Assessing the neural mechanisms of chronic knee osteoarthritis pain using functional magnetic resonance imaging

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Abstract

Chronic pain is a multifactorial experience combining sensory, affective and cognitive components and the underlying neural activity related to pain is subsequently diverse and encompasses widespread regions of the brain. Functional neuroimaging studies have suggested altered patterns of brain activity relating to chronic pain and in response to acute experimental pain but these findings have been inconsistent. Furthermore, research into chronic knee osteoarthritis pain (one of the most commonly presenting chronic pain states) has to date been lacking. The research here seeks to first assess the consistency of findings within the present literature and subsequently use these findings to motivate investigation into the neural correlates of chronic pain and its impact on brain state using advanced functional magnetic resonance imaging techniques alongside questionnaire-based participant report in a chronic knee osteoarthritis pain cohort.

The consistency of previously published functional neuroimaging findings of acute experimental pain in healthy and chronic pain cohorts was first established using coordinate based meta-analysis. A large-scale dataset was collated from the literature including over 200 published articles whilst a new coordinate based meta-analytic algorithm was applied that was shown to improve on the multiple-test correction of those previously available. Pain-related brain activity from healthy controls and chronic pain patient displayed no differences when assessed. Subsequent analysis found that application of a painful stimulus to the clinically affected site in a chronic pain patient displayed significant differences compared to that seen in healthy volunteers in the left lentiform nucleus, middle frontal gyrus and right posterior insula.

Investigation into other pain-related brain activity such as pain-anticipatory and intensity related displayed overlapping regional activity within the bilateral anterior insula and anterior cingulate (core regions of the salience network). Pain-related deactivation in healthy controls was significant within the subgenual cingulate and the paracentral lobule.

Subsequently, as over 200 studies collated did not prove the sensitivity of evoking experimental pain to elucidate alterations in brain activity related to chronic pain, the next study was motivated to directly study the neural correlates of chronic pain itself. Arterial spin labelling (a functional MRI technique that displays increased sensitivity to tonic stimuli such as chronic pain) was used to study 26 chronic knee osteoarthritis patients and 27 matched healthy controls. Reported pain perception was found to correlate significantly with cerebral blood flow (controlled for age, sex and mean whole-brain cerebral blood flow) in limbic regions in OA patients not consistently seen within acute experimental pain such as the bilateral amygdala and subgenual cingulate. Additionally controlling for reported trait anxiety markedly reduced this relationship but was not found to mediate it when tested. Comparisons between knee osteoarthritis pain patients and matched controls displayed no significant differences.

Lastly, as chronic osteoarthritis knee pain patients had been found to show an altered state of pain-related brain activity (as assessed via arterial spin labelling) and that networks such as the salience network had been observed in response to pain anticipation and intensity encoding (as assessed via coordinate based meta-analysis), the final study was motivated to study the effect of chronic knee osteoarthritis pain on the state of the brain. Specifically, using resting-state blood oxygenation level dependent functional MRI that is sensitive to the detection of oscillations and correlations. Via these

correlations, brain networks such as the salience, default mode and central executive brain networks are observable at rest. An in depth characterisation of connectivity between- and within-networks was carried out using functional, effective and dynamic connectivity analysis. Functional connectivity was assessed via seed-based correlations and found evidence of altered connectivity (increased anticorrelation) of the salience and default mode networks. Additional altered connectivity was found between the central executive network and the salience network. Effective connectivity analysis (via Granger causality analysis) displayed significantly increased negative outflow also from the salience to the default mode network in line with the functional connectivity finding. Lastly, dynamic functional connectivity analysis (as assessed via a 'sliding window' approach in which correlations between brain regions were calculated for subsequent 100-second windows along the functional MRI timeseries) analysis was carried out within each network. Dynamic functional connectivity was found to be significantly reduced within the default mode network of chronic pain patients.

The functional differences observed provide evidence to stress the role of negative affect on neural activity underlying perceived chronic knee osteoarthritis pain and the effect of chronic pain on the resting brain. These functional neuroimaging findings have potential implications for understanding the brain in chronic pain and may provide framework for future studies.

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statistical analysis on the CBMA data that had been ran by Dr Tench for the published manuscript. I made all the relevant figures within this thesis.

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List of accepted papers and conference abstracts

Accepted papers

1. **Cottam WJ**, Iwabuchi SJ, Drabek MM, Reckziegel D, Auer DP. Altered connectivity of the right anterior insula drives the pain connectome changes in chronic knee osteoarthritis. PAIN 2018, (in print); doi: 10.1097/j.pain.0000000000001209).
2. Tench CR, Tanasescu R, **Cottam WJ,** Constantinescu CS, Auer DP. Coordinate Based Random Effect Size meta-analysis of neuroimaging studies. NeuroImage 2017; 153, 293-306.
3. Reckziegel D, Bailey H, **Cottam WJ**, Tench CR, Mahajan RP, Walsh DA, Knaggs RD, Auer DP. Imaging pain relief in osteoarthritis (IPRO): protocol of a double-blind randomised controlled mechanistic study assessing pain relief and prediction of duloxetine treatment outcome. BMJ Open 2017; 7(6); e014013
4. **Cottam WJ**, Condon L, Alshuft H, Reckziegel D, Tench CR, Auer DP. Limbic-affective brain activity is associated with severity of ongoing chronic arthritis pain and partially moderated by emotional traits. NeuroImage: Clinical 2016; 12, 269-276.
5. Reckziegel D, Raschke F, **Cottam WJ**, Auer DP. Cingulate GABA levels inversely correlate with the intensity of ongoing chronic knee osteoarthritis pain. Molecular Pain 2016; 12.
6. **Cottam WJ**, Tanasescu R, Condon L, Tench CR, Auer DP. Functional reorganisation in chronic pain and neural correlates of pain

sensitisation: a coordinate based meta-analysis of 266 cutaneous pain fMRI studies. Neuroscience & Biobehavioural Reviews 2016; 68, 120-133.

7. Tench CR, Tanasescu R, **Cottam WJ**, Constantinescu CS, Auer DP. Coordinate based meta-analysis does not show grey matter atrophy in narcolepsy. Neuroscience & Biobehavioural Reviews 2016.
8. Tanasescu R, Tench CR, **Cottam WJ**, Constantinescu CS, Auer DP. Coordinate based meta-analysis does not show grey matter atrophy in narcolepsy. Neuroscience & Biobehavioural Reviews 2015; 57; 297-298
9. Tench CR, Tanasescu R, Auer DP, **Cottam WJ**, Constantinescu CS. Coordinate Based Meta-Analysis of Functional Neuroimaging Data Using Activation Likelihood Estimation; Full Width Half Max and Group Comparisons. PLoS One 2014; 9(9).

Conference abstracts

1. **Cottam WJ**, Auer DP. Group differences in default mode network connectivity not just anti-correlation depend on choice of nuisance regressor model. Joint Annual Meeting ISMRM_ESMRMB, April 2017
2. **Cottam WJ**, Reckziegel D, Drabek MM, Auer DP. Sub-clinical trait anxiety relates to cerebral blood flow in brain regions related to autonomic arousal. Joint Annual Meeting ISMRM_ESMRMB, April 2017
3. Drabek MM, Reckziegel D, **Cottam WJ**, Li X, Frowd N, Alshuft H, Scammell B, Kurien T, Auer DP. Chronic pain-related sexual dimorphism in gray matter density: A whole-brain voxel-based morphometric study on Osteoarthritis patients. Joint Annual Meeting ISMRM_ESMRMB, April 2017

4. Reckziegel D, Bailey H, Chana A, **Cottam WJ**, Tench CR, Mahajan RP, Walsh D, Knaggs R and Auer DP. Opioid Reduces Nociceptive Activation of the Anterior Cingulate Preferentially in Patients with Impaired Conditioned Pain Modulation: a BOLD fMRI study in Chronic Osteoarthritis Pain. World Congress on Pain (IASP), September 2016
5. **Cottam WJ**, Drabek M, Reckziegel D and Auer DP. Subregion-specific Resting-State Amygdala Connectivity in Chronic Knee Osteoarthritis Pain: Towards a Brain Network Signature of OA Pain. Joint Annual Meeting ISMRM-ESMRMB, May 2016
6. Kurien T, Reckziegel D, **Cottam WJ**, Petersen KK, Cooper A, Pearson RG, Arendt-Nielsen L, Graven-Nielsen T, Auer DP and Scammell BE. Neural Correlates of Temporal Summation in Knee Osteoarthritis Pain – a Preliminary Study at 3T. Osteoarthritis Research Society International World Congress, March 2016
7. Reckziegel D, Raschke F, **Cottam WJ** and Auer DP. Ongoing Pain Intensity is Associated With Cingulate GABA and NAA in Osteoarthritis. ESMRMB Annual Meeting, October 2015
8. **Cottam WJ**, Dashdorj N, Abaei M and Auer DP. Cerebral Blood Flow Changes Related to Pain Intensity in Chronic Knee Osteoarthritis. Joint Annual Meeting ISMRM-ESMRMB, May 2014.
9. Tanasescu R, **Cottam WJ**, Tench CR and Auer DP. Studying The Brain Signature in Chronic Pain: A Systematic Review and Meta-Analysis of 146 Pain fMRI Experiments. 8th Congress of the European Federation of IASP Chapters (EFIC), October 2013.

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List of Abbreviations

ACC	Anterior cingulate cortex
aMCC	anterior mid-cingulate cortex
ASL	Arterial spin labelling
BBR	Boundary-based registration
BDI	Beck’s depression inventory
BOLD	Blood oxygenation level-dependent
CBF	Cerebral blood flow
CBMA	Coordinate based meta-analysis
CEN	Central executive network
CNS	Central nervous system
CSF	Cerebrospinal fluid
dFC	Dynamic functional connectivity
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
FAST	FMRIB's automated segmentation tool
FC	Functional connectivity
FCDR	False cluster discovery rate
FDR	False discovery rate
FEAT	FMRIB expert analysis tool
FLAME	FMRIB's local analysis of mixed effects
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FLIRT	FMRIB linear registration tool
FSL	FMRIB software library
FWE	Family-wise error
FWHM	Full-width half max
GLM	General linear model
GM	Grey matter
HC	Healthy control
ICA	Independent component analysis
MRI	Magnetic resonance imaging
MSK	Musculoskeletal
MPQ	McGill pain questionnaire
OA	Osteoarthritis
PCC	Posterior cingulate cortex
PCS	Pain catastrophizing scale
PNS	Peripheral nervous system
rAI	Right anterior insula
ROI	Region of interest
S1	Primary somatosensory area
S2	Secondary somatosensory area
sgACC	subgenual ACC
SN	Salience network
SNR	Signal-to-noise ratio
T	Tesla
TE	Echo time
TI	Inversion time
TR	Repetition time

WM	White matter
VAS	Visual analogue scale

1 Introduction and general aim

1.1 Overview of chronic knee osteoarthritis pain

Chronic pain (across all underlying conditions) is a huge health problem for the aging population with approximately one-in-three adults in the UK affected (Fayaz et al., 2016). The recent meta-analysis of chronic pain prevalence studies by Fayaz et al. (2016) reported these numbers in order to display how large a burden this is on society. The burden of chronic pain is not small, with reports suggesting that pain accounts for up to 40% of medical visits and that the economic cost in the US in 2010 was estimated to be somewhere between $560-635 billion (Gaskin and Richard, 2012, Mantyselka et al., 2001). An earlier study from the Global Burden of Disease reviews also highlighted chronic pain, represented by (but not limited to) musculoskeletal conditions such as low back pain and osteoarthritis, as one of the most pronounced underlying reasons for disability worldwide (Vos et al., 2012). In addition to its relation with increased disability, chronic pain is commonly reported alongside raised levels of pain-related depression, dementia, sleep disturbance and an increased 10 year mortality rate (Breivik et al., 2006, Torrance et al., 2010, Whitlock et al., 2017).

The trademark symptom of osteoarthritis (OA), the most common form of arthritis, is pain and tends to have a large impact on quality of life of those affected (Arden and Leyland, 2013). Most commonly, osteoarthritis affects the knee or hip joints with risk factors for development including: older age (over 40), female sex (OA is twice as prevalent in women), being overweight (for every 5-point BMI increase there is a 35% increased risk of knee OA), injury to the joint, heritability (prevalence within the immediate family) and occupation

(for example jobs in which workers perform repetitious tasks overworking the joints and tiring the muscles that protect those joints) (Felson et al., 2000, Breivik et al., 2006, Johnson and Hunter, 2014, Srikanth et al., 2005). The clinical classification of OA described by Altman et al uses a mix of clinical and radiological descriptors including the presence of pain (but not duration or quality), radiographic and physical examinations but does not necessarily show sensitivity towards early or mild OA (Peat et al., 2006, Altman et al., 1986).

Knee OA (the most common form) is defined by the American College of Rheumatology as a “group of conditions that lead to…defective integrity of articular cartilage, in addition to related changes in the underlying bone and at the joint margins” (Altman et al., 1986). The pathophysiological mechanism of OA is fairly complex, but it can be generally described as a degenerative joint disease with inflammatory components. This degeneration and associated inflammation is due to a disruption of the dynamic equilibrium within the joint. That is, the ongoing breakdown and repair of joint tissues by articular chondrocytes via constant synthesis and degeneration of extracellular matrix components is disrupted leading to an increased cumulative loss of cartilage and cellular apoptosis (Lee et al., 2013). There is however no clear linear relationship between the degradation of the joint and the amount of pain reported suggesting that joint degradation is not the only factor required for knee pain and supporting the idea that there are likely both peripheral (outside the central nervous system) and central mechanisms (based within the central nervous system) at play (Link, 2009). As the relationship between knee OA (degeneration of the joint) and reported pain is not strong or consistent, it is clear that radiographic changes in the knee are only one potential risk factor for knee OA. Other broader factors such as a subjects demographic or

psychosocial status seem to play important roles in the development of chronic pain (Davis et al., 1992). In regards to central mechanisms, studies investigating the association between reported knee pain, anxiety and depression found that anxiety levels were significantly higher in women but not men who reported having experienced knee pain (current or previous) than those who hadn't and that depression displayed no relationship with pain in either sex (Creamer et al., 1999). Other studies of pain have also highlighted the potential role of anxiety and negative affect in musculoskeletal pain. For example, a recent prospective longitudinal study of adolescents reported that higher pain-related disability was predicted by higher depressive symptoms (Lewandowski Holley et al., 2016). A population-based study of Norwegian youth also reported that musculoskeletal pain was significantly associated with anxiety disorders in adolescence (Eckhoff et al., 2017). In addition to anxiety, catastrophizing - the tendency of an individual to focus on and exaggerate the threat or intensity of a painful stimuli and negatively view their ability to cope with pain - is another negative affect that has been seen to impact on musculoskeletal pain (Sullivan et al., 1995, Keefe et al., 2000).

