than when recalling a pain-unrelated stimulus (figure 6.2). We confirm the result of our previous experiment as pain scores for both physical pain intensity and unpleasantness significantly increase over time (figure 6.3, and 6.4). In our previous experiment, we found a significant increase over time, when a pain recall task preceded a physical pain event, relative to a control trial. The pain recall trial always preceded the control trial, so the confound of possible order effects could not be discounted. In the current experiment we pseudo-randomised the trials, so that half the subjects received trial A before trial B, and the other half reversed the order in which the trials were presented. In both groups, the trial presented first demonstrated a significant increase in physical pain ratings over time. In the second trial, however, the relationship between the number of repeating epochs and physical pain ratings was no longer significantly correlated (figures 6.5-6.8).

There may be several explanations for this result. The initial increase in physical pain ratings may be attributed to sensitisation as a result of repeating the physical pain stimulus. In the previous chapter, we used a control trial consisting solely of repeating pain stimuli, and showed no such behavioural increase in pain scores. As the paradigm in the current experiment differed to the control trial in the previous chapter, it is still possible that sensitisation may play a part. In order to explore other explanations correlation tests were run between vividness scores given for the preceding recall event and subsequent physical pain scores, however these were not shown to be significant. However recalled pain intensity scores correlated significantly with subsequent

physical pain intensity and unpleasantness scores that followed for both groups in trial A (figures 6.9 and 6.10). In previous chapters, we have demonstrated the strong relationship between recalled pain and the preceding stimulus. These results demonstrate how recalled pain can affect subsequent pain ratings of both physical pain intensity and physical pain unpleasantness. This however is only observed in the first group, for which the recall pain trial was presented first. This result, as well as the observation that this effect is present in both visual and pain trials, suggests an additional factor causes a gradual increase over time in the trial presented first.

The role of attention may be worth exploring as a possible candidate. In the trial A, pain recall attempts at focusing attention toward this present stimulus, this focus may initially act to increase physical pain ratings, as subjects improve their ability to recall (Miron et al., 1989, Villemure and Bushnell, 2002). If the pain recall task is presented second, subjects may not be attending to the task as well, and therefore the effect may not be as powerful. Visual recall, on the other hand, may serve as a distracter task increasing the level of uncertainty, therefore increasing physical pain ratings (Dannecker et al., 2003, Ploghaus et al., 2000).

6.4.2 Main effect of the manipulation

Despite increasing trends, physical pain intensity and unpleasantness scores for both groups were consistently lower in trial A following pain-related recall, than in trial B following pain unrelated recall (figure 6.11 and 6.12). This result is consistent with previous research involving imagery and attention management strategies, such as mindfulness meditation (Brefczynski-Lewis et al., 2007, Grant et al., 2011, Moseley, 2007, Ramachandran and Altschuler, 2009). Results comparing the effects on subsequent physical pain perception of pain-related recall and visual recall suggest that pain-relevant imagery aids in contextualising physical pain, and therefore can reduce the affective quality of physical pain.

Having examined the theory of internal models in the previous chapters, it is possible that the “imagine pain” event could act as part of the forward sensory model. This model predicts the sensory consequences of an event. Mental representations of pain have been shown to shape subsequent subjective ratings of pain and associated neural events (Koyama et al., 2005a). This has been demonstrated looking at prospective imagery, whereas pain imagery in the current study relates to previous recall of pain. Both memory processes have been suggested to form part of a generalised core-brain network, which includes imagining new events, recalling the past and simulating the future (Buckner and Carroll, 2007, Schacter et al., 2007a). Keeping in the mind the forward dynamics model, this future prediction, based on previous recall, can in turn shape subsequent neural responses to pain.

Our result is consistent with reductions in pain scores resulting from motor and visual imagery. The use of guided imagery and mirror imagery has been used effectively in patients suffering from chronic pain as it is said to correct for a cognitive mismatch between internal expectation and external sensory cues (Gregory, 1980, Ramachandran and Altschuler, 2009). Online sensory processing relies on the same areas responsible for sensory recall (Harris et al., 2001). In this way memory for pain may affect pain perception, and manipulating the memory template can change expectation. Repeated rehearsal of physical pain events may result in a more reliable mental representation and expectation of subsequent pain. This may increase certainty concerning the event, and therefore result in lower pain ratings (Dannecker et al., 2003, Ploghaus et al., 2003).

Many studies involving hypnosis and mindfulness mediation have explored specific reductions in pain unpleasantness scores relative to pain intensity scores. Many studies have shown that subjects under hypnosis and meditators can significantly reduce pain unpleasantness scores (Brown and Jones, 2010, Perlman et al., 2010, Rainville et al., 1999a). In studies using

hypnosis, it has been suggested that less hypnotic involvement is necessary to produce this effect (Rainville et al., 1999a). Just as different brain mechanisms are responsible for processing sensory and affective qualities of pain, they seem to be encoded separately in memory (Albanese et al., 2007a, Morley, 1993). These techniques therefore may be specifically modulating activity in regions associated with affective pain processing.

Mindfulness meditation

Obtaining the same results in experiments that utilise mindfulness meditation practices may be due to the fundamental objectives of this technique. Mindfulness meditation involves specifically focusing attention to a present stimulus with an emphasis on unbiased judgement (Brown and Jones, 2010, Perlman et al., 2010). This technique shares many similarities to other imagery techniques, and the paradigm utilised in this study. Trial B introduced a recall event unrelated to pain, and therefore may be regarded as a distracter task, prohibiting the participant from attending to the previous pain stimulus. Whereas, trial A involved a cognitively demanding task, for which subjects were instructed to specifically attend to intensity qualities of the preceding painful stimulus. Analogous to mindfulness meditation practices, however, the context in which pain was recalled was neutral. By the nature of being an "imagined" pain event, it however should have seemed non-threatening, as subjects were told no painful stimulus would be administered during the recalled event. Participants were also made aware that this was an experimental trial, with few related risks. As such, we hoped to establish a neutral context with which to experience pain. The recalled pain event demands focused attention on the stimulus itself, which may not initially suggest a reduction in pain unpleasantness.

However, a recent study exploring the efficacy of experienced meditators in focusing attention away from the stimulus, found the opposite result (Brown and Jones, 2010). The training of mindfulness meditation involves specifically focusing attention to the stimulus, but away from

the effects of anticipation. In this way anticipatory effects, which normally can increase pain perception are replaced with less negative bias (Perlman et al., 2010). This process may be considered to have the opposite effect of catastrophising. Catastrophising, as a result of persistent rumination on the negative aspects of pain, increases subjective perception of pain (Edwards et al., 2006, Sullivan et al., 2006a, Sullivan et al., 2005, Sullivan et al., 2006b). As demonstrated in this study, focused attention on aspects of a painful experience, with a low-threat value, can provide a neutral context for subjects to evaluate the painful experience. This may reduce effects of anticipation, and therefore show a significantly lower perception of pain unpleasantness.

Perceiving pain before and after imagery

While few imaging studies have explored this phenomenon, one recent study by Grant et al. exploring the effect of meditation on pain unpleasantness found significantly lower activation in pain related areas in a between subjects design comparing a group of participants highly experienced in meditation and a naïve control group (Grant et al., 2011). In our present study, we confirm these results using a within subjects design, using only a cohort of naïve subjects with no previous training. A significantly different brain activation map associated with physical pain was demonstrated in both trials before and after having recalled pain (P1 and P2 respectively). The limitations of the study design prevented getting subjective ratings after P1, and therefore we are unable to measure subjective differences in pain for these events. Neural activation was shown to be significantly less extensive after the recalled event. Interestingly, in meditation studies, a reduction in BOLD activation is associated with the meditators group, who reported significantly lower unpleasantness scores (Brown and Jones, 2010, Grant et al., 2011). In the study by Grant and colleagues, the areas showing the highest decrease in activation in the experienced meditator group included the dorsolateral prefrontal cortex, the middle frontal gyrus, and the

mPFC/orbitofrontal cortex. In the current study, in both trials these areas were less active during physical pain after subjects performed a recalled task (Grant et al., 2011).

Reductions in BOLD activation following imagery was further emphasised by a contrast comparing physical pain – recalled pain, in which only the insula cortex and secondary somatosensory cortex were observed to be specific to physical pain, although the same analysis produced a much more extensive network (Malhotra-Kumar et al., 2010). Areas more active during imagery ("Imagine pain") show a range of areas specific to pain recall relative to imagining a visual "house" stimulus, and a reverse contrast (imagined house > imagined pain) reveals no regions specific to imagining the house. These results further demonstrate both the differences between the imagery priming tasks and the success with which subjects were able to respond to the different "imagine" cues. Furthermore, we report unique activation specific to pain related recall, which we posit to be a result of focusing attention toward the stimulus, in order to initiate a neutral appraisal of the pain and reduce the affective qualities of pain. To explore which areas characterise recall fundamental to both imagery tasks, a conjunction analysis identified areas, including the anterior insula, SMA, dlPFC, IFG, cerebellum and the precentral gyrus are all associated with memory, imitation and self-monitoring (Albanese et al., 2007a, Craig, 2009, Harris et al., 2002, Kim, 2010, Molenberghs et al., 2009).

Imagery and pain unpleasantness

Our behavioural results show a significant difference in pain unpleasantness scores dependent on which recall condition preceded the physical pain stimulus. As such, we hypothesised that activation during the recalled condition would predict unpleasantness scores. To specify regions that predicted unpleasantness for each trial relative to the other a subtraction contrast was run. Activation during recalled pain relative to recalled house that correlated with subsequent ratings for unpleasantness revealed an extensive network of regions classically

associated with pain. These included regions that were found to predict unpleasantness ratings in the experiment by Grant and colleagues, namely the IFG, the ACC and the dlPFC. Regions specific to the house trial included structures classically associated with recalling a scene such as the parahippocampal region, and the hippocampus (Grant et al., 2011). Activation that predicts unpleasantness ratings in both trials isolate areas that are fundamental to vivid recall of each stimulus. It may be suggested, therefore, that the success with which subjects were able to recall the stimulus determines the effect on subsequent pain ratings. Importantly, regions identified in previous studies as predicting a reduction in affective pain qualities were only present in the recalled pain contrast (Grant et al., 2011).

Attention effects on pain unpleasantness

By contrasting the recalled conditions and comparing the relative effects of imagery on subsequent pain perception, we are able to show the benefits of specifically directing attention toward salient stimuli to reduce pain unpleasantness. This result discards the possibility that the effect demonstrated in Chapter 5 was due simply to the element of distraction inherent in adding an additional task between pain stimuli. Although the paradigms utilised in these two experiments were similar, significant reductions in pain unpleasantness were not found when conducting a behavioural experiment relative to a control, not including a recalled event. One possible explanation for this might be that this experiment used a single cohort and comparisons could be made within-subjects not between subjects, thus decreasing inter-subject variability. Although the study design necessitated including a recall event in both trials, we were able to demonstrate significant neural changes between both physical pain events within each trial. Each repeated epoch included one physical pain event immediately preceded by a recall-pain event, and one that did not. In this way, we could compare the neural correlates of physical pain with and without prior recall.

Prefrontal cortex and neutral appraisal

Supporting results from previous studies (Brown and Jones, 2010, Grant and Rainville, 2009), we demonstrated significantly less activation in lateral and medial prefrontal areas during pain perception after subjects perform a recall task. It has been suggested that these areas, being associated with appraisal, demonstrate a "learned state" attributed to increased experience (Grant et al., 2011). However, as our manipulation did not include trained individuals we are able to, perhaps, extend this application more broadly. Lateral and medial prefrontal areas are commonly considered to encode for affect, associating affective value to primary reinforcers in learning. Error neurons within these areas have been associated with negative reward prediction and therefore learning of negative affect (Grabenhorst et al., 2008, Rolls and Grabenhorst, 2008). Previous research in meditators as well as the study presented here, suggest that neutral appraisal, or perhaps less learning of imposed negative value associated with a physical stimulus, may result in reductions in activity in these areas and subsequent reductions in pain unpleasantness ratings (Brown and Jones, 2010, Grant et al., 2011).

Training effects and possible therapeutic uses of imagery

While our study shares many common elements with others using hypnosis and meditation, it is unique in that subjects have no prior training. Other studies use naïve subjects as a control for participants with extensive experience in meditation. Every one of these studies shows that experience heightens the effect demonstrated by our results (Grant et al., 2011, Tang et al., 2007, Vestergaard-Poulsen et al., 2009).

This provides exciting potential for possibly beneficial clinical treatments in patients suffering from chronic pain. Just as previous research has demonstrated reductions in pain unpleasantness in chronic pain sufferers with mindfulness training (Brown and Jones, 2010, Grossman et al., 2007, Morone et al., 2008), we demonstrate the same effect when no prior

history of pain exists. As such, these mechanisms involved in reducing affective qualities of pain may prove effective as learnable skills to prevent or ameliorate pain suffering, which can improve with training (Grant et al., 2011, Tang et al., 2007, Vestergaard-Poulsen et al., 2009)

Future research might look more specifically at regions identified as being more or less active after pain recall and affecting affective qualities of subsequent pain recall, such as the lateral and medial prefrontal cortices, and perhaps plastic changes over time. Meditation studies suggest the possibility that the effect of decreased pain unpleasantness increases with training and experience (Grant et al., 2011, Hölzel et al., 2008). This paradigm might be adapted to allow for training and increased experience to investigate whether the same learning may effect a long-term change, either behaviourally, in neural activation or even in possible changes in white-matter connectivity.

6.5 Tables of activation

Pp1-Pp2

		voxelwise extent	Z score	X	Y	Z
superior lateral occipital	left	1572	3.67	-24	-58	42
occipital pole	right		3.17	8	-94	10
superior frontal gyrus	right		2.84	26	10	60
angular gyrus	left		3.57	-40	-58	44
angular gyrus	right		3.13	44	-50	42
supramarginal gyrus	right	1012	3.7	46	-40	42
supramarginal gyrus	left		3.36	-30	-48	34
intracalcarine cortex	right	1009	3.44	12	-82	6
intracalcarine cortex	left		3.2	-4	-84	0
midde frontal gyrus	right	539	3.4	26	16	54
midde frontal gyrus	left		3.88	-46	22	28
superior parietal cortex	right	482	3.42	42	-46	50
superior parietal cortex	left		3.22	-26	-54	38

Table 6.1: Mixed effects group contrast (Z = 2.3; p = 0.05), comparing first and second physical pain events for the trial A (Pp1 and Pp2, respectively) Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Hp1-Hp2

		voxelwise extent	Z score	X	Y	Z
angular gyrus	left	2718	3.76	-32	-54	34
angular gyrus	right		3.3	40	-52	50
lateral occipital cortex : inferior	left		3.03	-48	-72	-14
lateral occipital cortex : superior	left		3.7	-24	-66	38

lateral occipital cortex : superior	right		3.54	40	-82	20
superior pareital cortex	left		3.57	-26	-54	36
precuneus	left		3.58	-12	-74	38
inferior frontal gyrus	left	1952	3.59	-38	14	20
middle frontal	left		3.43	-48	12	40
superior frontal gyrus	left		3.55	-20	14	52
inferior frontal gyrus	right	1420	3.91	42	24	18
middle frontal	right		3.84	50	24	34
intracalcarine	right	1169	3.67	6	-74	8
lingual gyrus	left	1044	3.54	-4	-82	-2
lingual gyrus	right		3.31	14	-64	-2
occipital pole	left		3.5	0	-92	0
inferior temporal	right	693	3.69	52	-48	-24
middle temporal	right		3.18	60	-32	-12
inferior temporal	left	478	4.26	-56	-62	-14
paracingulate	right	613	3.76	0	22	40
paracingulate	left		3.34	-4	14	48

Table 6.2: Mixed effects group contrast, comparing first and second physical pain events for trial B (Hp1 and Hp2). Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

		PR -Pp1				
		voxelwise extent	Z score	X	Y	Z
precentral	left	1086	3.64	-40	-18	58
premotor	left		3.44	-4	10	54
paracingulate	left		3.4	-6	12	50
SMA	left		3.38	-2	2	62
SI	left		3.52	-52	-14	40
SII	left		2.9	-58	-8	20