Currently, the end-stage treatment for knee OA (and indeed hip OA) is total joint replacement. It is one of the most common elective surgeries performed in the UK (Judge et al., 2006) and current projections predict an increase in UK surgeries between 30-700% (depending on the model used) by 2035 (Culliford et al., 2015) or by approximately 670% in the US by 2030 (Kurtz et al., 2007). Considering how common this procedure is and how huge the burden is projected to be, it is alarming that up to 20% of patients continue to report persistent chronic postoperative pain after total joint replacement surgery (Beswick et al., 2012). Although this is not an exhaustive list of the studies investigating risk factors for knee OA pain, it is clear that joint

degeneration is not the only factor leading to reported pain if the pain can remain post-joint replacement.

A potential risk factor not yet mentioned is brain structure and function. There is recent evidence from a longitudinal study of back pain that suggests that structure and function of the brain can predict whether someone might develop chronic pain or not, when assessed within weeks of presenting in clinic with sub-acute back pain (Vachon-Presseau et al., 2016, Hashmi et al., 2013). Specifically, they reported that mesolimbic connectivity between the medial temporal lobe (amygdala-hippocampal complex) and medial prefrontal cortex via the nucleus accumbens was predictive of transition to chronic pain. This builds upon the idea presented (and reviewed) previously that brain function is plastic and likely changes with the presence of chronic pain and that this plasticity is likely to be non-permanent and so may be reversed with the correct treatment (Martucci and Mackey, 2016).

1.2 Problem statement

Chronic pain is a huge burden on society and in particular chronic knee osteoarthritis pain. Although many of the peripheral mechanisms of osteoarthritis are understood, the neural mechanisms underlying chronic knee OA pain are not. Considering that there are little efficacious choices of treatment for chronic pain and that approximately 1 in 5 patients who undergo total knee replacement surgery do not resolve their pain, it is of particular importance that the neural activity related to this pain be studied and better understood. A better of understanding of these neural mechanisms may present potential treatment targets or biomarkers that may be used for assessment of potential treatments.

1.3 Aim

The general aim of this thesis was to study the neural activity underlying chronic knee osteoarthritis pain (both in response to acute stimuli and at rest) and how this might be different to that same activity in healthy subjects. More specifically, the three following questions were addressed:

1. Do subjects with chronic pain have a different neural response to acute experimental pain to healthy subjects?
2. What brain regions relate to the perception of chronic knee OA pain at rest?
3. Do subjects with chronic knee OA display altered connectivity between- and within- brain networks compared to healthy subjects?

These questions will be answered using state-of-the-art human neuroimaging methods. Coordinate based meta-analysis of functional MRI (fMRI) is used to assess the neural response to acute experimental pain in healthy and chronic pain cohorts. Arterial spin labelling (ASL – a type of fMRI) is used to probe brain activity related to OA pain perception whilst blood oxygenation level dependent (BOLD fMRI) will be used to assess the connectivity between brain networks in OA pain patients.

2 Pain

2.1 Pain physiology

Pain (defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” by the International Association for the Study of Pain [IASP]; https://www.iasp-pain.org/Taxonomy) serves as an innate defence mechanism, its purpose being to stop or reduce damage to the bodily tissues. It is a percept, detected and made sense of by the nervous system via nociception - “the neural process of encoding noxious stimuli” (IASP; https://www.iasp-pain.org/Taxonomy). Nociception, whilst sufficient, is not however necessary for the perception of pain which is a psychological state.

Specialised primary afferent neurons within the peripheral nervous system (PNS) known as nociceptors remain constantly alert for any stimuli of an ample intensity as to cause damage to the body. When stimulated, these specialised neurons relay this information or signal to the spinal cord dorsal horn ready for further processing and relay to the brain via the central nervous system (CNS). If again of a sufficient intensity, withdrawal reflexes may be incurred via the ‘reflex arc’ via the dorsal root ganglion within the spinal cord (see figure 2.1 for visualisation). As this reaction follows a short pathway and is less convoluted than the ensuing pathway to pain perception within the CNS and brain it explains how one can have a withdrawal reflex whilst experiencing the related pain perception in the moments thereafter. It is this (supra-)spinal processing related to the perception of nociception and its subsequent interpretation/modulation that can be studied via functional neuroimaging.

Pain reflex arc

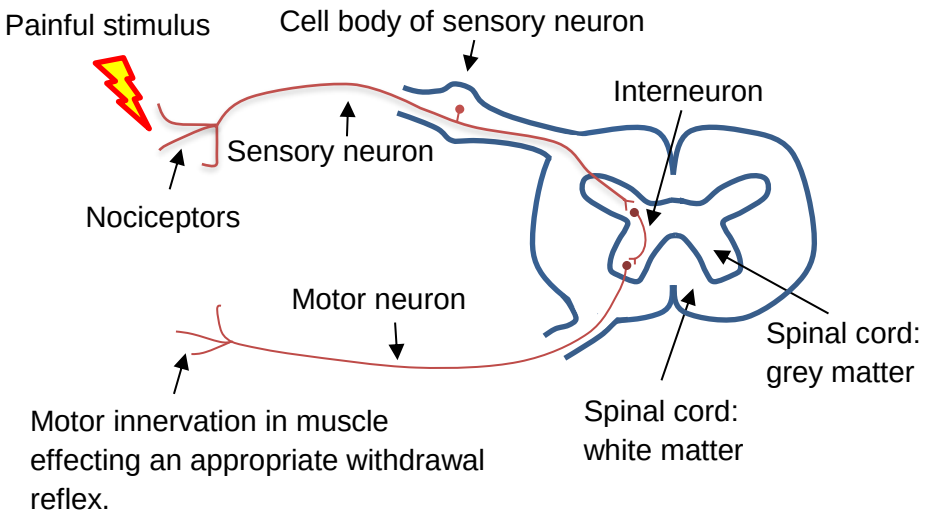


Figure 2.1. A sketch of the pain reflex arc in which a painful stimulus is detected by nociceptors (specialised pain receptors). A sensory signal is then sent up the sensory neuron and into the spinal cord grey matter via the dorsal horn. Subsequently, via an interneuron, a motor response is sent via the appropriate motor neuron.

As with most physiological processes, too much, or too little of something can be bad. Pain syndromes exist that suffer with both of these problems. Syndromes such as congenital insensitivity to pain and paroxysmal extreme pain disorder (due to inactivating and gain-of-function mutations in the SCN9A gene respectively) are prime examples of this with their physiological basis being generally understood (Bennett and Woods, 2014). SCN9A codes for the voltage-gated sodium channel $Na_v1.7$ which is part of the larger family ranging from $Na_v1.1$-1.10. These voltage-gated sodium channels are key factors in nociceptor excitability with $Na_v1.7$ being expressed preferentially in peripheral neurons. $Na_v1.7$ produce a ramp current in response to small and slow depolarisations and is thought to be vital in setting the threshold excitability of peripheral nociceptor terminals. The inactivity of $Na_v1.7$ leads to a condition known as congenital insensitivity to pain which manifests as a complete lack of nociception from birth with no other bodily defect than anosmia. Conversely, gain-of-function mutations in $Na_v1.7$ lead to conditions such as inherited

erythromelalgia in which subjects suffer severe and disabling pain in their peripheral limbs (e.g. hands and feet). Changes in the electrophysiology caused by gain-of-function mutations manifest commonly as a hyperpolarising shift in the voltage dependence of activation as well as other less common effects e.g. slowed deactivation (leading to longer periods of hyperpolarisation) or increased current response to slow depolarisation. Some pain syndromes, however, present with symptoms that are not necessarily attributable to any peripheral stimulation (such as prolonged tissue inflammation or degrading joints) but present with chronic pain which is defined as “pain which has persisted beyond normal tissue healing time” which is taken generally to be 3 months (Pain, 1986). The underlying maintenance of chronic pain presents as an unclear problem. It is, however, commonly attributed to central and/or peripheral sensitisation. These are defined by IASP as:

Central sensitisation – “Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input”.

Peripheral sensitisation – “Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields”.

Depending upon the underlying pathology, either of these states can be observed either separate or as a combination. For example, in OA, peripheral factors such as chemokines, cytokines and inflammatory cells can contribute to peripheral sensitisation (Syx et al., 2018), whilst central sensitisation can be observed via decreased widespread pain sensory thresholds (Graven-Nielsen et al., 2012, Suokas et al., 2012, Courtney et al., 2009), and differential brain activity (Kulkarni et al., 2007, Parks et al., 2011). Pain perception is a

subjective sensation that can be influenced by mood (as discussed in section 1.1), context and even other pain with central mechanisms able to provide both states of hyperalgesia and analgesia (Roy et al., 2009b, Leknes et al., 2013, Lewis et al., 2012). With this background, it is clear that study of the central nervous system (brain and spine) is warranted by the need to understand the mechanisms of pain perception and central sensitisation.

2.1.1 The anatomy of nociception

2.1.1.1 Ascending pathways

Receptors within the body that sense painful stimuli – otherwise known as nociceptors – are free or bare nerve endings that can be found in the skin, muscle, viscera and elsewhere within the body. There are various types of nociceptors that are specialised in regards to their sensory properties. For example, there are some skin nociceptors known as high-threshold mechanonociceptors which are involved in the sensing of strong mechanical stimulations such as cutting and stretching. There are also thermal nociceptors which are known to respond to intense hot or cold stimuli. There are specialised nociceptors such as these found throughout all of the aforementioned bodily tissues and these receptors convert the sensing of noxious stimuli into action potentials that are carried via Aδ- and C-fibres towards the spinal cord. These two fibres form a complementary pairing in the PNS; Aδ-fibres are thick, fast-conducting myelinated axons while C-fibres are thin, slow-conducting unmyelinated axons. These properties are reflective in regards to the sensations they convey, Aδ-fibres for example are associated with quick-onset pricking sensations whilst C-fibres are linked with slower sensations such as aching and burning pains. These differing speeds of signal transduction are what underlie the phenomena known as first and second-pain, with Aδ-fibers quickly responding to noxious stimuli resulting in a sharp,

localised sensation of pain whilst C-fibers respond slowly and provide a duller and more diffuse sensation of pain (Basbaum and Jessel, 2013). There are however situations in which this first/second pain phenomenon does not apply and subsequent perceptual responses or ratings can be different (Meyer et al., 2006).

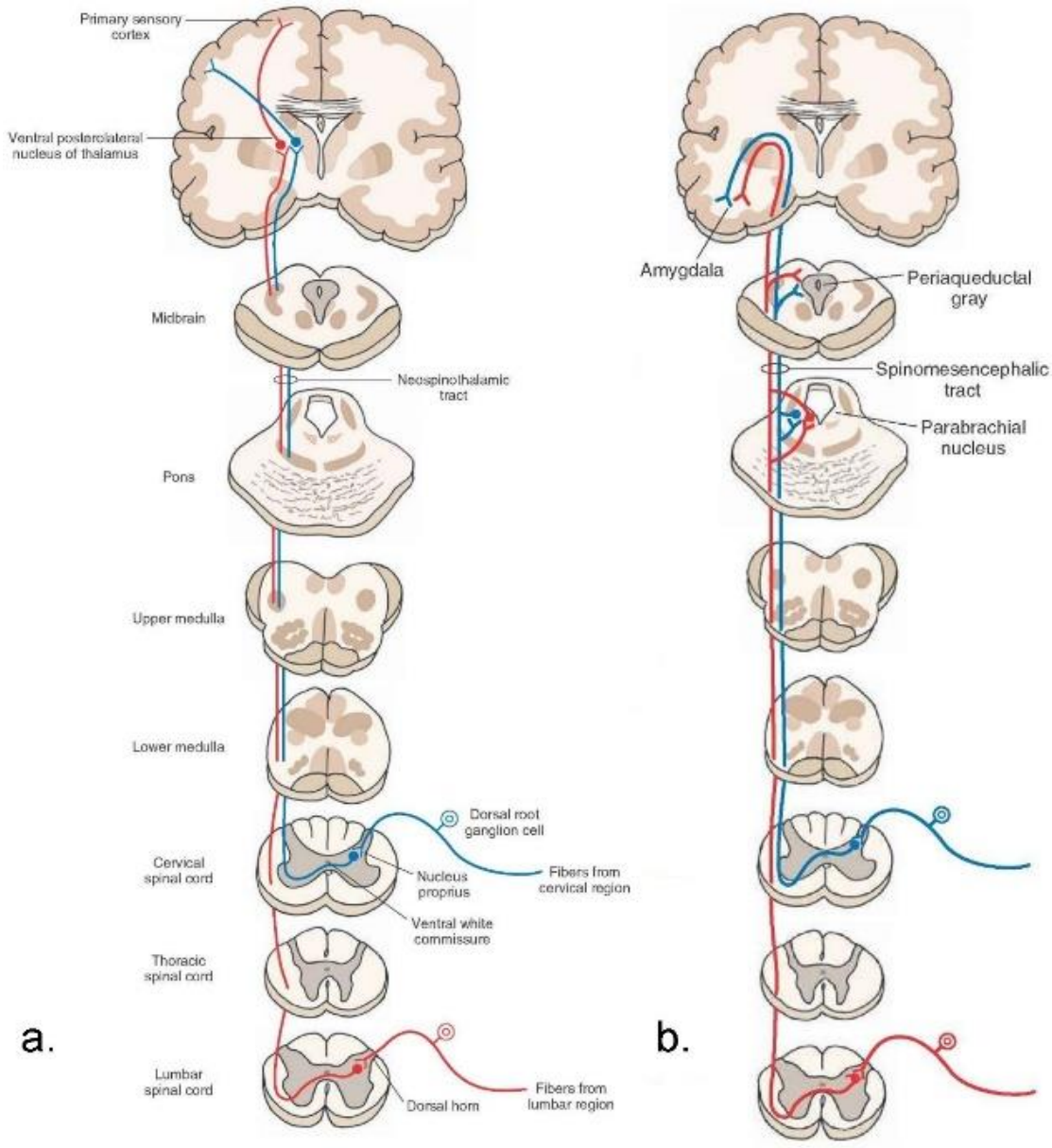


Figure 2.2. Visual representations of the a) neospinothalamic [direct spinothalamic] and the b) spinomesencephalic [indirect spinothalamic] tract (figure adapted from http://what-when-how.com/neuroscience/the-spinal-cord-organization-of-the-central-nervous-system-part-3/).

The primary spinal pathway involved in nociception once the afferent nociceptive signals are received at the dorsal horn of the spinal cord is the spinothalamic pathway within lamina I which projects almost entirely to various nuclei of the thalami (Todd, 2010). This spinothalamic pathway (see Figure 2.2 for examples of direct and indirect spinothalamic pathways) can be subdivided by functionality into two pathways: lateral and medial. The lateral pathway is associated with intensity and localisation aspects of nociception due to its cortical projections to areas such as the somatosensory cortices. The medial pathway, however, is related to the affective dimension of pain as it projects to limbic-affective brain regions such as the anterior cingulate cortex. The relationship of each pathway to different aspects of pain is thus reflective of the cortical projections onwards from the thalamus. Other brain regions are known to receive projections of the nociceptive dorsal horn such as the globus pallidus, amygdala and hypothalamic which are reported as receiving projections from the deeper lamina (Gauriau and Bernard, 2004). Other spinal pathways include the spinoreticular pathway and spinomesencephalic tracts (Raj, 1996). The lateral spinothalamic tract is considered phylogenetically more recent than the others and is alternatively known as the neospinothalamic tract, whereas the medial spinothalamic, spinoreticular and the spinomesencephalic can be collectively called the paleospinothalamic tract (Raj, 1996).

2.1.1.2 Descending pathways

As outlined in 2.1.1.1, there exists an ascending pain system that carries nociceptive input from the peripheral nervous system to the brain. However, the extent of any given injury to the tissue does not always relate to how painful the injury is. There are for instance, examples of severe injuries that don’t give rise to pain such as the classic case of the soldiers severely

wounded in battle but not reporting debilitating pain (Beecher, 1946, Melzack et al., 1982). This difference between levels of nociceptive input and perceived pain can be at least partly explained by the presence of an endogenous descending pain modulatory system that can send top-down signals (from brain to spine) that modify or inhibit incoming nociceptive signals (Hudspith, 2016). This observed reduction of pain in stressful or scary circumstances is widely viewed as being an innate system in mammals leading to stress-induced analgesia (Butler and Finn, 2009). Additionally, this same system can also facilitate pain related signalling and subsequently amplify the perceived pain (Tracey and Bushnell, 2009).

One of the earlier examples of studies that evidenced the idea of a descending pain modulatory system was that by Wall (1967), in which it was shown that the activity of nociceptive neurons in the dorsal horn could be altered via stimulation of a supraspinal site. Subsequent studies demonstrated that stimulation of the periaqueductal grey (PAG) in rodents could produce analgesic effects such as the inhibition of pain-related behaviour in response to noxious stimulation (Mayer et al., 1971, Reynolds, 1969). Similar findings were subsequently reported in cats, where stimulation of the PAG was found to inhibit dorsal horn neuronal activity, further evidencing the existence of a brain-spinal cord system for the modulation of pain (Liebeskind et al., 1973). This analgesic effect was also shown to be quite specific, with pre-clinical studies finding that responses to non-noxious stimulations (such as mechanical and thermal stimuli) did not change whether or not the PAG was stimulated (Basbaum and Jessel, 2013). Building on this, accumulated evidence of the neurobiology of this modulatory system have shown that it includes inputs from higher centres such as the medial temporal lobe (hypothalamus, amygdala), anterior cingulate cortex and prefrontal cortices

which interplay with the PAG subsequently outputting to the medulla (Bingel and Tracey, 2008, Fields, 2004, Parvizi et al., 2006). Additionally, the PAG interconnects with structures such as the locus coeruleus, nucleus raphe magnus, nuclei of the bulbar reticular formation and the rostral ventral medulla which are involved in the descending pathways down to the spinal cord (Fields, 2004, Willis and Westlund, 1997). Within these connections, several different neurotransmitters are at play including opioids, serotonin, noradrenaline and catecholamines (Basbaum and Jessel, 2013, Willis and Westlund, 1997).

Whilst the descending pain modulatory system is predominantly viewed as being antinociceptive, this system is bidirectional and can also facilitate pain. For example, there are also two neuronal subpopulations within the PAG known as “on” and “off” cells, these are thought to respectively facilitate or inhibit nociceptive transmission through their connections with the dorsal horn (Basbaum and Jessel, 2013, Fields, 2004). It is thought that maladaption of this endogenous system may underlie some chronic pain states (Tracey and Bushnell, 2009).

2.1.2 Chronic pain

Chronic pain can be resultant from differing underlying pathologies. Breivik et al. (2006) performed a Europe-wide telephone survey in which many causes of chronic pain were reported. The most common were musculoskeletal problems (including arthritis, osteoarthritis and back pain), neuropathic pain (defined as “pain caused by a lesion or disease of the somatosensory nervous system” by the International Association for the Study of Pain; https://www.iasp-pain.org/Taxonomy) or migraine.

Chronic pain disorders are commonly paralleled by states known as central and/or peripheral sensitisation. Central sensitisation is defined by the International Association for the Study of Pain (IASP – found at https://www.iasp-pain.org/Taxonomy) as “an increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs” and can be widespread throughout the body whilst peripheral sensitisation is usually localised to the area of tissue damage. This increased pain sensitivity can manifest with differential sensory perceptions. For instance, states of allodynia and/or hypo/hyperalgesia are common. The definitions of these sensory states as defined by the International Association for the Study of Pain are:

Allodynia – “Pain due to a stimulus that does not normally provoke pain”.

Hyperalgesia – “Increased pain from a stimulus that normally provokes pain”

Hypoalgesia – “Diminished pain in response to a normally painful stimulus”.

Central sensitisation can be measured via psychophysical examinations such as quantitative sensory testing (QST; an experimental approach in which a stimulus [usually thermal, electrical or pressure] is applied to measure either levels of pain in response to a set stimulus or thresholds of pain detection or tolerance). Reduced pain detection thresholds at body sites remote to the affected area for instance have been reported in many chronic pain conditions (Woolf, 2011). Central sensitisation is so named because the mechanism of this increased sensitivity lies predominantly within the central nervous system. For instance, the fact that the perceived pain no longer couples with the stimulus intensity is suggestive that the central response to normal sensory input has changed. See figure 2.3 for a pictorial explanation of the effect of

allodynia and hyperalgesia compared to normal pain perception or normalgesia.

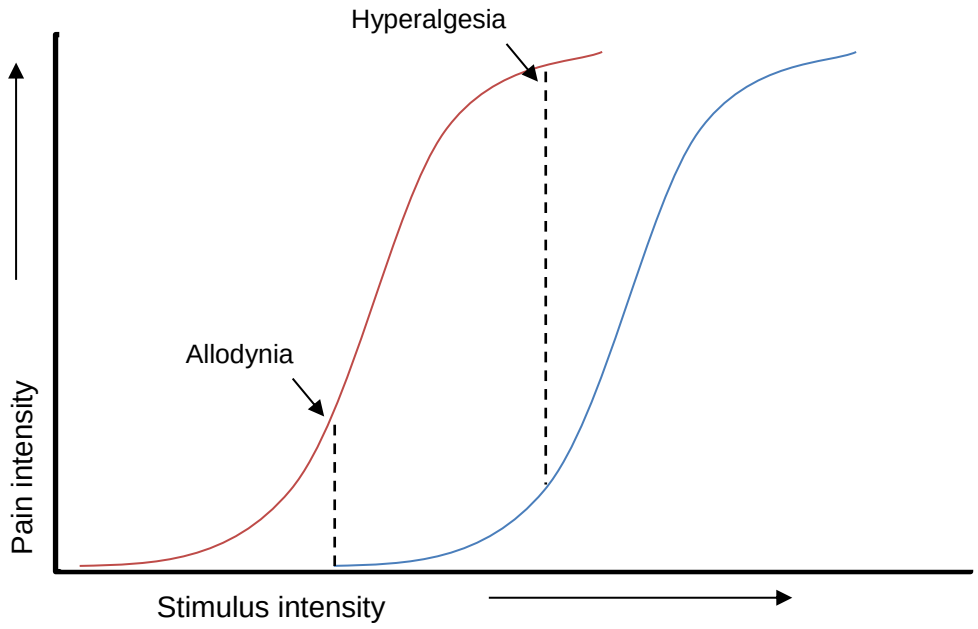


Figure 2.3. A line graph displaying the effect of pain sensitisation (including allodynia and hyperalgesia) on perceived pain and stimulus intensity. While the blue line reflects normalgesia where a moderate intensity stimulus provokes pain, the red line displays the shift to the left caused by increased pain sensitivity. This encompasses the presence of allodynia (in which a non-noxious stimulus is perceived as painful) and hyperalgesia (in which a painful stimulus is perceived as more painful).

Animal models of pain have displayed evidence for central sensitisation. For example, an early example of this is the experiment by Woolf (1983) in rats in which by using repeated noxious stimulation to induce peripheral inflammation he produced evidence for central (as well as peripheral) sensitisation. This included reductions in withdrawal thresholds (reduced pressure thresholds) ipsilateral to the injury site and also contralateral to it alongside changes in motor neurons. These changes included both increases in neuronal responses to ipsilateral and contralateral stimulation but also the presence of spontaneous neuronal activity where pre-injury there had been little or no spontaneous activity (Woolf, 1983).

Additionally, chronic pain commonly presents alongside reports of increased anxiety/low mood as discussed previously in relation to osteoarthritis (section

1.1) It is difficult however to assess whether the increased presence of negative affect is a predisposing factor to chronic pain or whether it is a consequence that would be reversed if pain was alleviated. Considering that there are published examples of chronic pain with minimally increased low mood (e.g. Ung et al. (2014)) and also examples of low mood scores helping to predict patients progressing into chronic pain (Vachon-Presseau et al., 2016) it is clear that this is a complex relationship which is yet to be fully understood.

2.1.2.1 Human models of chronic pain

Although there are a wide range of pre-clinical models of chronic pain, this thesis will concentrate on human models of chronic pain. There are several approaches to model chronic pain in healthy participants which in essence try to mimic the symptoms of central sensitisation. One way of doing this is to evoke hyperalgesia and/or allodynia. This can be done by using any of the following stimuli: electrical stimulation, capsaicin, mustard oil, acid, cutaneous burn via UV or heat or hypertonic saline. Capsaicin is also used clinically to reduce pain (Dosenovic et al., 2017) but has been used commonly in research to bring about observable states of sensitization (van Amerongen et al., 2016).

Another human model of chronic pain is achievable through the induction of low mood. Chronic pain disorders are commonly linked with increased reports of depression or low mood and as such, the induction of low mood in healthy participants allows for an experimental approach to investigate the interaction between low mood and pain. Induced negative mood is known to worsen affective pain ratings, that is, not the reported intensity of the pain but the unpleasantness or tolerability (Loggia et al., 2008, Zelman et al., 1991).

In regards to imaging studies, these approaches have both strengths and limitations in modelling chronic pain. For instance, models of hyperalgesia or allodynia allow the investigation of the supraspinal changes resulting from central sensitisation with which we can ask questions such as: “does the brain activity underlying hyperalgesia display the same brain regions as seen in normalgesia or are different brain regions implicated?” or “Does the activity in these regions simply track the increased perceived pain intensity as a result of increased spinal drive – e.g. more pain = more brain activity in the same regions?”. These models are all inherently limited however as they cannot fully reproduce the subjective nature of chronic pain. This exact point was made in a recent review of human neuropathic pain models by the IASP special interest group on neuropathic pain (NeuPSIG) in which they state “models seem to be suitable to investigate single or few sensory phenomena like spontaneous pain, allodynia, and/or hyperalgesia only” (Binder, 2016). For instance, even with low mood induction, it is unlikely that an application of acute pain in a healthy individual would be able to capture the learnt aversive nature of chronic pain related to each subject’s beliefs, fears and memories. As such, almost all models will fail to capture the full perception of chronic pain but will model specific factors such as central sensitisation or affective components.

2.1.3 Functional neuroimaging studies of pain

Pain is a multi-dimensional perception containing sensory-discriminative, affective and motor aspects, imaging brain activity during a pain state can give mechanistic insight into how this perception might arise in a healthy person and subsequently how this perception may have mechanistically changed in someone with an altered pain perception such as a chronic pain patient.

Over the 20th century, an abundance of electrophysiological studies focused only on the peripheral nervous system and the spinal cord leading to multiple physiologically based theories of pain (see Moayedi and Davis (2013) for a review). However, Melzack and Wall (1965) proposed the Gate Control theory in 1965 and this was arguably the most influential physiological theory of pain. Importantly, this theory held the brain as a potential influence on sensory input. Subsequently, building upon the Gate Control theory, pain was no longer thought of as purely a percept related to a sensory stimulus because of the ongoing processes in the brain that dynamically related to cognitive and emotional processes as well as other spontaneous processes that can facilitate, inhibit or modulate incoming sensory signals (Melzack, 1999). Melzack proposed that the brain possessed a neural network ("the body-self neuromatrix") which comprises several parallel components (e.g. somatosensory, limbic and thalamocortical) that would subserve the "sensory discriminative, affective-motivational and evaluative-cognitive dimensions of the pain experience" (Melzack, 1999).

The meanwhile development of human brain imaging techniques such as PET and fMRI subsequently provided the opportunity to measure the neural presentation of pain in humans. As this percept must lie within the brain, and subjective reports of pain intensities can be taken whilst being scanned, this approach had the potential to uncover the brain signature of pain. The idea of this signature gave arise to the idea of a 'pain matrix', a specific spatial pattern of brain activity (measured by functional imaging) that can be seen in any individual perceiving pain. In theory this could give rise to a static map of brain activity (the 'pain matrix') that when seen, infers that this person being scanned is perceiving pain. This argument, however, follows a flawed logic commonly known as a 'reverse inference, 'converse error' or 'affirming the

consequent' (Iannetti et al., 2013). This particular point has been eloquently reviewed by Iannetti et al who have argued and presented evidence that most of the brain activity seen during nociception is non-specific to the perception of pain (Iannetti and Mouraux, 2010, Iannetti et al., 2013). Using a set of sensory experiments (visual, somatosensory, aural) they convincingly show the non-specificity of this matrix (Iannetti et al., 2013). The pattern of brain activity common to pain perception in healthy individuals does however follow exactly what Melzack proposed initially containing a mix of several cortical and sub-cortical networks (not specific to nociception) that together collate sensory input into pain – accurately predicting the results of machine learning studies like that of Wager et al (2013). It is this interplay between spatially distinct regions over time that imaging allows us to study. This sensitive technique displays great potential for understanding the mechanism of chronic pain and assessing any differences in brain activity associated with the perception of chronic and acute experimental pain.