Table 6.3: Mixed effects group contrast (Z = 2.3 ; p = 0.05), comparing activation during recalled pain relative to the first physical pain events for trial A (Pp1). Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

PR-Pp2

		voxelwise extent	Z score	X	Y	Z
inferior frontal gyrus	left	15608	4.95	-46	18	22
angular gyrus	left		4.6	-44	-56	46
inferior parietal	right		2.92	40	-76	34
middle frontal gyrus	left		4.8	-30	-2	56
middle frontal gyrus	right		3.29	34	2	42
middle temporal	left		4.03	-58	-52	6
paracingulate	left		4.81	-6	12	50
prefrontal cortex: dorsolateral	left		3.97	-38	50	4
superior lateral occipital	right		3.09	32	-80	30
SI	left		3.15	-40	-30	56
superior frontal gyrus	right	751	3.15	32	-56	44
superior frontal gyrus	left		4.74	-2	16	56

Figure 6.4: Mixed effects group contrast (Z = 2.3 ; p = 0.05), comparing activation during recalled pain relative to the second physical pain events for trial A (Pp2, respectively). Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Pr-Hr

		voxelwise extent	Z score	X	Y	Z
cingulate cortex : anterior	right	2815	4.04	8	16	36
cingulate cortex: mid-anterior	right		3.5	10	6	36
cingulate cortex: rostral anterior	right		2.94	8	38	12
paracingulate	right		2.91	4	32	32
caudate	right		3.35	10	8	8
premotor	right		3.48	8	2	60
putamen	right		3.53	20	4	4
SMA	right		3.48	8	2	60
inferior parietal cortex	right		3.341	62	-34	-20
anterior insula	right		3.49	36	8	4
pallidum	right		3.11	-20	-4	2
pallidum	right		2.87	52	24	-2

supramarginal: posterior	right		2.5	52	-40	12
precentral	right		2.84	58	8	18
central opercular cortex	left	2182	3.92	-52	2	8
frontal orbital cortex	left		3.8	-36	24	-10
middle frontal gyrus	left		3.6	-36	34	24
precentral	left		3.85	-52	2	12
Inferior frontal gyrus	left		2.4	-48	34	6
prefrontal cortex: dorso-lateral	left		3.76	-42	32	24
putamen	left		3.65	-14	12	2
cingulate cortex : anterior	left		3.4	-2	32	22
cingulate cortex: rostral anterior	left		2.76	-4	34	16
paracingulate	left		3.24	-6	24	32
premotor	left		3.59	-8	0	60
SII	left	1193	3.77	-60	-24	22
SMA	left		3.74	-8	-2	60
supramarginal: posterior	left		3.1	-58	-44	20
prefrontal cortex: dorso-lateral	right	514	3.62	26	54	28
prefrontal cortex: dorso-medial	right		3.07	20	48	28
prefrontal cortex: ventral-lateral	right		2.58	42	48	-4
Inferior frontal gyrus	right		3.47	44	32	0
parietal operculum	left	475	3.88	-62	-36	24
SII	right	441	3.65	58	-24	20

Table 6.5 Mixed effects group contrast (Z = 2.3; p = 0.05), exploring significant activation associated with recalling pain relative to recalling a visual scene (Pr and Hr, respectively). Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Conjunction Analysis

		Z score	X	Y	Z
cingulate cortex: anterior	left	3.8	-8	16	36
cingulate cortex: anterior	right	3.95	8	14	36
cerebellum crus 1	left	4.15	-28	-66	-36
cerebellum crus 1	right	3.74	40	-66	-36
inferior frontal gyrus	left	4.08	-38	20	16
insula: anterior	left	4.13	-36	16	2
insula: anterior	right	3.63	34	20	2
inferior parietal cortex	left	4.7	-50	-52	42
middle temporal gyrus	left	3.94	-60	-48	-6
Paracingulate	left	4.13	-8	16	40
Paracingulate	right	4.69	4	10	46
precentral	left	4.63	-50	-2	36
precentral	right	4.22	42	-2	46
prefrontal cortex: dorso-lateral	left	4.29	-40	22	3.6
prefrontal cortex: dorso-lateral	right	3.91	38	36	26
premotor	left	4.74	-2	4	52
premotor	right	4.87	6	4	52
SMA	left	4.82	0	8	54
SMA	right	4.87	6	4	52

Table 6.6: Conjunction analysis using inclusive masking of activation maps for Pr and Hr (Z = 3.0; p = 0.05), exploring activation common to both recalled conditions that survive a 3.0 threshold.

Pr-Hr unpleasantness

		voxelwise extent	Z score	X	Y	Z
anterior insula	left	2654	4.22	-30	10	4
anterior cingulate cortex	left		3.51	-6	18	24
paracingulate	left		2.73	-6	12	40
caudate	left		3.19	-10	6	6
central opercular cortex	left		3.7	-52	4	2
putamen	left		4.07	-26	10	2
SII	left		4.22	-50	0	8
anterior insula	right	2302	4.35	36	6	4
anterior cingulate cortex	right		3.61	8	4	40
paracingulate	right		3.71	10	18	36
central opercular cortex	right		3.97	52	6	2
putamen	right		3.99	30	14	0
caudate	right		2.96	10	6	8
premotor	right	2246	4.1	8	2	58
premotor	left		3.49	14	4	60
precentral	left		4.12	56	8	16

precentral	right		3.81	58	8	16
prefrontal cortex: dorsolateral	left	747	3.88	-40	42	16
prefrontal cortex: ventrolateral	left		2.46	-52	36	-2
prefrontal cortex: ventrolateral	right		3.14	40	36	2
inferior frontal gyrus	left		3.76	-54	28	-6
supramarginal gyrus anterior	left	628	4.5	-60	-38	28
supramarginal posterior	left		3.3	-58	-48	28

Table 6.7: Mixed effects group contrast (Z = 2.3; p = 0.01), using behavioural ratings for pain unpleasantness as a regressor and subtracting activation during recall in trial A and trial B (Pr > Hr and Hr > Pr). Structures containing the peak voxels for the major clusters are highlighted, and cluster extent is given in number of voxels.

Chapter 7

White Matter connectivity changes associated with Neuropathic Pain

Chapter 7:
White Matter connectivity changes associated with Neuropathic Pain

7.1 Introduction

In previous chapters we have explored how a memory template for pain may be updated with each new pain event, and how recalling that event can influence future pain processing. We have focused on short-term and working memory, and how a mental representation of pain may be kept in mind and alter affective aspects of subsequent pain perception. All previous experiments looked at pain processing in healthy individuals with no history of any pain condition. Many studies have shown that in patients suffering chronic pain brain mechanisms related to pain and cognition show significant structural and functional changes in the brain associated with their pathology (Apkarian et al., 2004a, Apkarian et al., 2004b, Buckalew et al., 2008, Di Piero et al., 1991, Draganski et al., 2006, Geha et al., 2008, Gustin et al., 2010, Hsieh et al., 1995, Jeanmonod et al., 1994, Ling et al., 2007, Lorenz, 2010, May, 2008, Oosterman et al., 2006, Rocca et al., 2006, Schmidt-Wilcke et al., 2006, Schmidt-Wilcke et al., 2007, Teutsch et al., 2008, Tracey and Bushnell, 2009, Tracey and Mantyh, 2007, Valfrè et al., 2008).

These include changes in grey matter activation, volumetric differences in certain areas of the brain and changes in white matter connectivity between patients and controls. Cognitive deficits associated with chronic pain include attentional processes, as well as lower scores on measures of working memory function (Apkarian et al., 2009, Dick and Rashiq, 2007a, Etherton et al., 2006, Kuhajda et al., 2002, Ling et al., 2007, Lorenz, 2010). Additionally, a recent study showed lower functioning related to short-term prospective memory (Ling et al., 2007). In this chapter, we explore connectivity changes using probabilistic tracking on diffusion tensor imaging data from a

seed region associated with working memory in patients suffering from neuropathic pain, matched with healthy controls.

Clinical presentation of neuropathic pain can include increased sensitivity to painful stimuli (hyperalgesia), or pain perception in response to non-noxious stimuli (allodynia), and its origin may be a result of a disorder of the peripheral or central nervous system (Hansson, 2003, Scadding…, 2005). Neuropathic pain is a major health problem with limited treatment options (Collins…, 2005). Pain can be severe, and is often chronic. Chronic pain has been associated with long-term changes in both grey and white matter, although at this stage it is unknown what these changes mean at the cellular/histological level as they are reversible in some pain conditions where remission of pain has occurred (Apkarian et al., 2004a, Buckalew et al., 2008, Gwilym et al., 2010, Oosterman et al., 2006, Oosterman et al., 2011, Rocca et al., 2006, Schmidt-Wilcke et al., 2006, Schmidt-Wilcke et al., 2007, Tracey and Bushnell, 2009, Valfrè et al., 2008). Nevertheless, it is apparent that plastic processes occur in the brain in patients with chronic pain – perhaps reflecting adaption to how this condition impacts multiple aspects of their behaviour.

In this study, we use probabilistic tracking to explore white-matter connectivity differences, between patients and controls, specifically projecting from the superior temporal cortex. This was done to test the hypothesis that memory networks might be altered in chronic pain patients due to the rehearsal of pain memories. Such changes in white matter connectivity consequent to alterations in behaviour or learning have been now widely shown in recent studies outside the pain field (Della-Maggiore et al., 2009, Johansen-Berg and Behrens…, 2004, Johansen-Berg et al., 2010).

7.1.1 Superior Temporal cortex

The superior temporal cortex is a region involved in a diverse range of processes from audio-visual processing, to empathy and theory of mind (Habas et al., 2010, Hein and Knight, 2008). Many studies have attempted to pin-point a more generalised role that this region serves which explains its involvement in such a wide range of specific tasks. Some have speculated functional divisions between the anterior and posterior portions (Karnath, 2001, Samson et al., 2004, Samson et al., 2005). Much of these claims are based on lesion studies. However, while regional specificity may exist, functional specification may rely on co-activity with other regions of the brain (Hein and Knight, 2008).

Few studies have explored the role of the superior temporal cortex in pain. While not commonly included among the structures classically associated with pain perception, it seems to play a major role in processing emotional memory associated with pain, in terms of empathy, and future emotional expectation (Hooker et al., 2008, Lamm et al., 2011, Ruby and Decety, 2004, Stoeter et al., 2007). Hyperactivity of this region has been demonstrated in response to persistent emotional demands (Zhao et al., 2006). Furthermore, in chronic pain sufferers significant reductions in gray matter in this area have been found in Fibromyalgia and migraine patients (Schmidt-Wilcke et al., 2007, Valfrè et al., 2008).

7.1.2 Diffusion-Weighted Imaging

In each of the preceding experimental chapters, we explore event-related activation with FMRI. Diffusion weighted imaging (DWI) is a complimentary technique that allows for the exploration of white matter connectivity between grey matter regions known to be involved in these cognitive tasks (Johansen-Berg et al., 2004, Johansen-Berg et al., 2005). The usefulness of

this technique lies in the ability to predict the directionality of axons, otherwise too small to examine, and therefore the probability of anatomical connectivity between two brain areas. Fractional anisotropy (FA) is a measure most commonly used with DWI data. FA gives a quantitative measure of tracts running parallel relative to those with perpendicular diffusivity. As this is a relative measure, it cannot differentiate between increased parallel diffusivity and decreased perpendicular diffusivity.

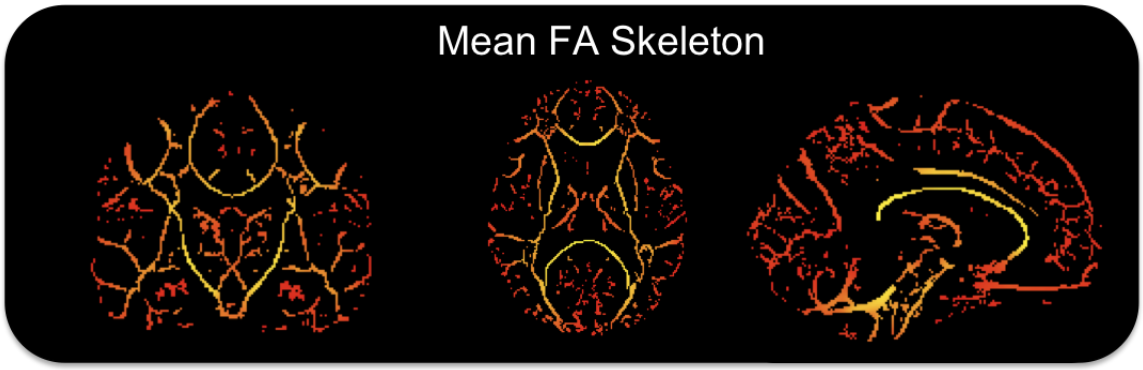


Figure 7.1 Mean FA skeleton map for all subjects (patients and controls) acquired prior to the analysis discussed in this chapter to illustrate white matter tracts.

In this study, we use probabilistic tracking which gives an estimate of the likelihood of the existence of a pathway between two regions. By measuring the relative difference between patients and healthy controls, we are able to see connectivity changes associated with chronic pain. The connection probability between voxels from the seed to the target region is then estimated by the sum of fibres connecting these two voxels (Beckmann et al., 2009). Deriving an estimate for the probability of connecting tracts between regions can demonstrate long-term changes in the brain associated with pathology. Distinct DWI profiles characterise distinct cognitive processes (Johansen-Berg et al., 2004, Johansen-Berg et al., 2005).

Here, we used a seed mask for the posterior superior temporal cortex (STC) (see figure 7.2), and a diverse set of target regions in cortical and sub-cortical regions associated with pain and memory. A recent connectivity study demonstrated extensive bilateral projections from this

region to parietal, temporal, insula, prefrontal, premotor areas, as well as occipital cortices and subcortical structures including the striatum and the thalamus (Habas et al., 2010). This extensive network may explain the diverse range of tasks in which the superior temporal cortex is involved (Hein and Knight, 2008).

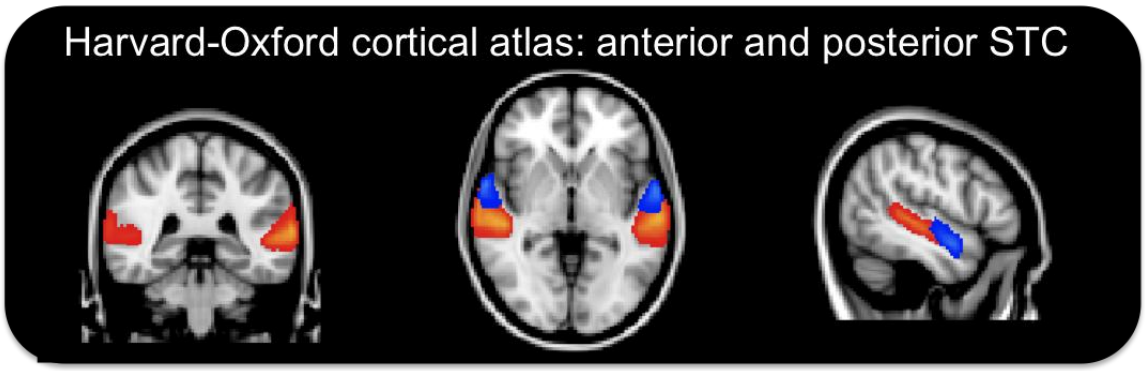


Figure 7.2: Superior temporal cortex probability masks drawn from the Harvard-Oxford cortical structural anatomical atlas. Bilateral anterior STC is shown in blue, whereas the posterior STC mask used to create the seed mask used in this experiment is shown in red.