The results from Iannetti et al. (2013) provide clear evidence of the non-specificity of pain-related brain activity showing that many of these brain areas are also related to other sensory processes. Whilst all of the different facets that together make up pain perception have their own patterns of non-pain related activity (e.g. affect, sensory and motor processes) it is their presence together that underlie pain without being specific to it. This fits very well with the idea of the body-self neuromatrix proposed by (Melzack, 1999) in that the percept of pain was generated within the brain by a widespread network of convergent and divergent loops (e.g. between the thalamus, cortices and limbic brain regions). Although these same networks / regions may be involved in different percepts (e.g. the ACC being evoked by both somatic pain and non-noxious sensory stimuli (Iannetti and Mouraux, 2010)), the

overall ‘pattern’ or fine-grained activity will differ. Recent evidence of this can be found in studies by Chang et al. (2015), Krishnan et al. (2016) and Woo et al. (2014) whom all used multivariate analyses to assess the fine-grained responses (based upon BOLD fMRI) to stimuli of negative affect, vicarious pain and social rejection respectively. All found that when comparing specific multivariate patterns (an approach that can utilise the information in every voxel within the brain rather than only cluster-based values) to these stimuli and comparing against the response of the previously found ‘neurological signature of pain’ (Wager et al., 2013), each of these stimuli had differing and specific multivariate predictive patterns. Converse to this idea, a recent study stated that the region they found to significantly correlate with subject-reported pain intensity (the dorsal posterior insula) using arterial spin labelling fMRI was specific to pain (Segerdahl et al., 2015b). However, this particular study faced a backlash from the field (e.g. Iannetti et al, 2015) for overstating the importance of only one particular region in the processing of pain and was advised that the only inference should be to take it as further evidence that the dorsal posterior insula is important regarding the intensity of perceived pain in line with previous BOLD fMRI studies. The original authors subequently replied to agree that this view of a pain-specific region was not what they intended to convey (Segerdahl et al., 2015a).

Apkarian et al (2005) hypothesised that brain activity in chronic pain patients may differ from healthy acute pain perception related to a reduced sensory input and the increase in emotional/cognitive processing associated with chronic pain. Early meta-analyses and reviews reported evidence that supported this hypothesis with regions important for cognitive or emotional assessments being upregulated in chronic pain compared to acute pain in healthy individuals (Peyron et al., 2000, Apkarian et al., 2005). Although

evidence is accumulating along these lines, the precise neural mechanisms underlying chronic pain are still unclear and will be discussed further in subsequent chapters.

3 Functional MRI-based methods used to elucidate mechanisms of normal and altered pain perception

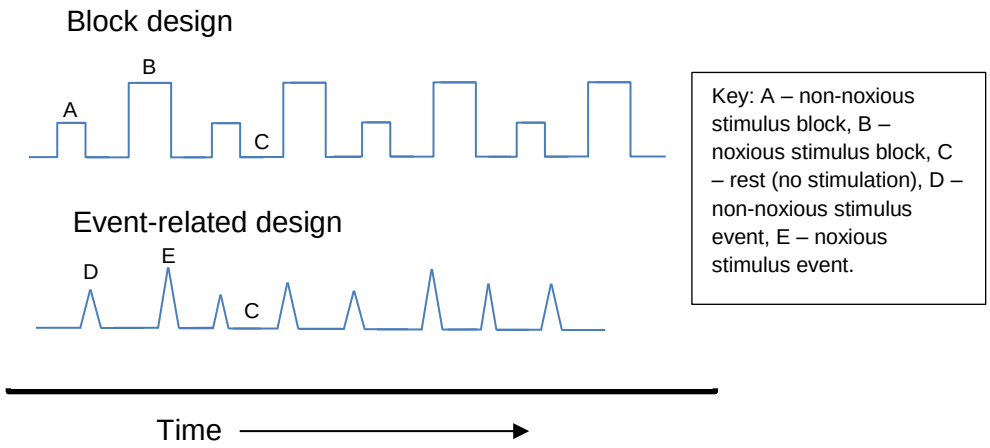
This chapter is going to review and summarise the current state-of-knowledge of acute and chronic pain related brain activity as assessed by functional MRI in order to identify gaps in the knowledge and provide context for the ensuing studies.

It is an ongoing question in the field of pain of how the neural processing underlying chronic pain differs from that seen in healthy individuals experiencing acute pain. A common experimental approach therefore in the study of chronic pain is the application of an acute-experimental pain. In theory this approach allows for a relevant comparison of pain-related brain activity in healthy and disease. However, this approach has its limitations. For instance, while it is useful to study states of hyperalgesia and allodynia (as mentioned previously in chapter 2.1.2.1) it is important to note that this type of experiment will rarely be able to model the full subjective experience of chronic pain. As such, this chapter will outline the literature on brain activity recorded in the presence of acutely administered experimental pain in both healthy volunteers and chronic pain patients. Additionally, the study of brain activity related to chronic pain itself will also be summarised.

3.1 BOLD imaging during noxious stimulation

3.1.1 Healthy volunteer studies

Experiments using noxious stimulation can be used to understand many aspects of the pain experience ranging from the spatial patterns of brain activity during noxious stimulation, to modelling the chronic pain experience in healthy volunteers by inducing hyperalgesia or low mood (Baron et al., 1999, Berna et al., 2010). The first pain fMRI experiments asked simple but important questions such as which regions of the brain are active during noxious stimulation such as the study by Davis et al that used transcutaneous electrical nerve stimulators (TENS) to induce pain in 9 healthy participants (Davis et al., 1995). This evoked statistically significant brain activity in the cingulate cortex and both primary and secondary somatosensory areas. These 'basic' experiments would commonly use a noxious stimulus (either thermal [hot or cold], mechanical [usually a blunt pressure] or electrical) in block or event-related paradigms (Davis et al., 1998a, Disbrow et al., 1998). These two paradigms differ in that the brain activity is measured either during the application of the stimuli (block design), or during a length of time directly after the stimulus application (event-related design; see fig 3.1). Either measurement would then be taken empirically (i.e. the statistical height of the stimulus response only), compared to non-application of the stimulus (a rest or control condition) or application of an innocuous stimulus.



Potential statistical fMRI tests using the above designs:

Contrast analyses:

What brain regions are significantly active in response to a noxious stimulus?

Calculated main effect of stimulus B or E.

What brain regions are significantly more active during noxious than non-noxious stimuli?

Calculate where activity is more likely in response to B than A (or E than D).

What brain regions are significantly more active during noxious stimulation than rest?

Calculate where activity is more likely in response to B than C (or E than C).

Subtraction analyses:

What brain regions respond significantly to noxious stimulation and not non-noxious stimulation?

Calculate the main effect of noxious stimulus B minus non-noxious stimulus A (or E minus D).

Conjunction analysis:

What brain regions are common to both noxious and non-noxious stimulation?

Look at main effect of B + A (or E + D).

Figure 3.1. A graphical example of experimental designs commonly used in fMRI. Block designs compose of consistent blocks of repeated stimuli (e.g. A, B and C as denoted above) in order to test the response to particular stimuli. The stimulus response is modelled during the given stimulus for a block design. Event-related designs perform the same function but with short stimuli (e.g. D and E as denoted above) in which the stimulus response is modelled in reaction to a given stimulus rather than during an elongated stimulus (as is used with the block design).

These early experiments advanced quickly into new territory as knowledge and methodology improved trying to parse those regions that were involved in processing pain intensity. Of these fMRI pain intensity experiments, the earliest looked at only eight *a priori* regions of interest having only imaged two sagittal slices of the “medial hemispheric wall contralateral to the stimulated foot” (Porro et al., 1998) and another looked at only the cerebellum making a case for the regions importance in intensity processing (Helmchen et al., 2003). As two of the studies had performed region of interest (ROI) approaches (Porro et al., 1998, Helmchen et al., 2003) this left 3 studies in

which whole-brain analyses were reported and another that had performed both. These three cutaneous pain experiments used noxious heat as their stimuli (two used Peltier thermodes while the third used a thulium:yttrium-aluminium-granate (Tm:YAG) infrared laser) whilst the last used subcutaneously or intra-muscularly injected ascorbic acid (Bornhovd et al., 2002, Kong et al., 2006, Atlas et al., 2014, Favilla et al., 2014a). Interestingly, two of the later papers investigating stimulus intensity also looked at the cognitive appraisal of the reported pain intensity and performed conjunction and mediation analyses respectively (Kong et al., 2006, Atlas et al., 2014). These analyses both found that bilateral anterior insula and dorsal ACC activity was linked with stimulus intensity and cognitive processing of pain intensity (brain activity whilst intensity was reported by the subjects). Erstwhile, Atlas et al reported anterior-to-posterior gradients in both the ACC and left insula with anterior portions related to stimulus intensity, mid-portions related to both stimulus intensity and pain and posterior portions being pain-related. Favilla et al (2014a) however, used a whole-brain correlation that displayed results within the ACC and the bilateral insula whilst also employing an ROI-driven N-partial least squares analysis to rank the importance of each ROI within the task of intensity encoding. They reported that the bilateral posterior insula was the most statistically significantly related to pain intensity, fitting with the interpretation of previous functional and lesion studies that this is an important region in pain generation (Oertel et al., 2012, Treede et al., 2000).

Other studies have looked at the comparison of stimulus modalities to assess whether they evoked the same brain activity during the perception of pain. An early modality comparison study was carried out by Davis et al (1998b) who looked at noxious heat and cold stimuli alongside an innocuous tactile

stimulus. Both thermal stimuli evoked similar activity within the S2, anterior insula and thalami bilaterally whilst the tactile stimulus evoked similar activity in the posterior insula, S2 and thalami bilaterally. Activity in the S2 overlapped between all stimuli but S2, anterior insular and thalami activity was strongly related to pain perception. The posterior insula was suggested to be involved in the processing of tactile and innocuous stimuli (Davis et al., 1998b). It should be noted that the imaging in this study consisted of only 6 axial slices large enough to encompass the thalamus, S2 and insula regions so these results are certainly not fully inclusive of all possible brain activity during noxious stimulation. A later study also reported no significant regional differences in brain activity related to noxious hot and cold stimuli (Tracey et al., 2000). The only difference between the stimuli reported was the cold stimuli saw a trend towards increased frontal activity which was probably related to perceptual differences between the stimuli. A similar comparative study investigated noxious heat, mechanical and electrical pain perception (Disbrow et al., 1998). Having scanned the whole brain, they then carried out a region of interest analysis (in which you assess specifically the responses within specific regions as opposed the whole brain - usually based upon *a priori* hypothesis; ROI) looking at the: S1, parietal operculum (PO), thalamus, ACC, insula and cerebellum. Following this approach they were unable to make comparisons between stimuli as they found no significant activation in response to either mechanical or thermal stimuli whilst the electrical stimuli evoked activity in the S1, PO and cerebellum. Finding no brain activity in response to noxious thermal and mechanical stimuli is uncommon in comparison to many of the other studies mentioned here but it could have been due to their statistical approach. They took the average ROI activity and compared it to a control ROI (based in the visual cortex) and subsequently applied a very conservative statistical threshold ($P = 2.1x10^{-6}$) which the

authors mentioned as being high “even after Bonferroni adjustment” (Disbrow et al., 1998).

Using an ROI approach when comparing between noxious heat, tactile and vibrotactile stimuli, overlapping activity was found in the S1 (area 1) and primary motor area between all stimuli (Gelnar et al., 1999). These were the only areas of overlap between all stimuli as the noxious stimuli also saw additional significant activity within the S2, insula and PCC. These results display overlapping somatosensory activity evoked by cutaneous stimuli either innocuous or noxious. When two different methods of noxious heat pain induction were compared (contact thermode vs. laser) no spatial differences were seen in related brain activity (Helmchen et al., 2008). The thermode did evoke significantly higher activity within the S2, posterior insula, pregenual ACC and middle frontal cortices but these were likely due to the increased somatosensory stimulation considering that pain intensities were matched between stimuli. Similar results related to signal intensity rather than spatial differences were also reported in a study of trigeminal nerve stimulation using chemical (gaseous CO_2), electrical and mechanical (air puff) stimuli (Iannilli et al., 2008). All three modalities evoked bilateral activation within S1, S2, ACC, insula and middle frontal cortices and thalami. No difference was found subsequently when assessing cutaneous and muscular pain using mechanical stimulation (Uematsu et al., 2011). Using a pressure algometer (commonly used in QST studies to measure pressure pain thresholds (Rolke et al., 2006)) cutaneous pain was induced by applying a steady pressure of 20 Newtons for 20 seconds in a block design. Muscle pain was induced using the same algometer on an area of skin that had been locally anaesthetised using an injection of 1% lidocaine and due to the numbing of the skin and need to apply pressure deeper to the affected area, pressure was applied at 30 Newtons.

This ‘muscle’ pain was validated and used in prior QST studies (Graven-Nielsen et al., 2004, Takahashi et al., 2005). The single difference reported between these stimulations was that S2 activity was only seen during cutaneous (non-anaesthetised) stimulation which is in agreement with many of the mentioned studies in that S2 activity is more commonly reported in response to cutaneous pain.

As pain is such a multi-dimensional perception, it can be heavily affected by factors such as attention, anticipation and contextual modulation. Most people can attest to being able to distract themselves from pain to some degree, but it is the neural mechanism of this endogenous relief that neuroimaging has begun to elucidate. An early study of attention in pain asked participants to either attend to the induced pain or to ‘think of something else’ during the stimulation (Tracey et al., 2002). During the attention away or ‘think of something else’ task, subjects rated the same stimuli as less painful whilst displaying increased activity in the periaqueductal grey area (PAG) which is known to be part of the descending pain inhibitory pathway in humans. Increased activity in the PAG and dorsolateral prefrontal cortex (DLPFC) was also displayed alongside decreased pain ratings in a comparable study when attending to an auditory stimulus during pain induction (Dunckley et al., 2007). Activity in the bilateral anterior insula, however, was shown to correlate positively with reported pain ratings regardless of attentional state. Similar studies using cognitive tasks such as the Stroop test or odour stimuli alongside painful stimulation also consistently see decreases in pain intensity related to increased attention away from the stimulus (Bantick et al., 2002, Villemure and Bushnell, 2009). Use of pleasant and unpleasant odours alongside noxious stimulation also allowed a previous study to investigate the effects of emotional modulation against attention (Villemure and Bushnell,

2009). They found that changes in mood modulated unpleasantness of the stimuli but not the intensity and changes in attention away from the stimuli affected intensity but not the unpleasantness. The difference in the effect of these aspects was mirrored by differences in neural activity, attentional modulation away from pain exclusively reduced activity in the left anterior insula whilst the emotional modulation affected unpleasantness related activity in the ACC, primary and secondary somatosensory cortices and the medial thalamus. These findings suggest that attention and mood modulate pain via distinct neural mechanisms and have distinct behavioural effects.