These tasks include theory of mind, motion processing, empathy, emotional valence and it is even suggested to be a part of the "mirror neuron system" involved in imitation and learning (Charlton et al., 2010, Hein and Knight, 2008, Hooker et al., 2008, Molenberghs et al., 2010, Molenberghs et al., 2009, Moll et al., 2002, Samson et al., 2004, Zhao et al., 2006). Many of these functions have been included in a generalised theory of a core brain network which, through recall and future expectation, affects present sensory perception (Addis et al., 2007a, Buckner and Carroll, 2007, Schacter et al., 2007b). Perspective switching, as it has otherwise been termed (Schacter et al., 2007b), also includes the ability to switch and compare between self and other thus implicating theory of mind (Buckner and Carroll, 2007) and empathy (Lamm et al., 2007a), as well as prospective thinking which has been shown to be affected by chronic pain (Ling et al., 2007, Magni et al., 1994). By exploring connectivity changes in bilateral projections between the superior temporal cortex and pain areas, we hypothesise that patients suffering from chronic

neuropathic pain will show significant plastic changes associated with these aspects of memory processes and pain-related areas.

7.2 Materials and Methods

7.2.1 Subjects

Data for this study was collected prior to the start date for my thesis, for a different study examining brain whole brain structure. Nine patients suffering from neuropathic pain were recruited from the Oxford Pain Relief Unit, and 10 healthy controls matched for sex, age, and handedness were recruited locally. The following criteria determined patient recruitment: neuropathic pain of peripheral or spinal origin (Malhotra-Kumar et al., 2010). Subjects reported spontaneous, i.e. stimulus-independent pain higher than 3/10 (0 – 'no pain at all', 10 – 'worst pain imaginable'), mechanical allodynia greater than 3/10, and the absence of any major systemic disease, psychiatric disorder or neurological disorder other than neuropathic pain. Control subjects were also screened for any medical, neurological, or psychiatric condition. Written informed consent was obtained in accordance with the Declaration of Helsinki and the study approved in full by the Central Oxfordshire Research Ethics Committee.

Patient characteristics

Subject	Sex	Age	Handedness	Diagnosis	Affected body site	Current medication
1	F	59	R	Traumatic nerve lesion	Left foot	Co-codamol
2	F	54	R	Surgical nerve lesion	Right foot	Amitriptyline, Solpadol (codeine and paracetamol)
3	F	64	R	Post-operative pain (fusion vertebrae C4/5/6)	Right arm and leg	Amitryptyline, Co-proxamol
4	M	42	R	Brachial plexus avulsion	Left arm	Carbamazepine
5	M	53	R (before accident)	Brachial plexus avulsion	Right arm	None
6	M	38	R	Diabetic neuropathy	Feet bilat. (L>R)	Amitriptyline
7	M	71	R	Cervical Myelopathy	Legs bilat.	(Diazepine)
8	M	61	R	Cervical Myelopathy	Legs bilat.	Amitriptyline
9	M	46	L (before accident)	Brachial plexus avulsion	Left arm	None

Table 7.1 Patient characteristics including sex (3 female, 6 male), age (mean 54.2 STD ± 10.8), handedness (one left-handed, eight right-handed), diagnoses for each, site affected and medication.

Control subject's characteristics

Subject	sex	age	Handedness
1	M	36	R
2	F	59	R
3	M	51	R
4	F	53	R
5	M	37	R
6	M	25	R
7	F	57	L
8	M	70	R
9	M	58	R
10	M	45	R

Table 7.2 Patient characteristics including sex (3 female, 7 male), age (mean 49.1 STD ± 13.4), handedness (one left-handed, nine right-handed).

7.2.2 Image acquisition

All MR images were acquired on a Siemens Sonata 1.5 T MR scanner. The diffusion-weighted images were acquired using an echo planar imaging sequence according to (Johansen-Berg and Behrens…, 2004)(72 x 2mm thick axial slices, matrix size 128 x 104, field view 256 x 20mm^2 giving a voxel size of 2 x 2 x 2 mm^3). The diffusion weighting was isotropically distributed along 60 directions by using a b-value of 1000 s mm^{-2} according to research suggesting that isotropic voxels and the greater the number of diffusion-encoding gradient directions improves estimation of the diffusion tensor (Ni et al., 2006). For each diffusion-weighted set, five volumes with no diffusion weighting (b=0) were acquired. Averaging of three diffusion-weighted data sets were acquired for to increase the signal-to-noise ratio.

7.2.3 Image analysis

We repeated the Tract-Based Spatial Statistics (TBSS, also part of FSL) (Smith et al., 2006) on the whole brain for voxel-wise comparison of diffusion indices: fractional anisotropy (FA), diffusivity parallel (λ_1) and perpendicular (λ_2 and λ_3) to the principal diffusion direction between groups. FA maps were aligned to a standard space 1x1x1mm^3 FA using a constrained non-linear registration algorithm (IRTK,(Rueckert, 2002 #554)). A white matter tract 'skeleton' was created using a mean FA image across subjects, thresholded (FA ≥ 0.2) to include all major white matter tracts and exclude peripheral tracts. This skeleton was used to map FA values for each individual by searching perpendicular from the skeleton for the maximum FA values. Maximum values are chosen to restrict analysis to the centres of white matter tracts rather than considering voxels at the edges of tracts that might suffer from partial volume effects. Each subject's eigenvalue images (for λ_1, λ_2 and λ_3) were also wrapped onto the skeleton.

7.2.4 Masks

Target regions (table 7.3) were selected to include major areas normally associated with pain processing. Separate analyses were performed for each hemisphere, so that both seeds and targets were on the same side. The 3 dimensional masks used for the probabilistic tractography were taken from the Harvard-Oxford cortical structural anatomical atlas. All masks were mapped to each individual's T-1 weighted anatomical scan to fit within the anatomical boundaries of each region to establish the probability threshold (table 7.3). The seed region included the posterior portion of both the superior temporal gyrus and sulcus, which will be referred to inclusively as the superior temporal cortex. This mask included 50% of the probability threshold (figure 7.3).

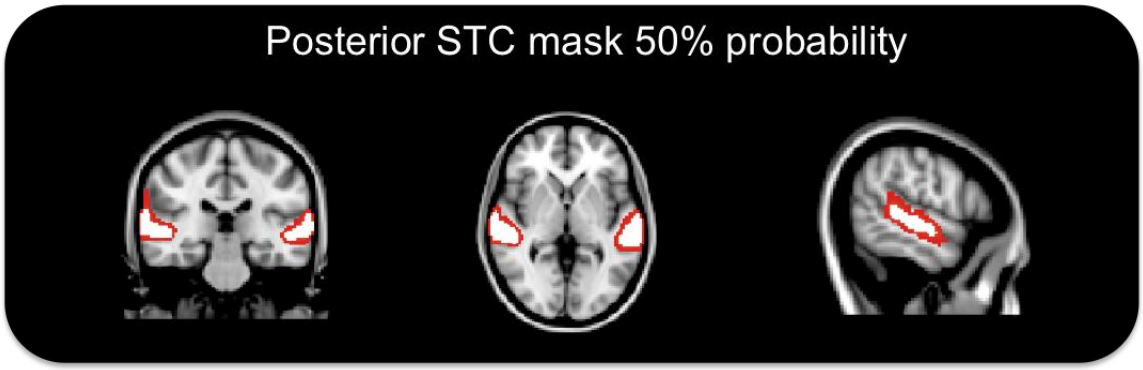


Figure 7.3 Bilateral seed masks drawn from the Harvard-Oxford cortical structural anatomical atlas, shown in white, overlaid on the larger posterior STC mask. This seed mask includes all voxels above the 50% probability threshold.

Seeds (left and right)	**Probability threshold**
Superior temporal cortex	50%
Targets (left and right)	**Probability threshold**
Amygdala	50%
Dorsal ACC	65%
Rostral ACC	65%
Hippocampus	90%
Anterior Insula	65%
Mid Insula	65%
Posterior insula	65%
Orbital frontal cortex	80%
Periaqueductal Grey	50%
Pars opercularis	80%
pars triangularis	80%
Primary somatosensory cortex	50%
Secondary somatosensory cortex	50%
Thalamus	50%

Table 7.3 List of seed and target regions used for analysis for both hemispheres and inclusive probability threshold for each regions.

A measure for clinical pain intensity was acquired using an 11-point numerical rating scale (NRS) with verbal anchors where 0 is 'no pain at all', 10 is 'worst pain imaginable'. Patients were asked to rate their average pain experienced over the past week. All neuropathic pain patients filled-out the McGill Pain Questionnaire (Melzack, 1975) and all subjects (patients and controls) completed the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) and the Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger, 1970).

Patient pain scores

Subject	Pain duration (yrs)	Allodynia	Spontaneous pain	Hours of spontanous pain per day	Intensity spontaneous pain (average day)
1	6	Yes	Yes	24	5.5
2	8	Yes	Yes	24	4
3	16	Yes	Yes	24	5
4	15	Yes	Yes	24	3
5	3	Yes	Yes	24	6.5
6	6	Yes	Yes	24	7.5
7	8	Yes	Yes	24	7.5
8	3	Yes	Yes	24	5.5
9	11	Yes	Yes	24	6.5

Predominant quality of spontaneous pain	McGill Pain Questionnaire	
	PRI(T)	PPI
'burning'	37	2.5
'pressure-like'	-	-
'electric shocks'	33	2
'nagging'	25	2
'burning'	14	2
'cutting'	35	4
'throbbing'	26	3
'burning'	27	4
'pressure-like'	39	1

Table 7.4 Patient pain scores: The duration of persistent chronic pain was measured (mean 8.44 STD ± 4.72 years). All patients reported allodynia, and spontaneous pain. All but one subject reported 24 hours of spontaneous pain. The mean intensity of spontaneous pain 5.67 STD ± 1.52 years. Quality of spontaneous pain varied according to individual, with many reporting burning, nagging or throbbing-like qualities.

7.2.5 Probabilistic tracking

After Bedpostx had been run on all subjects, probabilistic tracking using Probtrackx was run from all voxels within the seed region, the posterior superior temporal cortex (both Bedpostx and Probtrackx are part of the FSL software package). A transformation matrix was calculated to convert the seed mask from standard to Diffusion tensor imagining (DTI) space, which was incorporated into the analysis. All target masks were included as waypoint masks. Ten thousand samples were acquired from the connectivity distribution across each target region, and repeated for seed and target masks in the left and the right hemisphere.

Sampling results for each target were then divided by the total number of connections over all target regions and therefore represented a proportion to facilitate comparisons between target regions (See table 7.3). To accomplish this a mean number (M) was multiplied by the volume (V) of voxels showing connectivity between seed and targets. This was divided by the sum of all M*V values, so each target region had a number that corresponded to a proportion of projections from the seed region to each target. A t-test of these values for each subject for each target region was compared between patients and controls.

Following significant differences found between groups, post-hoc Pearson correlation tests were run between psychophysical measures and changes in connectivity. These measures included scores for pain duration, allodynia, spontaneous pain, hours of spontaneous pain per day, intensity of spontaneous pain per day, and scores on the McGill pain questionnaire. Finally, the relative volume (V) within the left superior temporal cortex that connected to the left thalamus was compared between patients and controls to demonstrate whether seed size difference could account for significant differences between groups. To do this, Probtrackx was run using only the left posterior superior temporal cortex as the seed mask and the left thalamus as a single

termination mask. Here, again, the number of samples acquired for this analysis was set to 10, 000. The volume (V) of voxels derived from the output of this analysis was calculated for all subjects in the patient and the control group, and a 2-tailed t-test was run to determine any significant differences between these two groups.

7.3 Results

A significant difference between the proportion of projections from the left superior temporal cortex only and the left thalamus was shown between patients and controls (thalamus mean proportion for controls 0.119 ± SD 0.08 Mean for patients 0.052 SD 0.02, 2-tailed t-test, $t_{(9)}$ = -2.713, $p < 0.02$). No significant differences were found between the seed and targets for the right hemisphere.

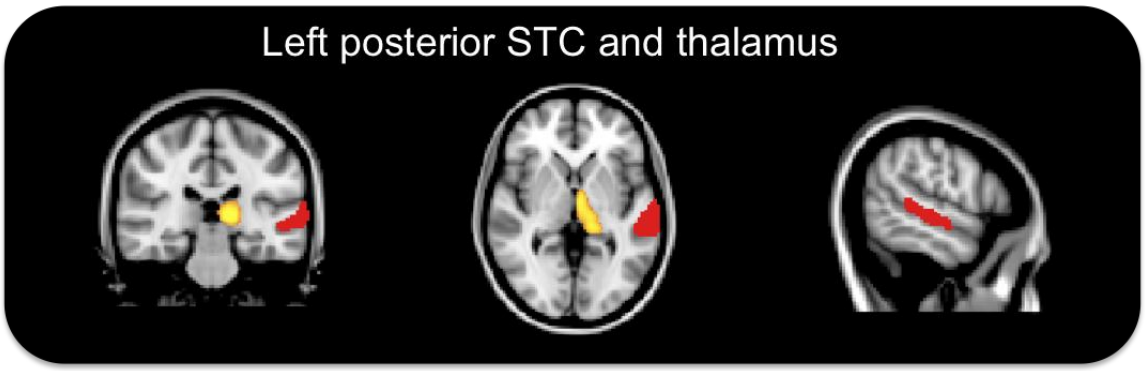


Figure 7.4 Significant differences in connectivity between the voxels within the left thalamus and the left posterior superior temporal cortex, defined by the masks shown above.

In order to account for this significant difference a correlation was run between each psychophysical measure. The Pearson correlation tests revealed no significant correlation for any psychophysical measure collected at the time of scanning. None of the pain reports, including duration of neuropathic condition, duration of spontaneous pain, intensity of spontaneous pain or McGill pain questionnaire scores, nor ratings on the depression scale or state or trait anxiety were shown to be significantly correlated with the decrease in connectivity shown in the patient group. No significant differences were found between seed sizes in patients relative to control from the left superior temporal cortex to the left thalamus.

7.4 Discussion

By comparing connectivity tracts from the posterior superior temporal cortex, we find a significantly lower proportion of projections from the superior temporal cortex to the left thalamus in neuropathic pain patients relative to healthy controls. The superior temporal cortex performs an extensive diversity of roles, with bilateral projections to an extensive network of regions throughout the brain (Habas et al., 2010, Hein and Knight, 2008). It is the coactivity with these regions that defines the specific function this region performs (Hein and Knight, 2008). Many tracts extend from the posterior superior temporal cortex to the thalamus, and this connectivity has been shown to be involved in theory of mind, empathy and expectation of future emotional states and working memory (Charlton et al., 2010, Habas et al., 2010, Hein and Knight, 2008, Hooker et al., 2008, Lamm et al., 2011, Lamm et al., 2007b). Our results demonstrate a unilateral decrease in projections connecting these regions establishing plastic changes associated with chronic pain in memory related areas.

7.4.1 Possible role for memory in chronic pain

Chronic pain has previously been linked with both working memory and episodic memory deficits (Etherton et al., 2006, Grisart et al., 2007). As has been demonstrated in research on depression (Bergouignan et al., 2008, Lo et al., 2008), memory impairments can induce false beliefs of self, when memories are not retrieved accurately. Differences in self-perception and negative beliefs about pain resulting from past pain memories could lead to a 'mismatch' and hyperalgesia (Gedney and Logan, 2006), one aspect of neuropathic pain.

7.4.2 The superior temporal cortex

The superior temporal cortex has been said to play a major role in many functions ascribed to perspective switching, including theory of mind, empathy and predictive future emotional responses (Hein and Knight, 2008, Schacter et al., 2007b). One study comparing mentalisation of false beliefs (relation to theory of mind) and empathy found that the same network of activation was common to both predicted and future emotional responses, and this included both the superior temporal cortex and the thalamus (Hooker et al., 2008). It is thought to be involved with the mirror-neuron system, corresponding visuo-motor information from oneself to others (Molenberghs et al., 2010, Molenberghs et al., 2009). This particular role may be crucial to our understanding of the possible beneficial effect of visual and motor imagery on pain perception in certain chronic pain conditions, like complex region pain syndrome (CRPS). Visual illusion using guided imagery and watching virtual walking has been shown to decrease sensory and affective qualities of neuropathic pain (Moseley, 2007).