Pain anticipation is an important and robust modulator of perceived pain. For instance, the anticipation of an intense pain leads to an increased perception of pain (a nocebo effect, see Freeman et al. (2015) for an example) and conversely the expectation of less pain has an analgesic effect (as shown in studies of placebo and expectancy modulation experiments (Bingel et al., 2011). Anticipation of pain subsequently displays potential benefits for clinical populations in which potential subjects may be able to increase treatment efficacy of real or placebo treatments via simply modulating their expectations (Wager et al., 2004, Watson et al., 2009, Schenk et al., 2014, Wiech et al., 2014b). Anticipation of pain is commonly accompanied by neural activity in the ACC, DLPFC, anterior insula with activity in the orbitofrontal cortex (OFC) only reported when placebo analgesia has also been investigated (Wager et al., 2004, Watson et al., 2009, Seifert et al., 2013b, Ter Minassian et al., 2013b). It has been suggested that activity in the DLPFC and ACC during pain anticipation is reflective of the magnitude of the expected pain whilst OFC activity has been hypothesised to be related to either top-down pain inhibitory processes or diversion of attention away from the pain due to its functional connectivity with the PAG area (Wager et al., 2004, Lobanov et al., 2014).

These neural processes are generally thought to be due to the preparation of the neural system to be able to best process the expected stimulus, assessing the competing demands and context of the current bodily situation and responding appropriately. Interestingly, one study looked at correlating measures of sympathetic activity (skin conductance response and skin blood flow) with neural activity during both pain anticipation and pain states (Seifert et al., 2013b). Using a conjunction analysis they found common activity during both states that correlated with sympathetic activity in areas such as the anterior insula, ACC, prefrontal cortices and midbrain.

Contextual modulation can be used to both reduce and increase pain. For example, one previous study manipulated subjects' expectations of the impending stimulus level by altering the cue given (Leknes et al., 2013). By running the same experiment twice (separate scans), the subject was cued to expect a high- or low-level painful stimulus but in reality there were three levels of stimulus presented – high, medium and low. In the first run, high and medium stimuli intensities were given and were cued as high and low level stimuli. Within the second run, the same high/low cues were given but with the medium and low stimuli intensities. Comparison of the pain ratings given for the medium stimuli across the two conditions shows a significant drop in associated pain intensity from 5.3 to 3.4 out of 10 but more interestingly, they see that the hedonic ratings of this stimulus which are negative in the high pain context are actually rated positively in the relative-relief context. This lower pain and relative pleasure of the stimulus is corroborated in the imaging results by an increase in activity in the ventromedial prefrontal cortices such as the subgenual and rostral ACC whilst PAG activity was found to correlate significantly with the hedonic ratings. These results point out the involvement

of the brainstem (PAG) and the reward circuitry in the contextual evaluation of a lesser pain (Leknes et al., 2013).

3.1.2 Chronic pain patient studies

An ongoing question in the field of pain neuroimaging is whether the neural processing underlying chronic pain differs from that observed in response to acute pain in healthy individuals. A common experimental approach therefore in the study of chronic pain is the application of an acute-experimental pain. In theory this approach allows for a relevant comparison of pain-related brain activity in health and disease. Such studies have been carried out using a range of mechanical, thermal, and electrical stimuli like mentioned previously in healthy controls. This approach has limitations however. For instance, while it is useful to study states of hyperalgesia and/or allodynia (as described in section 2.1.2), the neural correlates of pain intensity or the effect of analgesic interventions it is not the clinically relevant pain that these patients experience day to day. This acutely administered pain lacks the subjective and affective factors that are such an important part of the chronic pain experience. Thus reflecting the fact that chronic pain is a multi-system response in regards to neural networks (within the context of the body-self neuromatrix) (Melzack, 1999).

Experiments studying acute pain-related brain activity in chronic pain patients allows for a relevant comparison with healthy subjects. This comparison should allow any differentiated acute pain processing to be identified. As differences are hypothesised, differentiation of acute-pain-related brain activity in chronic pain cohorts is subsequently interpreted as a sign of chronic pain-related neuroplasticity (Davis and Moayedi, 2013). The most commonly studied disease-states are fibromyalgia and chronic lower back pain with a range of musculoskeletal (osteoarthritis) and neuropathic syndromes

(neuropathic pain, complex regional pain syndrome and postherpetic neuralgia) also being studied more sporadically.

Commonly, studies of acute pain processing in fibromyalgia (FM) patients have used a mechanical pressure device that is applied to the subjects thumb (Gracely et al., 2002, Giesecke et al., 2004b, Jensen et al., 2009, Pujol et al., 2009, Diers et al., 2012, Jensen et al., 2012, Kim et al., 2013b). Using this stimuli, experimenters have compared stimuli in patients and subjects that either matched perceived pain intensities and/or stimuli intensity. Studies have presented consistent results showing that when constant stimulus intensities were presented between FM and healthy subjects, FM patients presented with lower pain thresholds and increased pain intensities (defined as hyperalgesia earlier in section 2.1.2) (Gracely et al., 2002, Cook et al., 2004, Giesecke et al., 2004b). These psychophysical results were than matched with increased levels of somatosensory activity in the FM groups compared to controls. Later studies saw slightly different results such as one study that presented stimuli that were matched for perceived pain intensity reported increased paralimbic brain activity (anterior insula, basal ganglia and ACC) in the FM group compared to controls with a subsequent study reporting opposing results of reduced activity in the FM group (ACC and hippocampus) (Jensen et al., 2009, Pujol et al., 2009). This could have been due to the different stimulus intensities used or different experimental paradigms (one study presented with a jittered presentation of stimuli intensities whilst the other presented consistent stimuli) which could have possibly lead to participant habituation and reduced the response of brain activity imaged. The latest studies of FM subjects compared brain activity before and after psychological treatments (behavioural extinction training and cognitive behavioural therapy respectively) (Diers et al., 2012, Jensen et al., 2012). Both treatments seemed

to cause changes in brain activity during noxious stimulation with behaviour extinction improving pressure pain thresholds and increasing somatosensory brain activity in response to stimulation (posterior insula, thalamus, S1 and lenticular nucleus) (Diers et al., 2012). Cognitive behavioural therapy selectively increased prefrontal brain activity whilst not affecting clinical pain measures – suggestive of a change in pain processing with increased pain reappraisal (Jensen et al., 2012). The common thread to these studies of fibromyalgia is the persistent finding of hyperalgesic pain perception and corresponding increases in pain-evoked brain activity that remain malleable to intervention. It would be of interest to further investigate these states of hyperalgesia using a model in healthy controls of intensity coding (e.g. using a range of stimuli and pain intensities and assessing the brain regions involved in encoding the stimulus or pain perception) or indeed using perception-controlled designs in which pain intensities were the same across cohorts. This would subsequently allow the investigation of mechanisms underlying these differences – e.g. are they caused by increased ascending input or deficient descending inhibition (as posited in section 2.1.1.2) in the patient cohorts?

Studies of chronic back pain (CBP) initially confirmed the presence of hyperalgesia and central sensitisation when pressure stimuli were seen to cause higher reported pain intensities in CBP vs. control subjects (Giesecke et al., 2004a, Giesecke et al., 2006). fMRI, however, presented with a potential mechanistic explanation, alongside the increased pain intensity and somatosensory activity in response to the same stimuli intensity reported in the earlier study (S1, S2, inferior parietal and cerebellar cortices), the second study also reported that the patient cohort presented with reduced activity within the PAG when compared to controls. This is an area important in the

descending pain inhibitory pathway and to see a reduced level of activity that could be interpreted several ways. E.g. as a deficient pain inhibitory circuit, a pain inhibitory circuit that has instead become facilitatory, or indeed a circuit that has hit a ceiling effect due to the presence of ongoing clinical pain.

Subsequent studies of chronic back pain (CBP) subjects have presented data showing that spontaneous pain caused by CBP differs from acute noxious pain showing increased prefrontal and emotional-affective processing alongside altered reward processing in response to noxious stimuli (Baliki et al., 2006, Baliki et al., 2008b, Baliki et al., 2010). Using a paradigm that allows subjects to rate their pain constantly during fMRI scanning, experimenters were able to dissociate the effect of applying a second pain over the top of the underlying chronic back pain. Although this approach could lead to the introduction of attentional, motor and visual confounds, the addition of a visual rating control experiment was used to reduce any possible effect of this approach. The earliest study compared brain activity linked to spontaneous and evoked-pain finding that spontaneous pain was reflective of increased affective and emotional processing in areas such as the mPFC, amygdala and ACC whilst evoked-pain was reflected by somatosensory activity in regions most significantly in the insula (Baliki et al., 2006). A subsequent report focussed on treatment responses to lidocaine (before and after) in both CBP and knee-osteoarthritis (KOA) subjects, finding that spontaneous CBP related brain activity was greatly reduced after treatment whilst pressure-evoked brain activity in KOA subjects remained relatively similar (Baliki et al., 2008b). Only activity in the middle frontal gyrus, left anterior insula and thalami was reduced after treatment. In the context that the anterior insula has been previously implicated in pain intensity processing and activity in the thalami also correlated significantly with pain intensity, these findings likely reflect the fact

that the reported pain intensity of the stimuli was reduced after treatment. An additional study of CBP found that activity within the nucleus accumbens (NAc) – an area richly linked with reward processing and dopaminergic pathways – was altered in the presence of chronic back pain displaying different temporal activity and functional connectivity in the presence of evoked pain between cohorts (Baliki et al., 2010). These reported group differences seem to suggest that although the NAc activity during noxious stimulation is functionally connected to common pain-related areas such as the ACC, insula, thalami and putamen in both groups the CBP subjects display an increased mPFC and PCC connectivity not seen in the control group. In light of the known connectivity between the NAc<>mPFC related to motivation and appraisal (Moscarello et al., 2007), this connectivity with the mPFC was interpreted as representing altered pain reappraisal and motivational behaviour due to the presence of CBP. It is interesting to note that the basal ganglia wasn't found to differentiate between controls and CBP considering its dopaminergic connectivity with the NAc and its prevalent role in motivation and action-selection (Da Cunha et al., 2012).

Other studies of neuropathic states such as diabetic neuropathy (DN), complex regional pain syndrome (CRPS), postherpetic neuralgia (PHN), trigeminal neuralgia and burning mouth disorder have also displayed altered central processing (both hyperalgesic and allodynic states) in response to innocuous and noxious stimuli (Albuquerque et al., 2006, Becerra et al., 2006, Maihofner et al., 2006a, Geha et al., 2007, Tseng et al., 2013). These studies commonly report increased limbic and/or prefrontal brain activity in response to stimuli in either allodynic or hyperalgesic states. However, there is little consistency between studies or diseases as to specific brain regions that are specifically related. The overall result is that different regions involved in

somatosensory or emotional processing are up- or down-regulated due to the presence of chronic pain but specific regions are not clear currently due to differences between disease state, experimental paradigms and statistical analyses. Specifically in regard to disease state, Melzack also outlined the idea that different pain states may display different disease- or state-specific neurosignatures according to the levels of sensory input, cognitive-load and affect associated with each presentation (Melzack, 1999).

3.1.3 Task-free BOLD imaging (resting-state fMRI)

Task-free fMRI allows for the investigation of spontaneous low frequency oscillations of brain activity. These low frequency oscillations (within the range of 0.01-0.1Hz) give rise to synchronised spatial and temporal brain activity that can be differentiated into distinct networks of brain regions that are 'functionally connected'. This 'functional connectivity' is defined as 'temporal correlations between spatially remote neurophysiological events' (Friston, 1994). These networks have been found to present with differing cognitive qualities whilst presenting with an experiment that is easily administered (subject lying still with eyes open/closed) (Fox and Raichle, 2007). This activity that is thought to reflect neuronal activity at rest shows great potential in the understanding of disease states and as such has been applied to the understanding of chronic pain (Auer, 2008). This approach also allows the experimenter to identify a region of interest as a seed region from which an average time course is extracted. This time course can then be correlated across the whole brain to find out what other areas show synchronous activity (otherwise known as functional connectivity) without the presence of an overt stimulus (Biswal et al., 1995). These networks have been shown to be reproducible across large cohorts (Abrol et al., 2017) and also across other

imaging modalities such as PET (Spetsieris et al., 2015) and MEG (Brookes et al., 2011).

This approach has been applied in both acute and chronic pain cohorts such as subjects with CBP, diabetic neuropathy and fibromyalgia (Baliki et al., 2008a, Cauda et al., 2009a, Kong et al., 2010b, Cifre et al., 2012). The most common networks of interest to date have been the default mode network and the salience network. The default-mode (comprised most commonly of bilateral parietal regions, the posterior cingulate and the prefrontal cortex) is a network seen when a subject is at rest and is not performing any mental task or visualisation and is anticorrelated with goal-directed or attentional neuronal activity (Raichle, 2015). The salience network (observed most commonly as activity in the dorsal anterior cingulate and the bilateral anterior insulae), however, is involved in the orientation of attention and the coordination of brain activity in relation to stimuli (Uddin, 2015). CBP cohorts have been shown to have disrupted default-mode networks with reduced levels of deactivation during tasks when compared to controls (Baliki et al., 2008a, Balenzuela et al., 2010, Tagliazucchi et al., 2010, Baliki et al., 2014). This network has been shown to be disrupted in several other chronic pain states such as diabetic neuropathic pain (Cauda et al., 2009b), irritable bowel syndrome (Letzen et al., 2013), somatoform pain disorder (Otti et al., 2013a) and knee osteoarthritis (Baliki et al., 2014). All of these studies report disrupted resting neuronal activity caused by the persistent pain fluctuation suffered by all cohorts. A recent study in healthy controls performed resting state fMRI (task-free) to show that subjects who displayed higher tendencies for mind wandering during pain displayed increased default mode network activations (Kucyi et al., 2013). This increased activity was reported alongside stronger functional interactions between the default mode network (specifically

the medial prefrontal cortex) and the PAG (a key brain region in the descending inhibitory pain network) and was convergent with stronger anatomical connectivity. This provides a novel insight into how a disrupted default mode network may impact on a patients' ability to let their mind wander away from their pain alongside reductions in their ability to recruit the endogenous pain inhibitory pathways.