Although the results of our study may be attributable to many of these functions, perhaps most relevant to the results of our study may be the functional connectivity between these two regions involved in working memory processes (Charlton et al., 2010, Hein and Knight, 2008). As described in previous chapters, a mental representation of pain may be held in memory and retrieved to create vivid re-experiencing of pain. Furthermore, as demonstrated in chapters five and six, working memory can affect subsequent pain perception. As both the posterior superior temporal cortex and the left thalamus have been associated with working memory and prospective memory, changes in structural connectivity might indicate abnormal memory processing affecting or affected by persistent pain.

7.4.3 Related structural and functional changes

In recent years an increasing number of studies have explored structural changes associated with chronic pain, yet whether these changes are caused by chronic pain, lifestyle changes, the pharmacological agents being used to treat patients or normal adaptation to the condition are uncertain (Apkarian et al., 2004b, Buckalew et al., 2008, Gustin et al., 2010, May, 2008, Schmidt-Wilcke et al., 2006, Schmidt-Wilcke et al., 2007, Valfrè et al., 2008). Numerous studies have reported decreased grey matter in the thalamus observed in patient populations relative to healthy controls (Apkarian et al., 2004a, Draganski et al., 2006, Gwilym et al., 2010, Schmidt-Wilcke et al., 2006).

Encouragingly, one study demonstrated that decreases in thalamic grey matter resulting from pain were reversible after surgical intervention and recovery from pain (Gwilym et al., 2010). Further to this study, PET studies have shown that pain conditions can lead to reduced cerebral blood flow to the contralateral thalamus, but normal levels may resume if pain is alleviated (Di Piero et al., 1991). It is therefore clear that structural and physiological changes can occur in the thalamus as a result of persisting pain. Different changes in structure and function seem to depend on the individual pain pathology (Tracey and Bushnell, 2009). Neuropathic pain has been reported to show the greatest reduction in thalamic grey matter relative to other pain conditions (Apkarian et al., 2004a). Furthermore, spontaneous pain, a symptom present in all patients in this study, has been associated with thalamic infarcts for more than a hundred years (THUREL…, 2002).

7.4.4 The role of the thalamus relating to memory

The thalamus is a phylogenetically ancient structure involved in regulating the input from the environment to cortical structures. In particular, the medio-dorsal region of the thalamus plays an important role in working memory and prospective memory functioning (Piras et al., 2010).

Connectivity between the thalamus and the temporal cortex, posterior parietal cortex (neighbouring the posterior portion of the superior temporal cortex seeded in this study) and the prefrontal area plays a significant role in affective pain processing (Gwilym et al., 2010, Piras et al., 2010). Thalamic lesion studies have shown impaired working-memory function in animals (Bailey and Mair, 2005). In humans, lesions isolated to the left thalamus (consistent with our findings) have shown decreased working memory performance (Dagenbach et al., 2001, Kubat-Silman and Dagenbach…, 2002). Supported by research, linking the thalamus with prospective memory functioning, it is thought that it may serve to retain relevant information in the presence of distracter tasks or in the absence of stimuli (Piras et al., 2010). In this way, it is possible that in chronic pain states, activation as a result of peripheral input may be kept in mind, and contribute to the persistence of pain sensation.

Knowing the varied functions of the thalamus and the posterior superior temporal cortex, it would be difficult to determine the cause of fewer projections between these two regions in neuropathic pain patients and healthy controls. Both of these regions are involved in working memory as well as prospective memory, including expectation and affective pain processing (Charlton et al., 2010, Gwilym et al., 2010, Hein and Knight, 2008, Hooker et al., 2008, Piras et al., 2010). Following our results in Chapter Six, where we were able to establish the relationship between short-term working memory and affective evaluation of future pain reports, future research incorporating psychometric measures for different aspects of memory function in neuropathic pain patients might explore the relationship between white matter connectivity between the thalamus and working memory areas.

Studies exploring white matter changes have found significant differences in mean-diffusivity (MD) and working memory (Charlton et al., 2010, Piras et al., 2010). In aging populations MD maps correlating with working memory scores identified clusters in regions

including the superior temporal cortex and the thalamus (Charlton et al., 2010). Another found the opposite trend, where increased mean diffusivity related to reduced performance on memory tasks in healthy subjects (Piras et al., 2010). In the present study, our analysis was performed post-hoc following whole-brain TBSS tractography analysis, which found no significant differences in FA or MD. Many studies have found important physiological differences between healthy and patient populations (Tracey and Bushnell, 2009). As an example, increased blood flow has been found in healthy populations possibly as a result of arousal or heightened attention to pain (Peyron and Faillenot, 2011). However, several studies in patients have found the decreased cerebral blood flow to the thalamus associated with persistent pain (Di Piero et al., 1991). In the latter case, studies have found these changes to be reversible after the painful condition is treated. This suggests that the physiological shift happens as a result of the pathology not as a cause.

These changes to physiological structure and function might be an adaptive reaction to over use. Pertinent to our results, increased activity to grey matter has been shown to affect the strength of white matter connectivity (Charlton et al., 2010, Kochunov et al., 2009). Further exploration of the role of the thalamus in working memory related to neuropathic pain may elucidate important aspects contributing to persisting pain. Furthermore, testing the reversibility of these white matter changes, or working memory function could help determine whether memory deficits are the cause or result of chronic pain.

Although projections from the superior temporal cortex to the thalamus are bilateral, our result was lateralised to the left side. This result cannot be attributed to site of injury or pain, as this was mixed between patients. Little is yet known about the laterality of the superior temporal cortex (Habas et al., 2010). However, a study exploring cognitive deficits associated with a lesion in the upper part of the left posterior superior temporal cortex, overlapping with the

temporoparietal junction, found significantly poorer performance in a false-belief task, relative to healthy controls (Samson et al., 2004, Samson et al., 2005).

Changes in grey matter volume in the left thalamus have repeatedly been associated with chronic pain (Apkarian et al., 2004a, Gwilym et al., 2010, Schmidt-Wilcke et al., 2006, Schmidt-Wilcke et al., 2007). In Fibromyalgia patients grey matter volume of the left thalamus and the right superior temporal gyrus was significantly reduced relative to controls (Schmidt-Wilcke et al., 2007). However in a similar study, the same group reported grey matter increases in the left thalamus in a cohort of chronic back pain (Schmidt-Wilcke et al., 2006). While these studies demonstrate brain morphology changes in both these areas associated with chronic pain, the relative increase or decrease in grey matter volume and laterality effects may depend on type of chronic pain being examined and the time after injury (Tracey and Bushnell, 2009). Further research might focus on exploring lateral differences in pain and memory processes associated with the thalamus and superior temporal cortex, while controlling for site of pain as cerebral blood flow, which is said to be reduced to the thalamus contralateral to the site of injury (Di Piero et al., 1991).

7.4.5 Conclusions

In previous chapters in healthy volunteers, we discussed how memory for pain may be held in working memory and influence the affective quality of future pain perception. In the present study, we demonstrate a significant decreased proportion of projections from the left posterior superior temporal cortex to the left thalamus in patients suffering from neuropathic pain. Both the posterior portion of the superior temporal cortex and the left thalamus are involved in memory processes involving episodic memory, perspective switching as well as working memory. In the absence of psychometric measures for memory function the extent to which we are able to extrapolate conclusions from this data is limited. However, future studies may explore

whether these changes might be as a result of increased activity in both these areas ultimately causing damage to white matter tracts connecting these two areas, thereby contributing to possible memory deficits.

Chapter 8

Conclusions

8.1 Introduction

Taken together these studies explore the neural correlates of short-term recall of pain and how it may affect long-term pain processing. Using a "recall pain" task, we identify and distinguish between central and peripheral pain processing pathways. We explore the concept of a memory template for pain, which is adaptable following each new pain event. Furthermore, we examine the degree to which this template influences the evaluation of future pain events. We report findings from studies, which manipulate short-term memory for pain and pain recall, and how the affective value associated with pain perception can change as a result of repeated recall. We identify regions that characterise short-term pain re-experiencing, and regions specific to intensity and vividness encoding. Finally, we explore long-term anatomical changes associated with these memory processes in patients suffering from neuropathic pain. We put forward that a greater understanding of the memory template for pain offers new insights into modulation of pain perception.

8.2 Mental representation

The pain memory template as discussed in the preceding chapters, represents a bidirectional memory store. A mental representation of pain can be created, mimicking the neural signature of the preceding physical pain, which may be modified before storage into long-term memory. Finally, long-term rehearsal of this mental representation could potentially act to lesson the subjective feeling of pain; replacing maladaptive behaviours and beliefs about pain with more beneficial coping strategies. As in visual and motor memory, a mental representation of the original event is activated during short-term recall. The earliest reference to this mental trace of

"somatosensory memory" was first explored in phantom-limb patients. As the described pain in this case had no related nociceptive peripheral input, it was assumed that information coding for the location and sensation must originate in the brain as a "neuromatrix." It was suggested that although it was normally not consciously retrievable, it could be activated given a relevant sensory cue (Melzack, 1990b). Using our pain recall paradigm, we were able to activate a robust mental representation of pain (chapters 3, 4 and 6), which was shown to gradually degrade as the time-to-test delay increased (chapter 4).

Although it is difficult to ensure that participants in memory studies perform the desired task at the specified time, we demonstrated that the mental representation is dependent on the initial stimulus that is being recalled. The potential to change future pain perception by altering the mental representation of pain is therefore also dependant on each individual pain event. In Chapter Three, we demonstrated that changing the intensity of the physical pain event, altered the observed neural activity during the recall task. Specifically, the non-noxious "warm" condition significantly differed from the "low pain" condition, which in turn significantly differed from the "high pain" condition. This interdependence of the recall task on the stimulus type and intensity of the preceding perception stimulus was observed again in Chapter Six. In this chapter the mental representation of pain significantly differed from that of a visual stimulus.

Not only did activation during recall significantly overlap with that of the preceding stimulus, but in Chapter Four, we demonstrate that subjective ratings for recalled pain intensity and recalled pain vividness significantly correlate with brain activation of the preceding physical pain, even as intensity is not varied. Finally, subtraction analysis exploring significant differences between activation during physical pain and activation during recalled pain events demonstrated few areas specific to either condition. These results demonstrate that the recall pain paradigm is effective in prompting sensory re-experiencing with an accurate mental representation of pain.

8.2.1 Transitory nature of the mental representation

By demonstrating the clear relationship between recall and the initial stimulus, we demonstrate that a memory trace of the initial stimulus exists intact for only a short time before sensory information necessary to invoke sensory-re-experiencing is lost. In Chapter Four we explored the transitory nature of this memory trace or mental representation of pain by keeping the temperature of the stimulating thermode constant (i.e. not varying intensity) and instead varied and extended the delay between the physical pain stimulus and the recall event. Here we revealed that even after a minute a robust mental representation of pain was still active. However, we were also able to identify regions, which significantly attenuate as the time-to-test delay is extended beyond the limits of short-term recall. These regions include the primary somatosensory cortex, the premotor cortex, the posterior parietal cortex and the anterior cingulate cortex. These regions, with the exception of the anterior cingulate cortex, were present in the contrast of recalled high pain > physical high pain in Chapter Three. Incorporating recalled pain intensity and vividness ratings we were able to explore how these aspects of the recalled event are encoded in short-term memory and beyond into long-term storage.

8.2.2 Longer-term effects of rehearsal

After identifying the short-term memory trace and the change in activation associated with pain memory over time, we hypothesised that repeated rehearsal of recalled pain could affect subsequent pain perception. In chapters four, five, and six we demonstrate behavioural and neural changes associated with repeated rehearsal. In Chapter Four, we were unable to acquire physical pain intensity ratings apart from a rating before and after the experiment. However, the effect of time on brain activation during physical pain was explored by incorporating the time of each stimulus as a weighting for the explanatory variables. In this way we revealed an extensive

network of pain related areas that significantly increase as a function of time. This result suggests that repeated rehearsal has an effect on neural activation of physical pain. This is consistent with findings in the field of motor memory, showing that rehearsal of motor imagery can affect neural activation during physical performance (Meister et al., 2004, Stewart, 2008).

From this result, it was not clear whether repeated rehearsal of pain imagery would increase or decrease subsequent pain perception. Furthermore, we could not be sure that physical pain intensity reports before and after each trial were reliable enough to ensure no pain sensitisation occurred as a result of repeated rehearsal. Therefore, the paradigm employed in the previous experiments was adapted to incorporate a physical pain event and a chance to rate this pain in every epoch. This additional rating enabled us to explore whether repeated recalled pain affected subsequent physical pain ratings. This trial was contrasted with a control trial, which did not include any recalled events. No effects of sensitisation were observed and ratings for physical pain intensity and physical pain unpleasantness significantly increased over time. However, average physical pain ratings were not significantly different between trials. Additionally, as the control trial necessitated long periods of inactivity for the subject it is possible that participants were not engaged enough in the paradigm for their ratings to be truly representative of physical pain in the absence of a recalled event. Therefore, it was not possible to attribute the significant changes of physical pain over time to the repeated rehearsal of pain recall, as it might be due to attention effects related to any event occurring between physical pain stimuli. Furthermore, the two trials compared in this experiment were performed on two separate days, in two separate cohorts of volunteers. The pain recall trial was always presented before the control implicating the possible confound of order effects.

For this reason we adapted this paradigm in Chapter 6 to further explore this phenomenon. By using visual recall in conjunction with pain recall, we were able to isolate

significant effects due to recalling a painful event, relative to the effects of recalling an event unrelated to pain. Our results demonstrate that physical pain preceded by recalled pain significantly reduces average pain unpleasantness ratings relative to recall unrelated to pain. This result is consistent with studies in imagery and mindfulness meditation. Individual's trained in this technique, which requires management of attention processes before experiencing physical pain, which has been shown to specifically reduce the affective quality of pain (Elomaa et al., 2009, Grant et al., 2011, McCracken et al., 2007a). During the recall paradigm subjects are instructed to attend to sensory aspects of the physical pain stimulus, re-experiencing pain in the absence of threat (Grant et al., 2011, Wiech et al., 2010, Wiech and Tracey, 2009). Changing the context, within which pain is experienced and kept in working memory, can change negative to neutral associations (Moseley and Arntz, 2007, Tracey, 2010). Furthermore, our imaging results coincide with those associated with the reduction in pain unpleasantness ratings; namely those normally found to be involved in cognitive appraisal (Grabenhorst et al., 2008, Grant et al., 2011, Rolls and Grabenhorst, 2008). These results confirm our hypothesis that physical pain relies on memory processes to evaluate physical pain perception.

8.3 Pain memory in healthy subject relative to patient populations

As physical pain can affect the mental representation of pain in short-term memory, we hypothesised that areas involved in short-term memory of pain would show plastic changes as a result of a chronic pain condition. Chapter Five explored whether white matter connectivity between areas devoted to memory processing significantly differed between patients suffering from neuropathic pain and healthy controls. As psychometric measures for memory were not taken at the time of scanning, we are not able to draw definitive conclusions as to the extent to which memory deficits relate to decreased white matter connectivity. However as the posterior superior temporal cortex and the thalamus are both seen to be involved in working and

prospective memory. This functional similarity is consistent with the bidirectional nature of pain memory explored in our previous chapters; as retrospective recall can act prospectively to influence future pain perception. Therefore these results taken together with the experiments using healthy volunteers suggest a compelling avenue for future research. Adapting the "imagine pain" paradigm for use with patient populations, might explore more clearly how working memory for pain would differ from healthy individuals. Additionally, the inclusion of questionnaires measuring for differing types of memory might further specify memory processes affecting both white and grey matter.

8.3.1 Limitations

The investigation of short-term memory for pain is still in its nascent stages. In these chapters we demonstrate the potential of exploring this field further. However, there are several limitations to the designs and conclusions we may draw from each of these experiments. To begin with, in the first two chapters, we were not able to collect behavioural measures for each physical pain event, and yet, fluctuations in recalled pain intensity and vividness, may be dependent on changes in physical pain intensity. More specifically, an alternative explanation for the increase in activation associated with pain in Chapter Four could potentially be a result of sensitisation. In chapter's Five and Six, we attempted to modify the paradigm to include behavioural ratings for physical pain. However, as these were separate experiments, the paradigms were not identical and included a different number of subjects it could not be used to definitively explain the results of the previous chapter.

The conclusions drawn from Chapter Four may also be limited by possible attention differences between the conditions. By extending the delay from 20 seconds to the long delay of a minute, it is possible that attentional effects might affect behavioural responses. However, the imaging data demonstrating physical pain predicting activation in the recalled pain condition, as well as the attenuation of activation involved in physical pain, shows the recalled task is effective in creating a mental representation of physical pain and that an increase in delay, decreases activation in these areas.

Limitations explored in Chapter five include possible order effects, and loss of statistical power resulting from how subjects were recruited. Choosing a control trial, which repeated noxious stimuli with no interceding event may have resulted in additional attentional confounds. An attempt was made in the subsequent chapter to correct for these problems. In Chapter 6 we chose a different control, which required each participant to be attentive during the gap, but was unrelated to pain. This however, may have had its own drawbacks. By requiring attention unrelated to pain, it may be considered as a possible distractor task. As a distractor, we might expect differing effects on subsequent physical pain. This being said, other studies have shown that distraction from pain should lower both pain intensity and pain unpleasantness scores (Bantick et al., 2002a, Boyle et al., 2006, Tracey et al., 2002). In this study we show that relative to our "imagine house" control trial, being attentive toward the pain showed the opposite effect that one would normally expected relative to a distractor task. Thereby furthering the hypothesis that attending to pain before receiving a noxious stimulus, may decrease pain unpleasantness scores, perhaps more effectively than disctraction away from pain.

A further complication arising from using the visual stimulus, was finding a matching behavioural score that matched the "pain intensity" score used in the other trial. While pain intensity gave an indication as to the accuracy of recall, we employed a question task, related to aspects of the visual image. However, given that participants would be motivated to perform this task correctly, it is possible that error-related processing could have influenced subsequent pain perception. Further analysis might obtain a measure of certainty for these replies, which would give an indication of perceived error, or including additional physiological measures such as measuring the galvanic skin response. This would give further insight both in terms of potential stress related to error-processing, as well as that related to pain unpleasantness. Further experimentation might also include several control trials within the same paradigm, using different sensory modalities (visual or motor imagery, as an example) as well as no recall task, to explore each of these effects relative to pain-specific recall. These tests may be done psychophysically avoiding limitations of the time subjects are put in the scanner.

Further disadvantages with comparing recalling a visual stimulus relative to a house is that they are not matched for spatial attention. This may, however be an interesting avenue to persue which aspects of pain-specific imagery are responsible for these significant reductions in pain unpleasantness ratings. Future work might explore this in patients, whether specifiy the site of pain imagery relative to injury might show differential effects. Finally, a surprising result of this

study are seemingly contradictory reductions in pain unpleasantness scores as a main effect, and an increasing trend of both physical pain intensity and unpleasantness over time. We cannot be certain that sensitisation might not occur as a result of repeated highly noxious stimuli and confound our results. However, as we find that on average comparing trials, participants demonstrate a lowering of subjective reports, we are still able to show that pain unpleasantness scores decrease as a result of pain-specific recall.

In the final chapter, we were limited by the restrictions imposed by adopting a data-set aquired for different purposes than our own. Therefore, while we are able to present a compelling argument for how short-term memory processing could be affected by prolonged chronic pain, we do not have any measures indicating that functional memory impairment was a symptom of their disease. The cohort of subjects that were available for recruitment was perhaps too small to detect any psychophysical relationship between aspects of the disease such as how long each patient had suffered from pain, or psychological scores. Therefore, we cannot discount that despite no significant correlation between physiological scores and the imaging data, these factors may influence white matter connectivity between these regions we identified. However, having demonstrated less connectivity between the posterior superior temporal cortex and the thalamus in patients suffering from neuropathic pain we may design more specific analyses looking specifically at short-term memory, chronic pain and either functional or structural changes in these areas.

8.3.2 Pain imagery

The fields of pain and memory although fundamentally entertwined, each individually pose tight experimental constraints. Successively through these chapters we attempt to overcome these limitations, though these experiments are still exploratory. In the preceding chapters we present and test variations in a novel approach to use pain imagery to explore short-term recall of pain in the absence of hypnosis. In this way, we are able to induce physical re-experiencing of pain in the absence of nociceptive input; separating central from peripheral pain modulation. Furthermore, we are able to expand on other studies looking at pain memory, which utilise sensory discrimination as a tool to measure the extent of recall. Through various analyses, in

chapters 3, 4 and 6 we demonstrate the strong relationship between pain recall and the physical pain event that precedes it, with both psychophysical as well as imaging data. By inducing re-experiencing of the pain stimulus we are able to capture more fully how pain may be kept in mind; beyond the limitations of comparing the relative accuracy of separate pain scores in time.

By adapting this paradigm, we are able to explore the bi-directionality of pain memory: not only is pain recall affected by the experience of pain, but pain perception is influenced by recalling the pain experience. We demonstrate significant differences in pain ratings when a recall event precedes a physical pain event. These results emphasise the potential for pain-imagery as a tool for modulating affective dimensions of pain perception. Important clinical applications of visual and motor imagery in chronic pain are becoming increasingly more apparent, whereas the utility of pain imagery as a therapeutic tool is relatively unexplored. Future research might explore the efficacy of relevant pain imagery both in conjunction with and relative to visual and motor imagery.

Our findings in chapter 6, might lead to more effective paradigm designs using imagery to produce lower ratings for pain. We suggest the effectiveness of imagery might depend on re-contextualising pain: adopting a neutral affective bias over a learned negative bias. Future studies might take into account that the relevance of imagery as well as the context within which individuals are expected to practice imagery may determine whether pain is increased, decreased or unchanged.

List of Figures

List of Tables

References

ADDIS, D., WONG, A. & SCHACTER, D. 2007a. Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. Neuropsychologia, 45, 1363-77.

ADDIS, D. R., WONG, A. T. & SCHACTER, D. L. 2007b. Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. Neuropsychologia, 45, 1363-77.

ALBANESE, M., DUERDEN, E., RAINVILLE, P. & DUNCAN, G. 2007a. Memory traces of pain in human cortex. J Neurosci, 27, 4612-20.

ALBANESE, M.-C., DUERDEN, E. G., BOHOTIN, V., RAINVILLE, P. & DUNCAN, G. H. 2009. Differential effects of cognitive demand on human cortical activation associated with vibrotactile stimulation. Journal of Neurophysiology, 102, 1623-31.

ALBANESE, M. C., DUERDEN, E. G., RAINVILLE, P. & DUNCAN, G. H. 2007b. Memory traces of pain in human cortex. J Neurosci, 27, 4612-20.

ALLAMI, N., PAULIGNAN, Y., BROVELLI, A. & BOUSSAOUD, D. 2008. Visuo-motor learning with combination of different rates of motor imagery and physical practice. Exp Brain Res, 184, 105-13.

ANDERSON, W. S., WEISS, N., LAWSON, H. C., OHARA, S., ROWLAND, L. & LENZ, F. A. 2010. Demonstration of motor imagery movement and phantom movement-related neuronal activity in human thalamus. Neuroreport.

ANDERSON-BARNES, V. C., MCAULIFFE, C., SWANBERG, K. M. & TSAO, J. W. 2009. Phantom limb pain--a phenomenon of proprioceptive memory? Med Hypotheses, 73, 555-8.

APKARIAN, A., SOSA, Y., SONTY, S., LEVY, R., HARDEN, R., PARRISH, T. & GITELMAN, D. 2004a. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci, 24, 10410-5.

APKARIAN, A. V., BALIKI, M. N. & GEHA, P. Y. 2009. Towards a theory of chronic pain. Prog Neurobiol, 87, 81-97.

APKARIAN, A. V., BUSHNELL, M. C., TREEDE, R.-D. & ZUBIETA, J.-K. 2005. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain, 9, 463-84.

APKARIAN, A. V., SOSA, Y., SONTY, S., LEVY, R. M., HARDEN, R. N., PARRISH, T. B. & GITELMAN, D. R. 2004b. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci, 24, 10410-5.

AVANZINO, L., GIANNINI, A., TACCHINO, A., PELOSIN, E., RUGGERI, P. & BOVE, M. 2009. Motor imagery influences the execution of repetitive finger opposition movements. Neurosci Lett, 466, 11-5.

BADDELEY, A. 2003. Working memory: looking back and looking forward. Nat Rev Neurosci, 4, 829-39.

BAER, R. 2003. Mindfulness training as a clinical intervention: A conceptual and empirical review. Clinical psychology: Science and practice.

BAILEY, K. R. & MAIR, R. G. 2005. Lesions of specific and nonspecific thalamic nuclei affect prefrontal cortex-dependent aspects of spatial working memory. Behavioral neuroscience, 119, 410-9.

BANTICK, S., WISE, R., PLOGHAUS, A., CLARE, S., SMITH, S. & TRACEY, I. 2002a. Imaging how attention modulates pain in humans using functional MRI. Brain, 125, 310-9.

BANTICK, S. J., WISE, R. G., PLOGHAUS, A., CLARE, S., SMITH, S. M. & TRACEY, I. 2002b. Imaging how attention modulates pain in humans using functional MRI. Brain, 125, 310-9.

BAR-GAD, I., MORRIS, G. & BERGMAN, H. 2003. Information processing, dimensionality reduction and reinforcement learning in the basal ganglia. Prog Neurobiol, 71, 439-73.

BECKMANN, M., JOHANSEN-BERG, H. & RUSHWORTH, M. F. S. 2009. Connectivity-Based Parcellation of Human Cingulate Cortex and Its Relation to Functional Specialization. Journal of Neuroscience, 29, 1175-1190.

BENSAFI, M., PORTER, J., POULIOT, S., MAINLAND, J., JOHNSON, B., ZELANO, C., YOUNG, N., BREMNER, E., AFRAMIAN, D., KHAN, R. & SOBEL, N. 2003. Olfactomotor activity during imagery mimics that during perception. Nat Neurosci, 6, 1142-4.

BERGOUIGNAN, L., LEMOGNE, C., FOUCHER, A., LONGIN, E., VISTOLI, D., ALLILAIRE, J. & FOSSATI, P. 2008. Field perspective deficit for positive memories characterizes autobiographical memory in euthymic depressed patients. Behav Res Ther, 46, 322-333.

BISHOP, G. H., LANDAU, W. M. & JONES, M. H. 1958. Evidence for a double peripheral pathway for pain. Science, 128, 712-4.

BLOMQVIST, A., ZHANG, E. T. & CRAIG, A. D. 2000. Cytoarchitectonic and immunohistochemical characterization of a specific pain and temperature relay, the posterior portion of the ventral medial nucleus, in the human thalamus. Brain, 123 Pt 3, 601-19.

BORSOOK, D., UPADHYAY, J., CHUDLER, E. H. & BECERRA, L. 2010. A key role of the basal ganglia in pain and analgesia--insights gained through human functional imaging. Mol Pain, 6, 27.

BOYLE, Y., BENTLEY, D. E., WATSON, A. & JONES, A. K. P. 2006. Acoustic noise in functional magnetic resonance imaging reduces pain unpleasantness ratings. NeuroImage, 31, 1278-83.

BREFCZYNSKI-LEWIS, J. A., LUTZ, A., SCHAEFER, H. S., LEVINSON, D. B. & DAVIDSON, R. J. 2007. Neural correlates of attentional expertise in long-term meditation practitioners. Proc Natl Acad Sci USA, 104, 11483-8.

BRODIE, E., WHYTE, A. & NIVEN, C. 2007. Analgesia through the looking-glass? A randomized controlled trial investigating the effect of viewing a 'virtual' limb upon phantom limb pain, sensation and movement. Eur J Pain, 11, 428-36.

BROOKS, J. & TRACEY, I. 2007a. The insula: a multidimensional integration site for pain. Pain, 128, 1-2.

BROOKS, J. C. & TRACEY, I. 2007b. The insula: a multidimensional integration site for pain. Pain, 128, 1-2.

BROWN, C. A. & JONES, A. K. P. 2010. Meditation experience predicts less negative appraisal of pain: electrophysiological evidence for the involvement of anticipatory neural responses. Pain, 150, 428-38.

BUCKALEW, N., HAUT, M. W., MORROW, L. & WEINER, D. 2008. Chronic pain is associated with brain volume loss in older adults: preliminary evidence. Pain Med, 9, 240-8.

BUCKNER, R. & CARROLL, D. 2007. Self-projection and the brain. Trends Cogn Sci, 11, 49-57.

BUHLE, J. & WAGER, T. D. 2010. Does meditation training lead to enduring changes in the anticipation and experience of pain? Pain, 150, 382-3.

BUSHNELL, M. C., DUNCAN, G. H., DUBNER, R., JONES, R. L. & MAIXNER, W. 1985. Attentional influences on noxious and innocuous cutaneous heat detection in humans and monkeys. J Neurosci, 5, 1103-10.

BYRNE, P., BECKER, S. & BURGESS, N. 2007. Remembering the past and imagining the future: a neural model of spatial memory and imagery. Psychol Rev, 114, 340-75.

CHARLTON, R. A., BARRICK, T. R., LAWES, I. N. C., MARKUS, H. S. & MORRIS, R. G. 2010. White matter pathways associated with working memory in normal aging. Cortex, 46, 474-89.

CHEN, Y. L. & FRANCIS, A. J. P. 2010. Relaxation and imagery for chronic, nonmalignant pain: effects on pain symptoms, quality of life, and mental health. Pain Manag Nurs, 11, 159-68.

CHOI, D., CHOI, D., WHITTINGTON, R. & NEDELJKOVIC, S. 2007. Sudden amnesia resulting in pain relief: the relationship between memory and pain. Pain, 132, 206-10.

COHEN, R. A., KAPLAN, R. F., ZUFFANTE, P., MOSER, D. J., JENKINS, M. A., SALLOWAY, S. & WILKINSON, H. 1999. Alteration of intention and self-initiated action associated with bilateral anterior cingulotomy. J Neuropsychiatry Clin Neurosci, 11, 444-53.

COLLINS…, S. 2005. Emerging therapies for neuropathic pain. emd.

COSLETT, H. B., MEDINA, J., KLIOT, D. & BURKEY, A. R. 2010. Mental motor imagery indexes pain: the hand laterality task. Eur J Pain, 14, 1007-13.

COSTANTINI, M., GALATI, G., ROMANI, G. L. & AGLIOTI, S. M. 2008. Empathic neural reactivity to noxious stimuli delivered to body parts and non-corporeal objects. European Journal of Neuroscience, 28, 1222-1230.

CRAIG, A. D. 2003. Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol, 13, 500-5.

CRAIG, A. D. & BLOMQVIST, A. 2002. Is there a specific lamina I spinothalamocortical pathway for pain and temperature sensations in primates? J Pain, 3, 95-101; discussion 113-4.

CRAIG, A. D., BUSHNELL, M. C., ZHANG, E. T. & BLOMQVIST, A. 1994. A thalamic nucleus specific for pain and temperature sensation. Nature, 372, 770-3.

CRAIG, A. D. B. 2009. How do you feel--now? The anterior insula and human awareness. Nat Rev Neurosci, 10, 59-70.

CRITCHLEY, H. D., MATHIAS, C. J. & DOLAN, R. J. 2001. Neural activity in the human brain relating to uncertainty and arousal during anticipation. Neuron, 29, 537-45.

CRITCHLEY, H. D., WIENS, S., ROTSHTEIN, P., OHMAN, A. & DOLAN, R. J. 2004. Neural systems supporting interoceptive awareness. Nat Neurosci, 7, 189-95.

DAGENBACH, D., KUBAT-SILMAN, A. K. & ABSHER, J. R. 2001. Human verbal working memory impairments associated with thalamic damage. Int J Neurosci, 111, 67-87.