Functional MRI data can also be interrogated by investigating the power spectra of low frequency fluctuations in groups or individuals to assess whether different oscillatory frequencies can be found between chronic pain and control subjects. Several studies have used this approach showing that chronic pain patients display increases in higher frequency bands compared with controls in states of diabetic neuropathy, chronic back pain, fibromyalgia, osteoarthritis, chronic pain disorder and complex regional pain syndrome (Cauda et al., 2009b, Baliki et al., 2011, Kim et al., 2013a, Baliki et al., 2014, Otti et al., 2013b). This spectral shift is suggested to be indicative of increased high frequency oscillations within networks such as the default-mode during spontaneous pain however this remains speculative as this link has only been tested in CBP subjects and the functional relevance of these findings is yet to be fully understood (Baliki et al., 2011). Additionally, knowing how sensitive BOLD fMRI is to noise such as motion, analysis of frequency spectra is of interest but should be approached with caution as for example, increased high frequency spectra in patient groups could simply be indicative of an increased presence of motion in these groups. The use of imaging techniques with higher temporal resolution such as EEG or MEG could be used to assess whether this is the case. A relevant example of this would be the MEG study by Lim et al. (2016) whom provide potential confirmatory data in fibromyalgia

patients displaying increased high (and low) frequency oscillations in patients compared to controls.

Further to the study on mind-wandering during pain mentioned earlier, multimodal connectivity also allows the combination of structural and functional connectivity to give a greater understanding to the interplay between specific regions. An example of this was investigating the differential connectivity of the insular subdivisions; anterior, mid- and posterior insula (Wiech et al., 2014a). Using resting state fMRI data alongside DTI it was shown the anterior insula was predominantly connected to orbitofrontal and ventrolateral prefrontal cortices (VLPFC) whilst the posterior insula was strongly connected to the somatosensory cortices (SI and SII). Mid-insula unsurprisingly displayed a mixed connectivity pattern of the anterior and posterior regions with structural and functional connections to the VLPFC, SII and SI. This connectivity strengthens the knowledge that anterior insula activity is implicated in emotional-affective discrimination of painful stimuli whilst the posterior region is heavily linked with sensory-discriminative aspects of pain perception. Due to the mixed connectivity displayed by the mid-insula it is thought that this area is involved in the integration of sensory, cognitive and emotional information (Wiech et al., 2014a).

Although increasingly useful, resting-state BOLD fMRI still has its limitations. For instance, resting-state data allows the study of correlations and oscillatory characteristics of brain activity but not an absolute measure of metabolism or haemodynamic activity. Additionally, as mentioned previously BOLD fMRI is especially sensitive to motion and haemodynamic based noise artefacts and each analysis should always attempt to remove or control for these confounds as best as possible with thorough quality assurance and denoising steps.

3.2 Arterial spin labelling (ASL)

3.2.1 What does the image represent?

Arterial spin labelling is an alternative to BOLD contrast fMRI. It allows the quantitative measurement of perfusion in a non-invasive fashion (Detre et al., 1992, Williams et al., 1992). This technique is implemented by using the water in arterial blood as an endogenous tracer. This is achieved by applying radio frequency and magnetic field gradient pulses to invert water spins in the targeted arteries which are usually the carotid arteries in neuroimaging (see figure 4.3 for diagram) (Dai et al., 2008a). This technique has several sub-types, namely continuous ASL (CASL), pulsed ASL (pASL) and pulsed CASL (pCASL) also known as pseudo-continuous ASL (Dai et al., 2008a, Edelman et al., 1994, Williams et al., 1992). The newest type of ASL – pCASL displays the most advantages for neuroimaging in pain with improved spatial resolution, signal-to-noise and reproducibility having shown itself to be highly reproducible between sessions and comparable to PET imaging techniques (Dai et al., 2008a, Hodkinson et al., 2013, Xu et al., 2010).

All of these sequences have slight differences but they all give quantitative readouts of cerebral blood flow (CBF) in millilitres per 100g of tissue per minute (ml/100g/min). These readouts have great use clinically in diseased states such as stroke and vascular dementia allowing identification of areas of increased and decreased blood flow. In the field of pain neuroimaging, ASL has recently increasingly realised as a tool of great usefulness. This is because for all of the advantages of BOLD functional imaging, it is not as sensitive to tonic stimuli (lasting over 2 minutes or more) as ASL. In the context of chronic pain, BOLD fMRI can identify stimulus evoked (e.g. allodynic or hyperalgesic stimulation) or low frequency functional connectivity (resting-state analysis) but it cannot sensitively measure the ongoing

spontaneous pain that is the most pronounced and problematic feature of chronic pain. With this sensitivity, it is easy to see why ASL imaging is becoming more prevalent in the study of neural processes underlying chronic pain.

3.2.2 ASL imaging during noxious stimulation

The first record of ASL imaging in the pain literature was a study investigating the potential use in measuring cerebral blood flow in healthy volunteers (n=14) in response to a noxious thermal stimulation of the left hand (Owen et al., 2008). They found that using a previously established stimulation paradigm they could measure regional CBF changes throughout brain regions commonly seen in previous pain studies such as bilateral insula, and S2 regions as well as the cingulate cortex and supplementary motor area (Davis et al., 1998b, Owen et al., 2008). The study was the first to show that ASL provides a complementary and comparable imaging measure to BOLD. The same research group then proceeded to publish two subsequent task-based pain ASL studies. Both of these studies used hypertonic saline infusions into the left brachio-radial muscle to induce an ongoing deep muscle ache comparable to that endured in some chronic pain states (Owen et al., 2010, Owen et al., 2012). The first of these studies was interested in imaging the neural mechanisms involved in the transition between acute and tonic pain states (Owen et al., 2010). This was achieved by giving an initial 0.5ml bolus of hypertonic saline into the muscle to model acute pain whilst following up with a consistent infusion of 300µl/min afterwards for 15 minutes. Subjects rated their pain once every minute throughout the whole procedure. Interestingly, they found that this acute pain sensation initially evoked increased CBF within widespread pain processing areas such as the bilateral insula, anterior mid-cingulate cortex (aMCC), bilateral thalamus and the right

S2. It was found that the transition into tonic pain occurred after approximately 5 minutes with most of those regions that had displayed increased CBF returning to near baseline whilst only the bilateral insula remained significantly increased for the whole 15 minutes infusion. The reported pain intensity, however, remained constant throughout the duration of the infusion and as such it was thought that the decreases in CBF were due to reappraisal of the pain. For example, the reduction in CBF within the aMCC was thought to be due to a reduced affective component of the tonic pain vs. the acute onset. This is interesting considering that several studies have shown the mid-cingulate to correlate with participant reported pain intensities – further studies are needed to assess whether this is the effect of habituation or potentially an insensitivity of the experimental approach (Bornhovd et al., 2002, Favilla et al., 2014b, Helmchen et al., 2008, Kong et al., 2006). The second study subsequently looked only at the neural mechanisms during tonic pain perception (Owen et al., 2012). This was achieved by using a slower infusion of hypertonic saline (200µl/min) without an initial bolus. This allowed the pain to present in a gradual manner over a few minutes. Increased CBF was then seen in the bilateral insula, inferior frontal gyrus and the right middle frontal gyrus. Without CBF increases in somatosensory and affective regions it was thought that the results were reflective of the processing of pain intensity and unpleasantness (bilateral insula) and the cognitive evaluation of the stimulus (frontal activations).

A separate ASL study using thermal (heat and cold) and ischemic noxious stimuli also found that areas of pain processing could be imaged, displaying changes in CBF in response to stimuli using a short block stimulus design (8 seconds on/off for heat, 10 seconds on/off for cold) (Frolich et al., 2012). Interestingly, although statistically significant activations were found in pain

processing areas during the ischemic pain condition, ROI analyses revealed that these ‘activations’ were due to decreased CBF values where they were due to increases in response to the thermal stimuli. This is likely a reflection of the ischaemic condition which maintained the ischemic stimulation for 4 minutes rather than using a block design. Two other studies also investigated neural responses to noxious heat. An earlier study investigated CBF in patients with chronic lower back pain in comparison to healthy controls also using clinical manoeuvres to exacerbate clinical pain as a second stimulus (Wasan et al., 2011). They found that these manoeuvres could cause CBF increases in the dorsolateral prefrontal cortex, S1, anterior insula and medial prefrontal cortices in patients but not the healthy volunteers. Noxious heat pain however caused no such CBF increases in the patients even though the stimulus was matched to be as painful as the clinical manoeuvres. This was indicative that ASL was sensitive to exacerbation of the clinical pain state but not necessarily to the pain induced via a 2nd mechanism in addition to the ongoing clinical pain (Wasan et al., 2011). A later study using thermal stimuli in HC compared pain intensity and neural activity during noxious heat pain at baseline and then a second time whilst the subject also performed mindfulness meditation (Zeidan et al., 2011). The subjects had four days of meditation classes and then completed their second scan during which they were instructed to meditate whilst undergoing noxious stimulation. Meditation during stimulation reduced pain intensity by 40% and unpleasantness by 57%. These psychological ratings were associated with meditation-induced increases in activity of the ACC and right anterior insula in regards to reduced pain intensity whilst reductions in reported unpleasantness were linked with activity of the orbitofrontal cortex and deactivation of the thalamus (Zeidan et al., 2011). Interestingly, it seems both increased and decreased ACC CBF is related to decreased pain intensity (Owen et al., 2010, Zeidan et al., 2011). It

is plausible that these potentially discrepant results could be explained by the ACC's role as part of the salience network in that reduced ACC CBF could be due to reappraisal of a tonic stimuli's salience. A subsequent study using noxious thermal stimuli compared the newer pCASL sequence to the established BOLD imaging which was an improvement in the imaging as the previously mentioned ASL studies had used either the CASL or pASL imaging sequences (Maleki et al., 2013). This study found that very similar spatial patterns of brain activity were seen in response to noxious heat whether it was measured via ASL or BOLD furthering the argument that ASL is a robust and complementary measure to BOLD.

3.2.3 Task-free ASL imaging (resting-state fMRI)

As previously mentioned, one of the advantages of ASL is that it is superior to BOLD in the imaging of tonic and ongoing changes in neural activity (reflected in CBF) due to not being affected by low frequency drift over 1 minute of stimulus. As such, numerous studies have taken advantage of this in the imaging of chronic pain cohorts. The first cohort was reported in 2010 looking at CBF during the onset of a migraine and its subsequent treatment with rizatriptan (Kato et al., 2010). Using a PASL sequence it was found that onset of migraine was characterised by reduced CBF in the thalamus, posterior cingulate and cerebellum alongside increases in the frontal lobe. Treatment with rizatriptan was seen to return hypothalamic CBF levels to those at baseline.

A 2011 study used pCASL to measure ongoing pain using a post-surgery pain model showing imaging reproducibility over 2 separate sessions giving evidence that ASL provides a plausible readout for pain interventions without reliance on patient self-report (Howard et al., 2011). Regional CBF increases of 5-10% were seen in the post-surgical pain state as compared with pre-

surgery in bilateral S1, S2, insula, cingulate cortex, thalamus and more. This was the first study to show the reproducibility of ASL imaging in a spontaneous pain state. A subsequent study in hand osteoarthritis patients also displayed high replicability between scan sessions when reported pain intensity at the time of scanning was controlled for (Howard et al., 2012).

A case study assessing the neural correlates of pain and pain relief of a patient with inherited erythromelalgia (a state characterised by severe ongoing pain in the peripheral areas caused by an L858F mutation in the voltage-gated sodium channel $Na_v1.7$) was imaged using ASL (Segerdahl et al., 2012). Using a block design of 5 minutes in pain state and then 5 minutes of pain relief by cooling of the skin revealed widespread CBF increases in pain processing areas during the pain state which were then completely abolished during the cooling pain relief. Having used the ASL imaging alongside quantitative sensory testing (see Rolke et al. (2006) for examples of protocols) the group were able to take a multi-disciplinary approach to assess the mechanism of this pain state. For example, the QST assessed the peripheral sensitivity of the affected foot which displayed the expected heat pain sensitivity but also an unexpected hyposensitivity to deep pressure pain (attributed to a thickening of the affected skin), whilst assessment of central processes related to the perception of the clinical pain allowed an insight into the underlying processes. A more recent ASL study used a multimodal MRI approach to investigate the mechanisms of neuropathic pain after spinal cord injury (SCI) (Gustin et al., 2014). Concentrating on the thalamus in 23 patients and 21 age- and gender-matched controls they used ASL to measure ongoing activity alongside magnetic resonance spectroscopy to give a readout of the levels of metabolites within the thalamus. The results saw reduced CBF in the reticular nucleus of the thalamus which was accompanied by reductions of N-

acetylaspartate (NAA) and gamma amino butyric acid (GABA) which are related to neuronal viability and inhibitory functions respectively. This is suggestive that neuropathic pain after SCI is associated to both functional and metabolic changes within the thalamus leading to reduced inhibition and hyperexcitability of the affected neurons. Whilst interesting, the inference from this study is limited considering its observational design. Ideally, the evidence would be strongest with longitudinal data displaying changes from one state to another e.g. from acute to chronic pain condition or vice-versa.

Lastly, two task-free ASL studies have taken similar functional connectivity approaches as those commonly seen in BOLD resting-state analyses. The first investigated static CBF measurements and functional connectivity postherpetic neuralgia patients (Liu et al., 2013). In comparison to healthy controls, patients displayed increased CBF in regions of reward processing (left caudate nucleus/lentiform nucleus) and affective regions such as the left insula and amygdala among others. When functional connectivity of the left caudate nucleus was compared also between patients and controls, patients displayed increased connectivity between the caudate and the insula, S1 and right thalamus. These CBF increases seen only within the patient cohort were then investigated for correlation with reported pain intensities with several areas showing high correlations between increasing levels of CBF and reported pain these differences were thought to be due to the substantial level of clinical pain experienced by the patient group (average group pain was rated as 8.3 out of 10). The second study looked at default mode network connectivity in chronic low back pain patients and healthy controls (Loggia et al., 2013). Using resting-state images before and after clinical manoeuvres designed to induce the chronic pain they found that patients displayed increased DMN connectivity to the right insula in comparison to controls. This

connectivity was additionally found to highly correlate with reported pain intensities of the subjects whilst connectivity with the pregenual ACC was found to be anti-correlative. These findings of altered communication within the DMN of chronic pain patients is an extension of previous BOLD resting-state analyses mentioned previously not just noting the disruption but providing a possible mechanism of disruption due to reported pain intensities at rest (increased insula connectivity) and decreased pain inhibition (decreased connectivity of the pregenual ACC) (Loggia et al., 2013).

In the study of resting-state networks and functional connectivity, ASL provides potential benefits in comparison to BOLD imaging. The first of which being that whilst the signal in BOLD imaging is dominated by venous signal ASL signal is generally localised to the capillary bed which is closer to the level of energy use in neurons and synapses. Secondly, ASL demonstrates a flat or neutral power spectrum which compared to BOLD imaging which contains peak power at low frequencies (generally between 0.008-0.1 Hz) and contains increasing levels of noise at low frequencies should be less affected by low frequency drifts which are potentially not of neural origin. Considering these benefits, it is interesting that so few experiments have been published investigating CBF in chronic pain patients. An approach similar to that taken in Liu et al. (2013) in which chronic pain patients are studied at rest would certainly take advantage of the sensitivity that ASL has to tonic changes. However, combining this with an approach such as that taken by Segerdahl et al. (2015b) in which perceived pain ratings are correlated with CBF could prove a powerful approach in understanding the neural underpinnings of chronic pain.