DANNECKER, E. A., PRICE, D. D. & ROBINSON, M. E. 2003. An examination of the relationships among recalled, expected, and actual intensity and unpleasantness of delayed onset muscle pain. J Pain, 4, 74-81.

DE PASCALIS, V., CACACE, I. & MASSICOLLE, F. 2008. Focused analgesia in waking and hypnosis: effects on pain, memory, and somatosensory event-related potentials. Pain, 134, 197-208.

DECETY, J. 1996. Do imagined and executed actions share the same neural substrate? Brain Res Cogn Brain Res, 3, 87-93.

DEICHMANN, R. 2005. Optimized RF excitation for anatomical brain imaging of the occipital lobe using the 3D MDEFT sequence and a surface transmit coil. Magn Reson Med, 53, 1212-6.

DELLA SALA, S., COWAN, N., BESCHIN, N. & PERINI, M. 2005. Just lying there, remembering: improving recall of prose in amnesic patients with mild cognitive impairment by minimising interference. Memory, 13, 435-40.

DELLA-MAGGIORE, V., SCHOLZ, J., JOHANSEN-BERG, H. & PAUS, T. 2009. The rate of visuomotor adaptation correlates with cerebellar white-matter microstructure. Hum. Brain Mapp., 30, 4048-53.

DERBYSHIRE, S., WHALLEY, M., STENGER, V. & OAKLEY, D. 2004a. Cerebral activation during hypnotically induced and imagined pain. NeuroImage, 23, 392-401.

DERBYSHIRE, S. W., WHALLEY, M. G., STENGER, V. A. & OAKLEY, D. A. 2004b. Cerebral activation during hypnotically induced and imagined pain. Neuroimage, 23, 392-401.

DI PIERO, V., JONES, A. K., IANNOTTI, F., POWELL, M., PERANI, D., LENZI, G. L. & FRACKOWIAK, R. S. 1991. Chronic pain: a PET study of the central effects of percutaneous high cervical cordotomy. Pain, 46, 9-12.

DICK, B. & RASHIQ, S. 2007a. Disruption of attention and working memory traces in individuals with chronic pain. Anesth Analg, 104, 1223-9, tables of contents.

DICK, B. D. & RASHIQ, S. 2007b. Disruption of attention and working memory traces in individuals with chronic pain. Anesth Analg, 104, 1223-9, tables of contents.

DRAGANSKI, B., MOSER, T., LUMMEL, N., GÄNSSBAUER, S., BOGDAHN, U., HAAS, F. & MAY, A. 2006. Decrease of thalamic gray matter following limb amputation. NeuroImage, 31, 951-7.

DVIR, Z., GAL-ESHEL, N., SHAMIR, B., PEVZNER, E., PERETZ, C. & KNOLLER, N. 2004. Simulated pain and cervical motion in patients with chronic disorders of the cervical spine. Pain Res Manag, 9, 131-6.

EBISCH, S. J. H., PERRUCCI, M. G., FERRETTI, A., DEL GRATTA, C., ROMANI, G. L. & GALLESE, V. 2008. The sense of touch: embodied simulation in a visuotactile mirroring mechanism for observed animate or inanimate touch. J Cogn Neurosci, 20, 1611-23.

ECCLESTON, C. & CROMBEZ, G. 2007. Worry and chronic pain: a misdirected problem solving model. Pain, 132, 233-6.

EDWARDS, R., BINGHAM III, C. & BATHON…, J. 2006. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. Arthritis Care & ….

ELOMAA, M. M., DE C WILLIAMS, A. C. & KALSO, E. A. 2009. Attention management as a treatment for chronic pain. Eur J Pain, 13, 1062-7.

ETHERTON, J., BIANCHINI, K., CIOTA, M., HEINLY, M. & GREVE, K. 2006. Pain, malingering and the WAIS-III Working Memory Index. Spine J, 6, 61-71.

FAIRHURST, M., WIECH, K., DUNCKLEY, P. & TRACEY, I. 2007. Anticipatory brainstem activity predicts neural processing of pain in humans. Pain, 128, 101-10.

FARRELL, M. J., LAIRD, A. R. & EGAN, G. F. 2005. Brain activity associated with painfully hot stimuli applied to the upper limb: a meta-analysis. Hum. Brain Mapp., 25, 129-39.

FAYMONVILLE, M., LAUREYS, S., DEGUELDRE, C., DELFIORE, G., LUXEN, A., FRANCK, G., LAMY, M. & MAQUET, P. 2000a. Neural mechanisms of antinociceptive effects of hypnosis. Anesthesiology, 92, 1257-67.

FAYMONVILLE, M. E., LAUREYS, S., DEGUELDRE, C., DELFIORE, G., LUXEN, A., FRANCK, G., LAMY, M. & MAQUET, P. 2000b. Neural mechanisms of antinociceptive effects of hypnosis. Anesthesiology, 92, 1257-67.

FELDNER…, M. 2001. Perceived control over anxiety-related events as a predictor of pain behaviors in a cold pressor task. Journal of behavior therapy and experimental ….

FERNANDEZ, E. & TURK, D. 1989. The utility of cognitive coping strategies for altering pain perception: a meta-analysis. Pain.

FLANAGAN, J. R. & JOHANSSON, R. S. 2003. Action plans used in action observation. Nature, 424, 769-71.

FLOR, H. 2004. [Visualisation of phantom- and backpain using imaging techniques. Implication for treatment]. Orthopade, 33, 553-7.

FLOR, H. 2008. Maladaptive plasticity, memory for pain and phantom limb pain: review and suggestions for new therapies. Expert Rev Neurother, 8, 809-18.

FRANKENSTEIN, U. N., RICHTER, W., MCINTYRE, M. C. & RÉMY, F. 2001. Distraction modulates anterior cingulate gyrus activations during the cold pressor test. NeuroImage, 14, 827-36.

FRISTON, K., WORSLEY, K. & FRACKOWIAK…, R. 1993. Assessing the significance of focal activations using their spatial extent. Human brain ….

GEDNEY, J. J. & LOGAN, H. 2006. Pain related recall predicts future pain report. Pain, 121, 69-76.

GEHA, P., BALIKI, M., HARDEN, R., BAUER, W., PARRISH, T. & APKARIAN, A. 2008. The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions. Neuron, 60, 570-81.

GENTILI, R., PAPAXANTHIS, C. & POZZO, T. 2006. Improvement and generalization of arm motor performance through motor imagery practice. Neuroscience, 137, 761-72.

GERARDIN, E., SIRIGU, A., LEHERICY, S., POLINE, J. B., GAYMARD, B., MARSAULT, C., AGID, Y. & LE BIHAN, D. 2000. Partially overlapping neural networks for real and imagined hand movements. Cereb Cortex, 10, 1093-104.

GEUZE, E., VERMETTEN, E., RUF, M., DE KLOET, C. S. & WESTENBERG, H. G. M. 2008. Neural correlates of associative learning and memory in veterans with posttraumatic stress disorder. J Psychiatr Res, 42, 659-69.

GIBSON, J. J. 1962. Observations on active touch. Psychol Rev, 69, 477-91.

GODINHO, F., MAGNIN, M., FROT, M., PERCHET, C. & GARCIA-LARREA, L. 2006. Emotional modulation of pain: is it the sensation or what we recall? J Neurosci, 26, 11454-61.

GOLD, J. I., BELMONT, K. A. & THOMAS, D. A. 2007. The neurobiology of virtual reality pain attenuation. Cyberpsychol Behav, 10, 536-44.

GRABENHORST, F., ROLLS, E. T. & PARRIS, B. A. 2008. From affective value to decision-making in the prefrontal cortex. Eur J Neurosci, 28, 1930-9.

GRAFTON, S. T., ARBIB, M. A., FADIGA, L. & RIZZOLATTI, G. 1996. Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. Exp Brain Res, 112, 103-11.

GRANT, J. A., COURTEMANCHE, J. & RAINVILLE, P. 2011. A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. Pain, 152, 150-6.

GRANT, J. A. & RAINVILLE, P. 2009. Pain sensitivity and analgesic effects of mindful states in Zen meditators: a cross-sectional study. Psychosom Med, 71, 106-14.

GRAY, J. R. & BRAVER, T. S. 2002. Personality predicts working-memory-related activation in the caudal anterior cingulate cortex. Cogn Affect Behav Neurosci, 2, 64-75.

GRAY, M. A., HARRISON, N. A., WIENS, S. & CRITCHLEY, H. D. 2007. Modulation of emotional appraisal by false physiological feedback during fMRI. PLoS ONE, 2, e546.

GREENBERG, D., RICE, H., COOPER, J. & CABEZA…, R. 2005. Co-activation of the amygdala, hippocampus and inferior frontal gyrus during autobiographical memory retrieval. Neuropsychologia.

GREGORY, R. L. 1980. Perceptions as hypotheses. Philos Trans R Soc Lond, B, Biol Sci, 290, 181-97.

GRISART, J., VAN DER LINDEN, M. & BASTIN, C. 2007. The contribution of recollection and familiarity to recognition memory performance in chronic pain patients. Behav Res Ther, 45, 1077-84.

GROSSMAN, P., TIEFENTHALER-GILMER, U., RAYSZ, A. & KESPER, U. 2007. Mindfulness training as an intervention for fibromyalgia: evidence of postintervention and 3-year follow-up benefits in well-being. Psychother Psychosom, 76, 226-33.

GU, X., LIU, X., GUISE, K. G., NAIDICH, T. P., HOF, P. R. & FAN, J. 2010. Functional dissociation of the frontoinsular and anterior cingulate cortices in empathy for pain. J Neurosci, 30, 3739-44.

GUSTIN, S. M., WRIGLEY, P. J., GANDEVIA, S. C., MIDDLETON, J. W., HENDERSON, L. A. & SIDDALL, P. J. 2008. Movement imagery increases pain in people with neuropathic pain following complete thoracic spinal cord injury. Pain, 137, 237-44.

GUSTIN, S. M., WRIGLEY, P. J., SIDDALL, P. J. & HENDERSON, L. A. 2010. Brain anatomy changes associated with persistent neuropathic pain following spinal cord injury. Cereb Cortex, 20, 1409-19.

GWILYM, S. E., FILIPPINI, N., DOUAUD, G., CARR, A. J. & TRACEY, I. 2010. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based morphometric study. Arthritis Rheum, 62, 2930-40.

HABAS, C., GUILLEVIN, R. & ABANOU, A. 2010. Functional connectivity of the superior human temporal sulcus in the brain resting state at 3T. Neuroradiology.

HALPERN, A. R. 2001. Cerebral substrates of musical imagery. Ann N Y Acad Sci, 930, 179-92.

HANAKAWA, T., DIMYAN, M. A. & HALLETT, M. 2008. Motor planning, imagery, and execution in the distributed motor network: a time-course study with functional MRI. Cereb Cortex, 18, 2775-88.

HANSSON, P. 2003. Difficulties in stratifying neuropathic pain by mechanisms. European Journal of Pain.

HARRIS, J. A., MINIUSSI, C., HARRIS, I. M. & DIAMOND, M. E. 2002. Transient storage of a tactile memory trace in primary somatosensory cortex. J Neurosci, 22, 8720-5.

HARRIS, J. A., PETERSEN, R. S. & DIAMOND, M. E. 2001. The cortical distribution of sensory memories. Neuron, 30, 315-8.

HAYES…, A. 2004. Clarifying the construct of mindfulness in the context of emotion regulation and the process of change in therapy. Clinical Psychology Science and ….

HEIN, G. & KNIGHT, R. T. 2008. Superior temporal sulcus--It's my area: or is it? J Cogn Neurosci, 20, 2125-36.

HÖLZEL, B. K., OTT, U., GARD, T., HEMPEL, H., WEYGANDT, M., MORGEN, K. & VAITL, D. 2008. Investigation of mindfulness meditation practitioners with voxel-based morphometry. Soc Cogn Affect Neurosci, 3, 55-61.

HOOKER, C. I., VEROSKY, S. C., GERMINE, L. T., KNIGHT, R. T. & D'ESPOSITO, M. 2008. Mentalizing about emotion and its relationship to empathy. Soc Cogn Affect Neurosci, 3, 204-17.

HOUTVEEN, J. & OEI, N. 2007. Recall bias in reporting medically unexplained symptoms comes from semantic memory. J Psychosom Res, 62, 277-82.

HSIEH, J. C., BELFRAGE, M., STONE-ELANDER, S., HANSSON, P. & INGVAR, M. 1995. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain, 63, 225-36.

HU, R., ESKANDAR, E. & WILLIAMS, Z. 2009. Role of deep brain stimulation in modulating memory formation and recall. Neurosurg Focus, 27, E3.

HUGDAHL, K., ROSEN, G., ERSLAND, L., LUNDERVOLD, A., SMIEVOLL, A., BARNDON, R. & THOMSEN, T. 2001. Common pathways in mental imagery and pain perception: an fMRI study of a subject with an amputated arm. Scand J Psychol, 42, 269-75.

JANTSCH, H., GAWLITZA, M., GEBER, C., BAUMGARTNER, U., KRAMER, H., MAGERL, W., TREEDE, R. & BIRKLEIN, F. 2009a. Explicit episodic memory for sensory-discriminative components of capsaicin-induced pain: Immediate and delayed ratings. Pain.

JANTSCH, H. H., GAWLITZA, M., GEBER, C., BAUMGARTNER, U., KRAMER, H. H., MAGERL, W., TREEDE, R. D. & BIRKLEIN, F. 2009b. Explicit episodic memory for sensory-discriminative components of capsaicin-induced pain: Immediate and delayed ratings. Pain.

JEANMONOD, D., MAGNIN, M. & MOREL, A. 1994. Chronic neurogenic pain and the medial thalamotomy. Schweiz Rundsch Med Prax, 83, 702-7.

JENKINSON, M. 2003. Fast, automated, N-dimensional phase-unwrapping algorithm. Magn Reson Med, 49, 193-7.

JENKINSON, M. & SMITH, S. 2001. A global optimisation method for robust affine registration of brain images. Med Image Anal, 5, 143-56.

JI, R., KOHNO, T., MOORE, K. & WOOLF, C. 2003. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci, 26, 696-705.

JOHANSEN-BERG, H., BEHRENS, T. E. J., ROBSON, M. D., DROBNJAK, I., RUSHWORTH, M. F. S., BRADY, J. M., SMITH, S. M., HIGHAM, D. J. & MATTHEWS, P. M. 2004. Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. Proc Natl Acad Sci USA, 101, 13335-40.

JOHANSEN-BERG, H., BEHRENS, T. E. J., SILLERY, E., CICCARELLI, O., THOMPSON, A. J., SMITH, S. M. & MATTHEWS, P. M. 2005. Functional-anatomical validation and individual variation of diffusion tractography-based segmentation of the human thalamus. Cereb Cortex, 15, 31-9.

JOHANSEN-BERG, H. & BEHRENS…, T. 2004. Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. Proceedings of the ….

JOHANSEN-BERG, H., SCHOLZ, J. & STAGG, C. J. 2010. Relevance of structural brain connectivity to learning and recovery from stroke. Front Syst Neurosci, 4, 146.

KARNATH, H. O. 2001. New insights into the functions of the superior temporal cortex. Nat Rev Neurosci, 2, 568-76.

KELLY, S., LLOYD, D., NURMIKKO, T. & ROBERTS, N. 2007. Retrieving autobiographical memories of painful events activates the anterior cingulate cortex and inferior frontal gyrus. J Pain, 8, 307-14.

KEOGH, E., ELLERY, D., HUNT, C. & HANNENT, I. 2001. Selective attentional bias for pain-related stimuli amongst pain fearful individuals. Pain, 91, 91-100.

KIHLSTROM, J. F. 1985. Hypnosis. Annu Rev Psychol, 36, 385-418.

KIKUCHI, H., YOSHIUCHI, K., MIYASAKA, N., OHASHI, K., YAMAMOTO, Y., KUMANO, H., KUBOKI, T. & AKABAYASHI, A. 2006. Reliability of recalled self-report on headache intensity: investigation using ecological momentary assessment technique. Cephalalgia, 26, 1335-43.