3.3 Meta-analyses of functional imaging studies: What have we learnt?

To date, only eleven whole-brain meta-analyses of pain imaging data have been carried out. These have covered a range of approaches with the earliest two manually counting the prevalence of reported areas (Peyron et al., 2000, Apkarian et al., 2005). As pain fMRI was still fairly new when these were published (2000 and 2005 respectively) the majority of reviewed studies were PET and SPECT studies. They both reported common spatial patterns of brain activity during acute experimental pain in healthy control subjects in regions including: SII, bilateral insula, ACC, thalamus, SI, posterior parietal and prefrontal cortices alongside striatal and cerebellar activity (Peyron et al., 2000, Apkarian et al., 2005).

Since these early publications this pattern of healthy acute pain processing has remained fairly consistent (Figure 3.2 shows results from an on-line meta-analytic tool called NeuroSynth when the search term “pain” was used). For instance, a meta-analysis of noxious upper arm stimulation including only 22 fMRI studies reported similar patterns in healthy controls with the addition of visualised clusters due to the use of the newly acquired Activation Likelihood Estimate (ALE) (Farrell et al., 2005). The ALE technique uses reported coordinates or foci and then models their spatial uncertainty using a Gaussian function of full width half max (FWHM) (Tench et al., 2013). Results are subsequently driven by foci from multiple studies that are clustered in the same region.

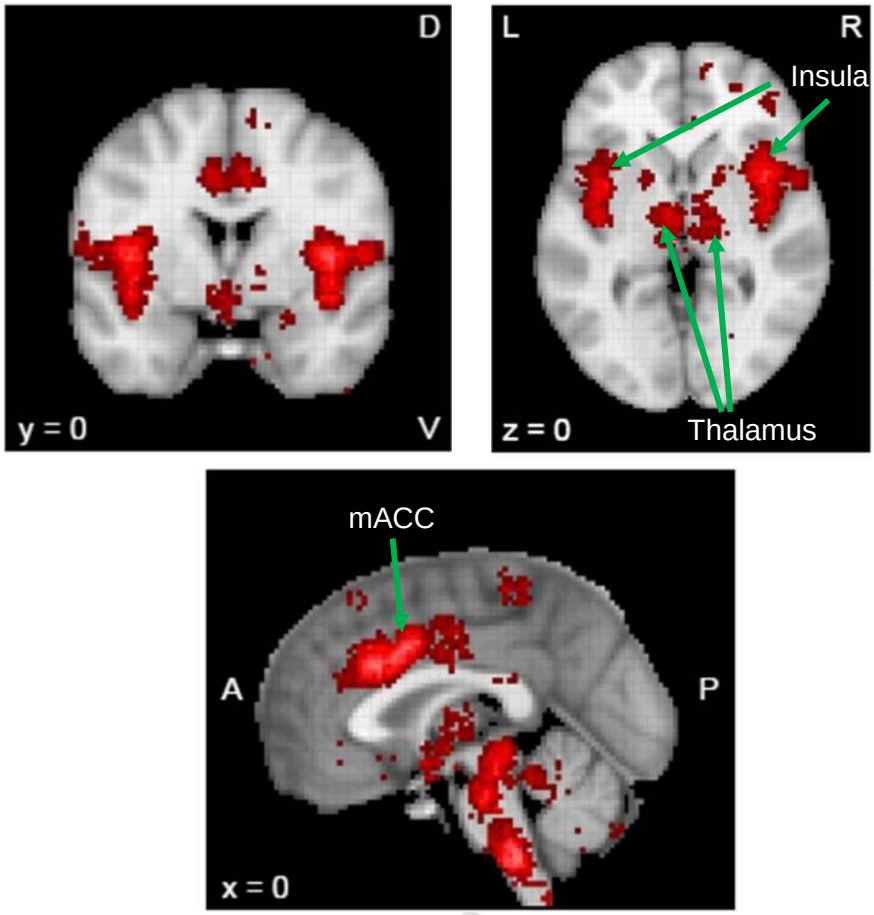


Figure 3.2. Coordinate-based meta-analysis results from 369 studies using an online meta-analytic toolbox in which search terms can be entered and then a databank of >10,000 collated studies will be searched (Neurosynth.org). Foci are then only included from studies that report the search term at a high frequency (Yarkoni et al, 2011). This is an example of the commonly reported brain regions using the search term "pain". Key: L – Left, R – Right, D – Dorsal, V – Ventral, A – Anterior, P – Posterior, mACC – mid-anterior cingulate cortex.

Meta-analyses using only fMRI studies have reported similar patterns of results in pain processing areas (Friebel et al., 2011, Lamm et al., 2011, Lanz et al., 2011, Cauda et al., 2012, Duerden and Albanese, 2013, Lin, 2014, Lin et al., 2014). As well as comparing this base pain processing in healthy controls, technical and clinical aspects were investigated such as evoked pain in healthy controls vs. chronic pain patients. Qualitative and quantitative meta-analytic comparisons have shown varying results e.g. that patients show increased limbic activity in areas such as the ACC and anterior insula or that patients show increased prefrontal activity with decreased insula, thalamus and ACC activity (Apkarian et al., 2005, Friebel et al., 2011). One novel meta-

analysis looked at the effect of placebo analgesia during pain induction showing that increased activity was seen in regions linked to emotional regulation (rostral ACC, medial and lateral PFC, anterior insula) whilst also showing reduced levels of activity in nociceptive processing areas (thalamus, posterior insula, mid and posterior CC) (Amanzio et al., 2013). Most of these analyses however, are highly underpowered with numbers of studies averaged ranging from 8 to 140 with inconsistent results when comparing between groups of interest. The latest meta-analysis however included 140 studies for its main contrast of acute pain in healthy controls alongside smaller groups of 9 and 10 studies for comparisons of stimuli modalities (noxious cold vs. heat, noxious muscle vs. cutaneous stimulation) (Duerden and Albanese, 2013). When comparing left- vs. right-sided stimulation a slight right-lateralisation of pain-related activity was located in the right ACC whilst noxious cold stimuli was linked to increased affective activity (subgenual ACC and amygdala) when compared to noxious heat. Overall, these meta-analyses suggest two main points: 1. That acute pain processing in healthy controls follows a fairly robust spatial pattern of brain activity and 2. That differences between brain activity during evoked-pain in healthy controls and chronic pain patients are not necessarily reflective of whole-scale changes in activity patterns but in more subtle changes in the dynamics of these patterns. This would suggest that the investigation of activity over time in these brain regions/networks rather than only acute responses to experimental nociception may provide additional information about the neural processes underlying these pain states.

3.4 Summary

As reviewed here, functional neuroimaging in pain has furthered our understanding allowing mechanistic insight into how the perception of pain

arises and confirming previous hypotheses that pain perception was multi-faceted combining “sensory-discriminative, affective-motivational and evaluative-cognitive” aspects (Melzack, 1999). During pain perception in healthy subjects, this is reflected by relevant activity in areas such as the: 1. SI, SII, thalami and posterior insular regions (sensory), 2. ACC and anterior insular regions with amygdala and subgenual ACC sometimes present (affective) and 3. Orbitofrontal and dorsolateral prefrontal cortices (evaluative). As well as subgroups of these regions combining to process intensity and context we have seen that altered pain-related activity in this regions can be imaged in chronic pain states displaying as upregulation of emotional processing in chronic pain states or increased somatosensory activity in response to allodynic or hyperalgesic sensations. A particular trend in the published literature however has been to simply observe group differences and then explain these differences away by the sheer presence of chronic pain. The following studies will attempt to move beyond this approach of reporting differences between groups by looking into either potential relations to reported psychometric data or by more in-depth analysis to make more sense of any potential findings. Knowledge gaps that are notably missing from the literature include up-to-date meta-analyses (to take advantage of improving methods and an increasing number of data to include for both healthy and chronic pain cohorts) and also primary neuroimaging studies investigating chronic osteoarthritis pain. Considering its prevalence (discussed in section 1.1) osteoarthritis is quite understudied in comparison to states such as chronic back pain or neuropathic disorders. Additionally, also missing from the literature are experiments investigating perceived pain in chronic pain cohorts using ASL, and studies of resting-state brain activity that goes beyond simply stating differences and attempts to give some explanation for observed changes.

4 Basic nuclear magnetic resonance theory underlying fMRI

This thesis is based predominantly on fMRI and as such it is important to understand how and why the signal is generated.

BOLD and ASL fMRI are currently the two most common types of fMRI used. They differ slightly in exactly what they represent but both have the inference of representing metabolic processes within the brain, specifically energy use. Following the neuronal-coupling hypothesis (that increasing/decreasing energy expenditure is tied to increasing/decreasing neuronal activity within the same area) we can infer that there was more or less brain activity occurring in a specific brain region (Logothetis, 2002b). These two imaging types can be used to study brain activity during experiments that study pain perception during: the presence of noxious stimuli and/or chronic pain states in the absence of an external noxious stimuli.

4.1 Basic nuclear magnetic resonance theory

Magnetic resonance imaging utilises the phenomena of nuclear magnetic resonance to generate measurable signal. Spin angular momentum is a quantum mechanical property of nuclei, and the most commonly investigated nucleus in MRI (and in this thesis) is hydrogen (^{1}H). This is in no small part due to its high concentration in the human body. At any present moment, hydrogen nuclei can be thought of as a rotating sphere rotating in any

direction (Figure 4.1a). This rotation can be influenced by the application of a magnetic field (further referred to as B_0), the introduction of which will mean that the nucleus will acquire energy and will most commonly end up in one of two spin states: 1. A low-energy parallel state or 2. A high-energy antiparallel state (Figure 4.1a+b).

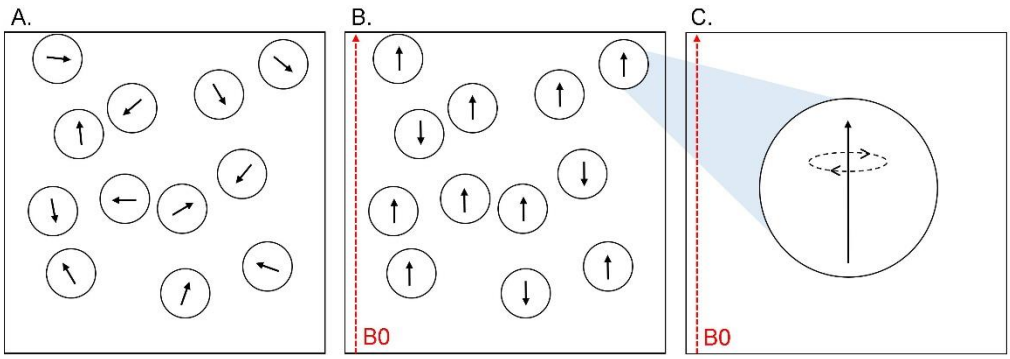


Figure 4.1. Visual representations of H^1 atoms processing (a) freely, (b) around a magnetic field (B0) in parallel and anti-parallel states and (c) an example of how a H^1 atom processes around B0 in the parallel state.

In essence, by providing a magnetic field, MRI scanners force the ^1H nuclei to line up parallel or anti-parallel to the applied magnetic field. Slightly more nuclei will occupy in the low-energy parallel state and so the net magnetisation achieved along B_0 will be non-zero. Even when aligned, these nuclei will continue to spin around the B_0 axis (Figure 4.1c). The frequency at which the nuclei precess around B_0 is known as the Larmor frequency (ω_0). This is a product of the gyromagnetic ratio (γ = 42.58 MHz/T for ^1H) and B_0. The Larmor equation to calculate this frequency is as follows:

$$\omega_0 = \gamma . B_0$$

At 3 Tesla, the Larmor frequency is 127.6MHz. This precession is then utilised to create signal. By application of a radiofrequency (RF) pulse to the samples being scanned, this pulse will flip the ^1H atoms a certain degree (for example

90°) and from then there are two (commonly) measured attributes: longitudinal (T_1) and transverse (T_2) relaxation (Figure 4.2).

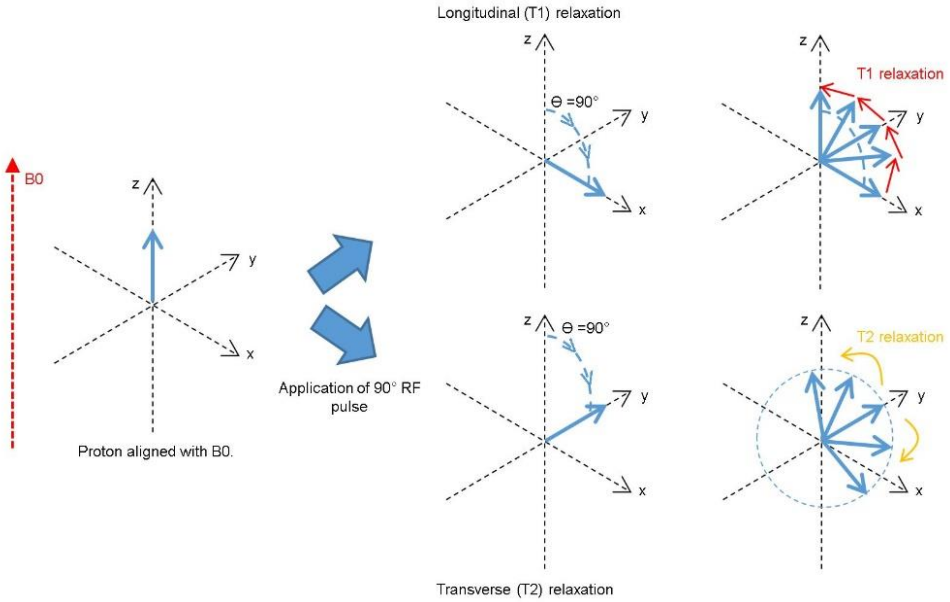


Figure 4.2. Visual representations of longitudinal (T1) relaxation from the x to z axis (top row) and transverse (T2) relaxation across the y and x axis (bottom row) after application of a 90° RF pulse.