KIM, H. 2010. Neural activity that predicts subsequent memory and forgetting: A meta-analysis of 74 fMRI studies. NeuroImage, 1-16.

KOCHUNOV, P., RAMAGE, A. E., LANCASTER, J. L., ROBIN, D. A., NARAYANA, S., COYLE, T., ROYALL, D. R. & FOX, P. 2009. Loss of cerebral white matter structural integrity tracks the gray matter metabolic decline in normal aging. NeuroImage, 45, 17-28.

KOSSLYN, S. & THOMPSON, W. 2003. When is early visual cortex activated during visual mental imagery? Psychol Bull, 129, 723-46.

KOSSLYN, S. M., GANIS, G. & THOMPSON, W. L. 2001. Neural foundations of imagery. Nat Rev Neurosci, 2, 635-42.

KOSSLYN, S. M., GANIS, G. & THOMPSON, W. L. 2003. Mental imagery: against the nihilistic hypothesis. Trends Cogn Sci, 7, 109-111.

KOYAMA, T., MCHAFFIE, J., LAURIENTI, P. & COGHILL, R. 2005a. The subjective experience of pain: where expectations become reality. Proc Natl Acad Sci U S A, 102, 12950-5.

KOYAMA, T., MCHAFFIE, J. G., LAURIENTI, P. J. & COGHILL, R. C. 2005b. The subjective experience of pain: where expectations become reality. Proc Natl Acad Sci U S A, 102, 12950-5.

KUBAT-SILMAN, A. & DAGENBACH…, D. 2002. Patterns of impaired verbal, spatial, and object working memory after thalamic lesions. Brain Cogn.

KUHAJDA, M., THORN, B., KLINGER, M. & RUBIN, N. 2002. The effect of headache pain on attention (encoding) and memory (recognition). Pain, 97, 213-21.

LAMM, C., BATSON, C. D. & DECETY, J. 2007a. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. J Cogn Neurosci, 19, 42-58.

LAMM, C., DECETY, J. & SINGER, T. 2011. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. NeuroImage, 54, 2492-502.

LAMM, C., NUSBAUM, H. C., MELTZOFF, A. N. & DECETY, J. 2007b. What Are You Feeling? Using Functional Magnetic Resonance Imaging to Assess the Modulation of Sensory and Affective Responses during Empathy for Pain. PLoS ONE, 2, e1292.

LANG, E. V., BENOTSCH, E. G., FICK, L. J., LUTGENDORF, S., BERBAUM, M. L., BERBAUM, K. S., LOGAN, H. & SPIEGEL, D. 2000. Adjunctive non-pharmacological analgesia for invasive medical procedures: a randomised trial. Lancet, 355, 1486-90.

LANG, P. J. 1995. The emotion probe. Studies of motivation and attention. Am Psychol, 50, 372-85.

LAVERDURE-DUPONT, D., RAINVILLE, P., MONTPLAISIR, J. & LAVIGNE, G. 2009. Changes in rapid eye movement sleep associated with placebo-induced expectations and analgesia. J Neurosci, 29, 11745-52.

LAZAR, S. W., KERR, C. E., WASSERMAN, R. H., GRAY, J. R., GREVE, D. N., TREADWAY, M. T., MCGARVEY, M., QUINN, B. T., DUSEK, J. A., BENSON, H., RAUCH, S. L., MOORE, C. I. & FISCHL,

B. 2005. Meditation experience is associated with increased cortical thickness. Neuroreport, 16, 1893-7.

LAZARUS…, R. 1984. Stress, appraisal, and coping. books.google.com.

LEPAGE, M., GHAFFAR, O., NYBERG, L. & TULVING, E. 2000. Prefrontal cortex and episodic memory retrieval mode. Proc Natl Acad Sci USA, 97, 506-11.

LEWANDOWSKI, W., GOOD, M. & DRAUCKER, C. B. 2005. Changes in the meaning of pain with the use of guided imagery. Pain Manag Nurs, 6, 58-67.

LI, C. R. 2000. Impairment of motor imagery in putamen lesions in humans. Neurosci Lett, 287, 13-6.

LING, J., CAMPBELL, C., HEFFERNAN, T. M. & GREENOUGH, C. G. 2007. Short-term prospective memory deficits in chronic back pain patients. Psychosom Med, 69, 144-8.

LO, C., HO, S. & HOLLON, S. 2008. The effects of rumination and negative cognitive styles on depression: A mediation analysis. Behav Res Ther, 46, 487-95.

LORENZ, J. 2010. Pain - not just a feeling, but a working brain. Pain, 149, 3-4.

LORENZ, J., MINOSHIMA, S. & CASEY, K. 2003a. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain, 126, 1079-91.

LORENZ, J., MINOSHIMA, S. & CASEY, K. L. 2003b. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain, 126, 1079-91.

LOUIS, M., GUILLOT, A., MATON, S., DOYON, J. & COLLET, C. 2008. Effect of imagined movement speed on subsequent motor performance. J Mot Behav, 40, 117-32.

MACIVER, K., LLOYD, D. M., KELLY, S., ROBERTS, N. & NURMIKKO, T. 2008. Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. Brain, 131, 2181-91.

MACLACHLAN, M., MCDONALD, D. & WALOCH, J. 2004. Mirror treatment of lower limb phantom pain: a case study. Disabil Rehabil, 26, 901-4.

MAGNI, G., MORESCHI, C., RIGATTI-LUCHINI, S. & MERSKEY, H. 1994. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. Pain, 56, 289-97.

MAGUIRE, E. A. 2001. Neuroimaging studies of autobiographical event memory. Philos Trans R Soc Lond B Biol Sci, 356, 1441-51.

MALHOTRA-KUMAR, S., VAN HEIRSTRAETEN, L., LEE, A., ABRAHANTES, J. C., LAMMENS, C., VANHOMMERIG, E., MOLENBERGHS, G., AERTS, M., HARBARTH, S., GOOSSENS, H. & TEAM, O.

B. O. T. M. W. S. 2010. Evaluation of molecular assays for rapid detection of methicillin-resistant Staphylococcus aureus. Journal of clinical microbiology.

MARTY, M., ROZENBERG, S., LEGOUT, V., DURAND-ZALESKI, I., MOYSE, D., HENROTIN, Y., PERROT, S., RHUMATOLOGIE, S. R. D. L. S. F. D. & SOCIETY, B. B. 2009. Influence of time, activities, and memory on the assessment of chronic low back pain intensity. Spine, 34, 1604-9.

MAY, A. 2008. Chronic pain may change the structure of the brain. Pain, 137, 7-15.

MCCRACKEN, L. & GAUNTLETT-GILBERT…, J. 2007. The role of mindfulness in a contextual cognitive-behavioral analysis of chronic pain-related suffering and disability. Pain.

MCCRACKEN, L. M. 2007. A contextual analysis of attention to chronic pain: what the patient does with their pain might be more important than their awareness or vigilance alone. J Pain, 8, 230-6.

MCCRACKEN, L. M., GAUNTLETT-GILBERT, J. & VOWLES, K. E. 2007a. The role of mindfulness in a contextual cognitive-behavioral analysis of chronic pain-related suffering and disability. Pain, 131, 63-9.

MCCRACKEN, L. M., VOWLES, K. E. & GAUNTLETT-GILBERT, J. 2007b. A prospective investigation of acceptance and control-oriented coping with chronic pain. J Behav Med, 30, 339-49.

MEAGHER, M., ARNAU, R. & RHUDY, J. 2001. Pain and emotion: effects of affective picture modulation. Psychosom Med, 63, 79-90.

MEISTER, I. G., KRINGS, T., FOLTYS, H., BOROOJERDI, B., MÜLLER, M., TÖPPER, R. & THRON, A. 2004. Playing piano in the mind--an fMRI study on music imagery and performance in pianists. Brain Res Cogn Brain Res, 19, 219-28.

MELZACK, R. 1975. The McGill Pain Questionnaire: major properties and scoring methods. Pain, 1, 277-99.

MELZACK, R. 1990a. Pain [] memories' in phantom limbs: review and clinical observations. Pain.

MELZACK, R. 1990b. Phantom limbs and the concept of a neuromatrix. Trends in neurosciences.

MELZACK, R. & CHAPMAN, C. 1973a. Psychologic aspects of pain. Postgrad Med, 53, 69-75.

MELZACK, R. & CHAPMAN, C. R. 1973b. Psychologic aspects of pain. Postgrad Med, 53, 69-75.

MENON, V., ANAGNOSON, R. T., GLOVER, G. H. & PFEFFERBAUM, A. 2000. Basal ganglia involvement in memory-guided movement sequencing. Neuroreport, 11, 3641-5.

MERSKEY, H. 1994. Pain terms. Classification of chronic pain.

MICHELS, L., MOAZAMI-GOUDARZI, M., JEANMONOD, D. & SARNTHEIN, J. 2008. EEG alpha distinguishes between cuneal and precuneal activation in working memory. NeuroImage, 40, 1296-310.

MIRON, D., DUNCAN, G. H. & BUSHNELL, M. C. 1989. Effects of attention on the intensity and unpleasantness of thermal pain. Pain, 39, 345-52.

MOLENBERGHS, P., BRANDER, C., MATTINGLEY, J. B. & CUNNINGTON, R. 2010. The role of the superior temporal sulcus and the mirror neuron system in imitation. Hum. Brain Mapp., 31, 1316-26.

MOLENBERGHS, P., CUNNINGTON, R. & MATTINGLEY, J. B. 2009. Is the mirror neuron system involved in imitation? A short review and meta-analysis. Neurosci Biobehav Rev, 33, 975-80.

MOLL, J., DE OLIVEIRA-SOUZA, R., ESLINGER, P. J., BRAMATI, I. E., MOURÃO-MIRANDA, J., ANDREIUOLO, P. A. & PESSOA, L. 2002. The neural correlates of moral sensitivity: a functional magnetic resonance imaging investigation of basic and moral emotions. J Neurosci, 22, 2730-6.

MORLEY, S. 1993. Vivid memory for 'everyday' pains. Pain, 55, 55-62.

MORLEY, S., WILLIAMS, A. & HUSSAIN, S. 2008. Estimating the clinical effectiveness of cognitive behavioural therapy in the clinic: evaluation of a CBT informed pain management programme. Pain, 137, 670-80.

MORONE, N. E., GRECO, C. M. & WEINER, D. K. 2008. Mindfulness meditation for the treatment of chronic low back pain in older adults: a randomized controlled pilot study. Pain, 134, 310-9.

MORRISON, I., PEELEN, M. V. & DOWNING, P. E. 2007. The sight of others' pain modulates motor processing in human cingulate cortex. Cereb Cortex, 17, 2214-22.

MOSELEY, G. L. 2007. Using visual illusion to reduce at-level neuropathic pain in paraplegia. Pain, 130, 294-8.

MOSELEY, G. L. & ARNTZ, A. 2007. The context of a noxious stimulus affects the pain it evokes. Pain, 133, 64-71.

NI, H., KAVCIC, V. & ZHU…, T. 2006. Effects of number of diffusion gradient directions on derived diffusion tensor imaging indices in human brain. American Journal of ….

NIVEN, C. & BRODIE, E. 1996a. Memory for labor pain: context and quality. Pain, 64, 387-92.

NIVEN, C. A. & BRODIE, E. E. 1996b. Memory for labor pain: context and quality. Pain, 64, 387-92.

OAKLEY, D. A., WHITMAN, L. G. & HALLIGAN, P. W. 2002. Hypnotic imagery as a treatment for phantom limb pain: two case reports and a review. Clin Rehabil, 16, 368-77.

OGINO, Y., NEMOTO, H., INUI, K., SAITO, S., KAKIGI, R. & GOTO, F. 2007. Inner experience of pain: imagination of pain while viewing images showing painful events forms subjective pain representation in human brain. Cereb Cortex, 17, 1139-46.

OOSTERMAN, J., VAN HARTEN, B. & WEINSTEIN…, H. 2006. Pain intensity and pain affect in relation to white matter changes. Pain.

OOSTERMAN, J. M., DERKSEN, L. C., VAN WIJCK, A. J. M., VELDHUIJZEN, D. S. & KESSELS, R. P. C. 2011. Memory functions in chronic pain: examining contributions of attention and age to test performance. Clin J Pain, 27, 70-5.

OSTROWSKY, K., MAGNIN, M., RYVLIN, P. & ISNARD…, J. 2002. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. Cerebral ….

PAGNONI, G. & CEKIC, M. 2007. Age effects on gray matter volume and attentional performance in Zen meditation. Neurobiol Aging, 28, 1623-7.

PATTERSON…, D. 2003. Hypnosis and clinical pain. Psychological Bulletin.

PEARSON, J., CLIFFORD, C. W. G. & TONG, F. 2008. The functional impact of mental imagery on conscious perception. Curr Biol, 18, 982-6.

PERLMAN, D. M., SALOMONS, T. V., DAVIDSON, R. J. & LUTZ, A. 2010. Differential effects on pain intensity and unpleasantness of two meditation practices. Emotion, 10, 65-71.

PETROVIC, P., KALSO, E., PETERSSON, K. M. & INGVAR, M. 2002. Placebo and opioid analgesia--imaging a shared neuronal network. Science, 295, 1737-40.

PEYRON, R. & FAILLENOT, I. 2011. [Functionnal brain mapping of pain perception.]. Medecine sciences : M/S, 27, 82-87.

PHELPS, E. A. 2004. Human emotion and memory: interactions of the amygdala and hippocampal complex. Curr Opin Neurobiol, 14, 198-202.

PICKERING, G., CHAPUY, E., ESCHALIER, A. & DUBRAY, C. 2004. Memory impairment means less pain for mice. Gerontology, 50, 152-6.

PIRAS, F., CALTAGIRONE, C. & SPALLETTA, G. 2010. Working memory performance and thalamus microstructure in healthy subjects. Neuroscience, 171, 496-505.

PLOGHAUS, A., BECERRA, L., BORRAS, C. & BORSOOK, D. 2003. Neural circuitry underlying pain modulation: expectation, hypnosis, placebo. Trends Cogn Sci (Regul Ed), 7, 197-200.

PLOGHAUS, A., NARAIN, C., BECKMANN, C., CLARE, S., BANTICK, S., WISE, R., MATTHEWS, P., RAWLINS, J. & TRACEY, I. 2001a. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci, 21, 9896-903.

PLOGHAUS, A., NARAIN, C., BECKMANN, C. F., CLARE, S., BANTICK, S., WISE, R., MATTHEWS, P. M., RAWLINS, J. N. & TRACEY, I. 2001b. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. J Neurosci, 21, 9896-903.

PLOGHAUS, A., TRACEY, I., CLARE, S., GATI, J. S., RAWLINS, J. N. & MATTHEWS, P. M. 2000. Learning about pain: the neural substrate of the prediction error for aversive events. Proc Natl Acad Sci USA, 97, 9281-6.

PLOGHAUS, A., TRACEY, I., GATI, J. S., CLARE, S., MENON, R. S., MATTHEWS, P. M. & RAWLINS, J. N. 1999. Dissociating pain from its anticipation in the human brain. Science, 284, 1979-81.

PLONER, M., LEE, M. C., WIECH, K., BINGEL, U. & TRACEY, I. 2010. Prestimulus functional connectivity determines pain perception in humans. Proc Natl Acad Sci USA, 107, 355-60.

PORRO, C. A., BARALDI, P., PAGNONI, G., SERAFINI, M., FACCHIN, P., MAIERON, M. & NICHELLI, P. 2002. Does anticipation of pain affect cortical nociceptive systems? J Neurosci, 22, 3206-14.

POSNER, M. I., SNYDER, C. R. & DAVIDSON, B. J. 1980. Attention and the detection of signals. J Exp Psychol, 109, 160-74.

PRICE, D. D. 2000. Psychological and neural mechanisms of the affective dimension of pain. Science, 288, 1769-72.

PRICE, D. D. & DUBNER, R. 1977. Neurons that subserve the sensory-discriminative aspects of pain. Pain, 3, 307-38.

PRICE, D. D., GREENSPAN, J. D. & DUBNER, R. 2003. Neurons involved in the exteroceptive function of pain. Pain, 106, 215-9.

PRICE, D. D. & VERNE, G. N. 2002. Does the spinothalamic tract to ventroposterior lateral thalamus and somatosensory cortex have roles in both pain sensation and pain-related emotions? J Pain, 3, 105-8; discussion 113-4.

RADLOFF, L. 1977. The CES-D Scale: A Self Report Depression Scale for Research in the General. Applied psychological measurement.

RAIJ, T. T., NUMMINEN, J., NARVANEN, S., HILTUNEN, J. & HARI, R. 2005. Brain correlates of subjective reality of physically and psychologically induced pain. Proc Natl Acad Sci U S A, 102, 2147-51.

RAINVILLE, P. 2008. Hypnosis and the analgesic effect of suggestions. Pain, 134, 1-2.

RAINVILLE, P., CARRIER, B., HOFBAUER, R. K., BUSHNELL, M. C. & DUNCAN, G. H. 1999a. Dissociation of sensory and affective dimensions of pain using hypnotic modulation. Pain, 82, 159-71.

RAINVILLE, P., DOUCET, J., FORTIN, M. & DUNCAN, G. 2004a. Rapid deterioration of pain sensory-discriminative information in short-term memory. Pain, 110, 605-15.

RAINVILLE, P., DOUCET, J. C., FORTIN, M. C. & DUNCAN, G. H. 2004b. Rapid deterioration of pain sensory-discriminative information in short-term memory. Pain, 110, 605-15.

RAINVILLE, P., HOFBAUER, R. K., PAUS, T., DUNCAN, G. H., BUSHNELL, M. C. & PRICE, D. D. 1999b. Cerebral mechanisms of hypnotic induction and suggestion. J Cogn Neurosci, 11, 110-25.

RAMACHANDRAN, V. S. & ALTSCHULER, E. L. 2009. The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain, 132, 1693-710.

RHUDY, J. L. & MEAGHER, M. W. 2000. Fear and anxiety: divergent effects on human pain thresholds. Pain, 84, 65-75.

ROBERTSON, E. M. 2009. Brain rhythms: enhancing memories. Curr Biol, 19, R992-4.

ROBINSON, M. D. & CLORE, G. L. 2002. Belief and feeling: evidence for an accessibility model of emotional self-report. Psychological Bulletin, 128, 934-60.

ROCCA, M., CECCARELLI, A., FALINI, A. & COLOMBO…, B. 2006. Brain Gray Matter Changes in Migraine Patients With T2-Visible Lesions. 中风学杂志.

RODRIGUEZ, M., LLANOS, C. & GONZALEZ…, S. 2008. How similar are motor imagery and movement? Behavioral neuroscience.

RODRIGUEZ, M. & LLANOS…, C. 2009. The kinematics of motor imagery: comparing the dynamics of real and virtual movements. Neuropsychologia.

ROLLS, E. T. & GRABENHORST, F. 2008. The orbitofrontal cortex and beyond: from affect to decision-making. Prog Neurobiol, 86, 216-44.

RUBY, P. & DECETY, J. 2004. How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. J Cogn Neurosci, 16, 988-99.

SAMSON, D., APPERLY, I. A., CHIAVARINO, C. & HUMPHREYS, G. W. 2004. Left temporoparietal junction is necessary for representing someone else's belief. Nat Neurosci, 7, 499-500.

SAMSON, D., APPERLY, I. A., KATHIRGAMANATHAN, U. & HUMPHREYS, G. W. 2005. Seeing it my way: a case of a selective deficit in inhibiting self-perspective. Brain, 128, 1102-11.

SARINOPOULOS, I., GRUPE, D. W., MACKIEWICZ, K. L., HERRINGTON, J. D., LOR, M., STEEGE, E. E. & NITSCHKE, J. B. 2010. Uncertainty during anticipation modulates neural responses to aversion in human insula and amygdala. Cereb Cortex, 20, 929-40.

SAWAMOTO, N., HONDA, M., OKADA, T., HANAKAWA, T., KANDA, M., FUKUYAMA, H., KONISHI, J. & SHIBASAKI, H. 2000. Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. J Neurosci, 20, 7438-45.

SCADDING…, J. 2005. Painful peripheral neuropathies. eprints.ucl.ac.uk.

SCHACTER, D., ADDIS, D. & BUCKNER, R. 2007a. Remembering the past to imagine the future: the prospective brain. Nat Rev Neurosci, 8, 657-61.

SCHACTER, D. L., ADDIS, D. R. & BUCKNER, R. L. 2007b. Remembering the past to imagine the future: the prospective brain. Nat Rev Neurosci, 8, 657-61.

SCHMIDT-WILCKE, T., LEINISCH, E., GANSSBAUER, S., DRAGANSKI, B., BOGDAHN, U., ALTMEPPEN, J. & MAY, A. 2006. Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. Pain, 125, 89-97.

SCHMIDT-WILCKE, T., LUERDING, R., WEIGAND, T., JURGENS, T., SCHUIERER, G., LEINISCH, E. & BOGDAHN, U. 2007. Striatal grey matter increase in patients suffering from fibromyalgia--a voxel-based morphometry study. Pain, 132 Suppl 1, S109-16.

SCHWEINHARDT, P., KUCHINAD, A., PUKALL, C. F. & BUSHNELL, M. C. 2008. Increased gray matter density in young women with chronic vulvar pain. Pain, 140, 411-9.

SHERRINGTON, C. S. 1903. Qualitative difference of spinal reflex corresponding with qualitative difference of cutaneous stimulus. J Physiol (Lond), 30, 39-46.

SKINNER, E. 1996. A Guide to Constructs of Control* 1,* 2. Journal of Personality and Social Psychology.

SMITH, K. A., PLOGHAUS, A., COWEN, P. J., MCCLEERY, J. M., GOODWIN, G. M., SMITH, S., TRACEY, I. & MATTHEWS, P. M. 2002. Cerebellar responses during anticipation of noxious stimuli in subjects recovered from depression. Functional magnetic resonance imaging study. Br J Psychiatry, 181, 411-5.

SMITH, S., JENKINSON, M. & JOHANSEN-BERG…, H. 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage.

SPIELBERGER, C. 1970. State-Trait Anxiety Inventory. Wiley Online Library.

SRIWATANAKUL, K., KELVIE, W., LASAGNA, L., CALIMLIM, J. F., WEIS, O. F. & MEHTA, G. 1983. Studies with different types of visual analog scales for measurement of pain. Clin Pharmacol Ther, 34, 234-9.

STEWART, L. 2008. Do musicians have different brains? Clin Med, 8, 304-8.

STOETER, P., BAUERMANN, T., NICKEL, R., CORLUKA, L., GAWEHN, J., VUCUREVIC, G., VOSSEL, G. & EGLE, U. T. 2007. Cerebral activation in patients with somatoform pain disorder exposed to pain and stress: an fMRI study. NeuroImage, 36, 418-30.

SULLIVAN, M., MARTEL, M., TRIPP, D., SAVARD, A. & CROMBEZ, G. 2006a. Catastrophic thinking and heightened perception of pain in others. Pain, 123, 37-44.

SULLIVAN, M. J., LYNCH, M. E. & CLARK, A. J. 2005. Dimensions of catastrophic thinking associated with pain experience and disability in patients with neuropathic pain conditions. Pain, 113, 310-5.

SULLIVAN, M. J., MARTEL, M. O., TRIPP, D. A., SAVARD, A. & CROMBEZ, G. 2006b. Catastrophic thinking and heightened perception of pain in others. Pain, 123, 37-44.

SUMITANI, M., MIYAUCHI, S., MCCABE, C. S., SHIBATA, M., MAEDA, L., SAITOH, Y., TASHIRO, T. & MASHIMO, T. 2008. Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: a preliminary report. Rheumatology (Oxford), 47, 1038-43.

SZPUNAR, K. K., WATSON, J. M. & MCDERMOTT, K. B. 2007. Neural substrates of envisioning the future. Proc Natl Acad Sci U S A, 104, 642-7.

TAN, A. M., STAMBOULIAN, S., CHANG, Y.-W., ZHAO, P., HAINS, A. B., WAXMAN, S. G. & HAINS, B. C. 2008. Neuropathic pain memory is maintained by Rac1-regulated dendritic spine remodeling after spinal cord injury. J Neurosci, 28, 13173-83.

TANG, Y.-Y., MA, Y., WANG, J., FAN, Y., FENG, S., LU, Q., YU, Q., SUI, D., ROTHBART, M. K., FAN, M. & POSNER, M. I. 2007. Short-term meditation training improves attention and self-regulation. Proc Natl Acad Sci USA, 104, 17152-6.

TERRY, R., NIVEN, C., BRODIE, E., JONES, R. & PROWSE, M. 2008a. Memory for pain? A comparison of nonexperiential estimates and patients' reports of the quality and intensity of postoperative pain. J Pain, 9, 342-9.

TERRY, R. H., NIVEN, C. A., BRODIE, E. E., JONES, R. B. & PROWSE, M. A. 2008b. Memory for pain? A comparison of nonexperiential estimates and patients' reports of the quality and intensity of postoperative pain. J Pain, 9, 342-9.

TEUTSCH, S., HERKEN, W., BINGEL, U., SCHOELL, E. & MAY, A. 2008. Changes in brain gray matter due to repetitive painful stimulation. NeuroImage, 42, 845-9.

THUREL…, C. 2002. Le syndrome thalamique. La douleur en pratique quotidienne: ….

TOMASI, D., CAPARELLI, E. C., CHANG, L. & ERNST, T. 2005. fMRI-acoustic noise alters brain activation during working memory tasks. NeuroImage, 27, 377-86.

TRACEY, I. 2005. Nociceptive processing in the human brain. Curr Opin Neurobiol, 15, 478-87.

TRACEY, I. 2010. Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. Nat Med, 16, 1277-83.

TRACEY, I. & BUSHNELL, M. C. 2009. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? J Pain, 10, 1113-20.

TRACEY, I. & MANTYH, P. 2007. The cerebral signature for pain perception and its modulation. Neuron, 55, 377-91.

TRACEY, I., PLOGHAUS, A., GATI, J. S., CLARE, S., SMITH, S., MENON, R. S. & MATTHEWS, P. M. 2002. Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci, 22, 2748-52.

TREEDE, R. D. 2002. Spinothalamic and thalamocortical nociceptive pathways. J Pain, 3, 109-12;discussion 113-4.

VALENTINI, E. 2010. The role of anterior insula and anterior cingulate in empathy for pain. Journal of Neurophysiology, 104, 584-6.

VALET, M., SPRENGER, T., BOECKER, H., WILLOCH, F., RUMMENY, E., CONRAD, B., ERHARD, P. & TOLLE, T. R. 2004. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain--an fMRI analysis. Pain, 109, 399-408.

VALFRÈ, W., RAINERO, I. & BERGUI…, M. 2008. Voxel-Based Morphometry Reveals Gray Matter Abnormalities in Migraine. Headache: The Journal ….

VAN DAMME, S., LEGRAIN, V., VOGT, J. & CROMBEZ, G. 2010. Keeping pain in mind: a motivational account of attention to pain. Neurosci Biobehav Rev, 34, 204-13.

VESTERGAARD-POULSEN, P., VAN BEEK, M., SKEWES, J., BJARKAM, C. R., STUBBERUP, M., BERTELSEN, J. & ROEPSTORFF, A. 2009. Long-term meditation is associated with increased gray matter density in the brain stem. Neuroreport, 20, 170-4.

VILLEMURE, C. & BUSHNELL, M. C. 2002. Cognitive modulation of pain: how do attention and emotion influence pain processing? Pain, 95, 195-9.

WALSH, N. D. & PHILLIPS, M. L. 2010. Interacting outcome retrieval, anticipation, and feedback processes in the human brain. Cereb Cortex, 20, 271-81.

WICKENS, J. R., REYNOLDS, J. N. J. & HYLAND, B. I. 2003. Neural mechanisms of reward-related motor learning. Curr Opin Neurobiol, 13, 685-90.

WIECH, K., LIN, C.-S., BRODERSEN, K. H., BINGEL, U., PLONER, M. & TRACEY, I. 2010. Anterior Insula Integrates Information about Salience into Perceptual Decisions about Pain. J Neurosci, 30, 16324-16331.

WIECH, K., PLONER, M. & TRACEY, I. 2008. Neurocognitive aspects of pain perception. Trends Cogn Sci, 12, 306-13.

WIECH, K. & TRACEY, I. 2009. The influence of negative emotions on pain: behavioral effects and neural mechanisms. Neuroimage, 47, 987-94.

WILLIS, W. D. & WESTLUND, K. N. 1997. Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol, 14, 2-31.

WILLIS, W. D., ZHANG, X., HONDA, C. N. & GIESLER, G. J. 2002. A critical review of the role of the proposed VMpo nucleus in pain. J Pain, 3, 79-94.

WOLFENSTELLER, U., SCHUBOTZ, R. I. & VON CRAMON, D. Y. 2007. Understanding non-biological dynamics with your own premotor system. NeuroImage, 36 Suppl 2, T33-43.

WOLPERT, D. M. & GHAHRAMANI, Z. 2000. Computational principles of movement neuroscience. Nat Neurosci, 3 Suppl, 1212-7.

WOLPERT, D. M. & KAWATO, M. 1998. Multiple paired forward and inverse models for motor control. Neural Netw, 11, 1317-29.

WOLPERT, D. M. & MIALL, R. C. 1996. Forward Models for Physiological Motor Control. Neural Netw, 9, 1265-1279.

WOOLF, C. J. & SALTER, M. W. 2000. Neuronal plasticity: increasing the gain in pain. Science, 288, 1765-9.

WOOLRICH, M., RIPLEY, B., BRADY, M. & SMITH, S. 2001a. Temporal autocorrelation in univariate linear modeling of FMRI data. NeuroImage, 14, 1370-86.

WOOLRICH, M., RIPLEY, B. & BRADY…, M. 2001b. Temporal autocorrelation in univariate linear modeling of FMRI data. NeuroImage.

WOOLRICH, M. W., RIPLEY, B. D., BRADY, M. & SMITH, S. M. 2001c. Temporal autocorrelation in univariate linear modeling of FMRI data. Neuroimage, 14, 1370-86.

WORSLEY, K., EVANS, A. & MARRETT…, S. 1992. A three-dimensional statistical analysis for CBF activation studies in human brain. Journal of Cerebral Blood ….

WYMBS, N. F. & GRAFTON, S. T. 2009. Neural substrates of practice structure that support future off-line learning. Journal of Neurophysiology, 102, 2462-76.

YOUELL, P. D., WISE, R. G., BENTLEY, D. E., DICKINSON, M. R., KING, T. A., TRACEY, I. & JONES, A. K. P. 2004. Lateralisation of nociceptive processing in the human brain: a functional magnetic resonance imaging study. NeuroImage, 23, 1068-77.

ZACKS, J., SPEER, N., SWALLOW, K., BRAVER, T. & REYNOLDS, J. 2007. Event perception: a mind-brain perspective. Psychol Bull, 133, 273-93.

ZEIDAN, F., JOHNSON, S. K., GORDON, N. S. & GOOLKASIAN, P. 2010. Effects of brief and sham mindfulness meditation on mood and cardiovascular variables. J Altern Complement Med, 16, 867-73.

ZHAO, X.-H., WANG, P.-J., LI, C.-B., WANG, J.-H., YANG, Z.-Y., HU, Z.-H. & WU, W.-Y. 2006. [Prefrontal and superior temporal lobe hyperactivity as a biological substrate of generalized anxiety disorders]. Zhonghua Yi Xue Za Zhi, 86, 955-60.

ZHUO, M. 2007. A synaptic model for pain: long-term potentiation in the anterior cingulate cortex. Mol Cells, 23, 259-71.