4.2 Blood oxygenation level dependent (BOLD) and arterial spin labelling (ASL)

BOLD fMRI makes use of the signal provided by transverse relaxation (T_2-weighted signal). More specifically, it relies upon T_2^* imaging which describes the decay in the transverse plane after the application of an RF pulse due to inhomogeneities in the B_0 caused by objects (or tissue) with magnetic susceptibility. In the case of BOLD fMRI, this technique takes advantage of the fact that haemoglobin in blood vessels has different magnetic properties in its oxygenated and deoxygenated forms. Oxyhaemoglobin is diamagnetic (weakly repulses by the magnetic field) whilst deoxyhaemoglobin is paramagnetic (attracted to the magnetic field) and as such, these properties alter T_2^*. Increases in deoxyhaemoglobin decrease BOLD signal whilst a decrease in deoxyhaemoglobin (or an increase in oxyhaemoglobin) increases

it. This signal is not only affected by levels of (de)oxygenated haemoglobin, but also by cerebral blood flow (CBF), cerebral blood volume (CBV) and cerebral metabolic rate (CMR_{O2}) (see figure 4.3 for a brief schematic) (Davis et al., 1998c). Davis et al were the first to propose the relationship between these parameters, noting that BOLD fMRI is reliant CBF changes being larger than changes in CMR_{O2}, therefore producing these localised regions of altered tissue oxygen content (Davis et al., 1998c). Additionally, it is known that baseline levels of haemoglobin oxygenation and CBV are determinants of the maximum BOLD signal change that can occur (Bright et al., 2017).

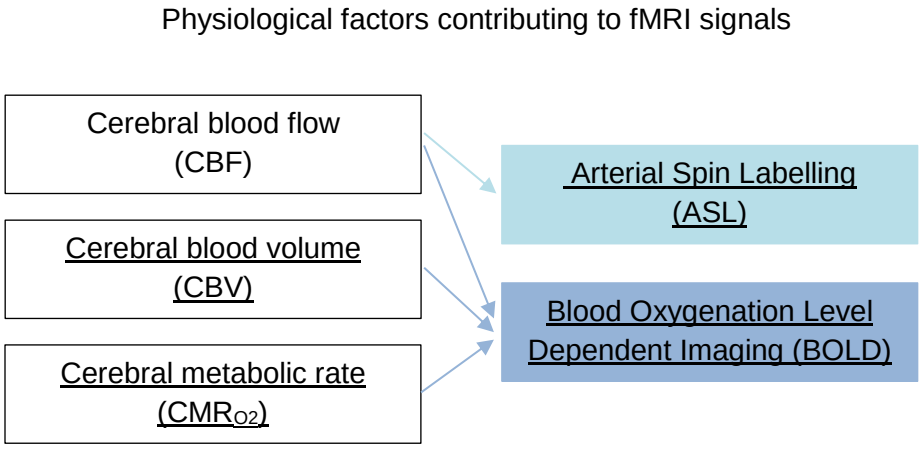


Figure 4.3. Pictorial example of which physiological factors contribute significantly to the measured signal in Blood Oxygenation Level Dependent (BOLD) and Arterial Spin Labelling (ASL) types of fMRI.

ASL on the other hand provides a quantifiable measure of cerebral blood flow by using blood water as an endogenous tracer. Figure 4.4 displays how ASL sequences apply an RF pulse to an area below the acquisition slab (usually placed in the neck to take advantage of the placement of the carotid arteries). After this pulse is applied, a short time (usually referred to as the inversion time or post-label delay, TI) is used to allow time for the blood to flow upwards through the label gap into the brain after which an image is taken known as the “label” image. A subsequent “control” image is also collected (in which the blood has not been previously excited or labelled). Subtracting the “label”

image from the “control” image is what gives the ASL perfusion weighted signal. The signal-to-noise ratio (SNR) of ASL images in comparison to BOLD fMRI is lower, with the SNR inherently limited by T1-longitudinal relaxation time of blood (Borogovac & Asllani, 2012; Alsop et al, 2015 white paper). This is because it is the ASL presents with other benefits however, for instance a flat power spectrum (as a result of the paired-image acquisition and subtraction needed to calculate CBF), sensitivity to long or tonic stimuli and a quantitative measurement of metabolism (ml per minute per 100g of tissue, as opposed to BOLD’s arbitrary measurement units) (Borogovac & Asllani, 2012).

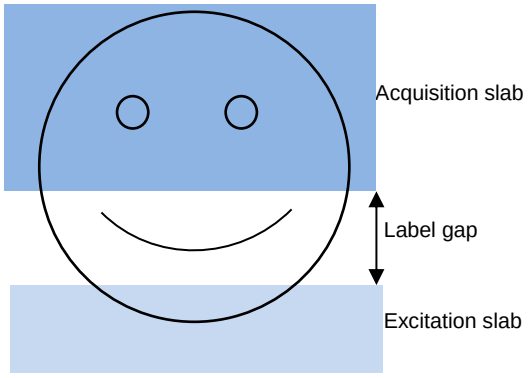


Figure 4.4. Schematic of ASL, showing locations of excitation and acquisition slabs.

4.3 Blood Oxygenation Level-Dependent Imaging (BOLD)

4.3.1 What does the image represent?

BOLD imaging measures differences in the levels of oxygenated- and deoxyhaemoglobin within blood. The signal change seen in BOLD imaging is reflective of increased regional levels of oxygenated-haemoglobin due to increased levels of cerebral blood flow and glucose metabolism (Fox et al., 1988). The glucose metabolism however, is higher than the associated oxygen uptake (which is limited by diffusion from the blood vessel). Decreases

in BOLD signal are therefore reflective of a decrease in oxygenated blood relative to deoxyhaemoglobin. This change in ratio between oxygenated and deoxygenated haemoglobin is therefore a surrogate-signal of neural energy use and subsequent activity.

The technique of BOLD imaging can achieve high temporal and spatial resolution (commonly achieving isotropic resolutions of 1-2mm^3 with whole-brain volumes collected every 2 seconds) allowing clear delineation of when and where significant changes in brain activity occur. It is not without its limitations, with the signal being an indirect marker of neuronal activity and that the temporal aspect is still slow in comparison to electrophysiological methods such as EEG and MEG that capture data in the order of milliseconds. Additionally, increases in spatial resolution are accompanied by reductions in SNR and as such, a balance will always be aimed for such as in the HCP study in which a resolution of 2mm isotropic was chosen over 1.6mm isotropic due to the higher reliability of the acquisition over the target recruitment of 1,200 people (Ugurbil et al., 2013). Multimodal studies however, do show a high degree of overlap between electrophysiological and BOLD signals suggesting that the different techniques allow for measurement of the same or overlapping activity without the need for radiation exposure or injection of any contrast agents (see Figure 4.5 for a visual comparison of how fMRI resolution compares with other imaging modalities) (Logothetis, 2002a, Logothetis, 2003).

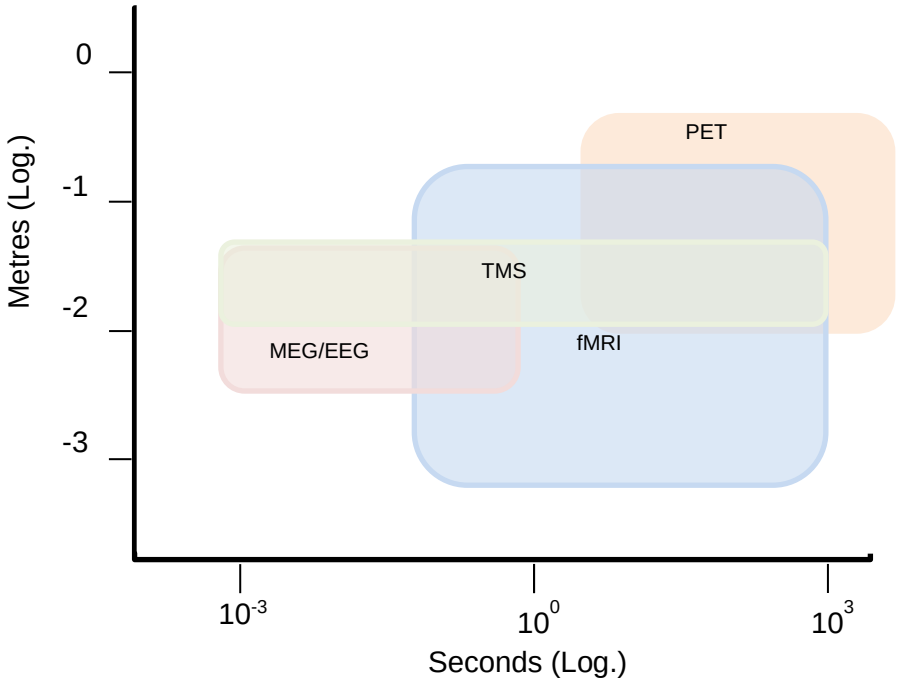


Figure 4.5. A graphical representation of the temporal and spatial resolutions of fMRI in comparison to other common brain imaging and investigative modalities. Legend: MEG – Magnetoencephalography, EEG – Electroencephalography, FMRI – Functional Magnetic Resonance Imaging, PET – Positron Emission Tomography, TMS – Transcranial magnetic stimulation.

5 Aims & Hypotheses

5.1 General Aims and Hypotheses

This thesis seeks to investigate the use of functional magnetic resonance imaging as an objective way of understanding the mechanisms of perceived chronic pain in knee osteoarthritis building upon the prior literature but also assessing gaps in the knowledge. Specifically, the following hypotheses will be tested:

1. **Chronic pain patients will exhibit altered brain responses to acute experimental pain in comparison to healthy controls.**
2. **Chronic pain patients will display cerebral blood flow in limbic regions related to reported pain intensities and that these relationships will further relate to reported negative affect.**
3. **Chronic pain patients will display altered functional connectivity within- and between-networks in comparison to healthy controls and that these differences will be centred on altered right anterior insula connectivity.**

These hypotheses will be assessed via 3 consecutive experiments:

1. **A coordinate-based meta-analysis of reported cutaneous pain-evoking BOLD experiments will be carried out to find the most consistently reported regions reported in experimental fMRI studies of pain in healthy volunteers and chronic pain populations. Firstly, the effects of including studies using different painful stimuli (such as thermal, mechanical and electrical stimuli) and laterality of stimulation will be assessed to**

test if they display significantly differing patterns of reported activity. If the effect of these variables is non-significant or minimal, these will subsequently be collated in order to provide the largest and most homogeneous sample-size achievable. Subsequently, the primary analysis (a group comparison) of pain-related brain activity in healthy and chronic pain cohorts will be carried out. Additionally, the brain activity of pain-related anticipation and deactivations reported during pain will be assessed. Models of chronic pain such as experimentally-induced low mood or hyperalgesia will also be assessed in comparison to pain-related brain responses in healthy and chronic pain cohorts. These tests will be carried out using a newly improved activation likelihood estimation algorithm shown to reduce the presence of false positives.

2. **Employing ASL imaging in chronic pain patients and healthy volunteers to assess the impact of ongoing pain on resting cerebral blood flow and how reported pain levels in chronic pain patients may be represented by neural activity in limbic regions (as measured by ASL). This will be assessed via a regression analysis in which reported knee osteoarthritis pain will be correlated with CBF maps of participants. Secondary analyses will also be carried out assessing the impact of reported negative affect scores (low mood, anxiety and pain catastrophizing) that correlate with reported pain in order to disentangle their effect. Additional post-hoc tests of mediation will be carried out with any**

scores found to significantly correlate with regional CBF and reported osteoarthritis pain.

3. **Lastly, in an overlapping cohort of patients and healthy volunteers to study 2, in depth functional-connectivity analyses will be utilised via BOLD imaging to examine whether the presence of chronic pain alters connectivity within- and between-networks observed during the resting-state. This will be done by employing a seed-based analysis assessing the default mode network (DMN), salience network (SN) and the central executive network (CEN). Networks will undergo group comparisons of three types of connectivity analysis: functional connectivity (correlational seed to whole-brain), effective connectivity (seed-to-seed) and dynamic functional connectivity analysis (sliding-window analysis of within-network connectivity). Group differences from the functional connectivity analysis will undergo secondary tests to investigate for further relationships with reported scores such as anxiety and low mood.**

6 Coordinate-based meta-analysis of cutaneous experimental pain[1]

6.1 Introduction

In healthy subjects, pain acts as an innate defensive response to prevent noxious stimuli from causing damage to bodily tissues. This innate sensation however, can become maladaptive and can cause chronic pain (defined as ongoing pain that persists after the expected time for tissue to heal; usually in the region of 12 weeks). Chronic pain is all too prevalent with large survey studies across both Europe and Canada finding that it affects roughly 19% of adults (Schopflocher et al., 2011, Breivik et al., 2006). Despite this prevalence, treatment is still poor for the majority of patients.

Brain imaging offers a technique for studying the neural mechanisms that underlie chronic pain. With the very definition of chronic pain stating that the any tissue damage has been repaired but the pain is ongoing, it is desirable to

[1] Some of this work has been previously published: Tanasescu, R., et al., *Functional reorganisation in chronic pain and neural correlates of pain sensitisation: A coordinate based meta-analysis of 266 cutaneous pain fMRI studies.* Neurosci Biobehav Rev, 2016. 68, 120-33. My role in the publication was as joint lead author, responsible for the literature search, data acquisition, preparation of tables, data and supplemental materials for the manuscript. Other contributors were Dr Radu Tanasescu (joint-lead author) who performed secondary literature search and quality checks on all data acquired and wrote the manuscript, Dr Christopher Tench also performed quality checks and statistical analysis on all data and co-drafted the manuscript. Dr Laura Condon performed some of the literature search and analysis. Professor Dorothee Auer was responsible for the concept and design of the study. All authors reviewed and commented on the final manuscript. CBMA of pain-related deactivations and pain anticipation and intensity was my work alone.

understand how this perception of pain is arising. The advent of techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI) has allowed investigators to non-invasively study brain activity during tasks and at rest.

Brain imaging studies of pain (as reviewed in section 3) have previously provided evidence of both differentiated and non-differentiated neural mechanisms during pain perception in healthy subjects (Davis et al., 1995, Becerra et al., 1999, Tracey et al., 2000) and chronic pain (Albuquerque et al., 2006, Baliki et al., 2010, Cifre et al., 2012). These differences however are not always consistent between studies and as such, methods have been created that allow investigators to collate results from previously published imaging studies to find the significant commonalities between them. These methods, known as coordinate based meta-analyses (CBMA) can use the published coordinates from a study or the original data from the study (with permission from the study authors). The most commonly used of these methods is activation-likelihood estimation (ALE) which uses reported coordinates or foci and then models their spatial uncertainty using a Gaussian function of full width half max (FWHM) (Tench et al., 2013). Results are driven by foci from multiple studies that are clustered in the same region. Other methods such as multi-kernel density analysis (MKDA) and signed differential mapping (SDM) are also well known (Radua and Mataix-Cols, 2009, Wager et al., 2003). Each of these perform similar analyses to ALE with MKDA using a spherical model of uncertainty rather than a Gaussian FWHM and SDM using statistical parametric maps rather than reported coordinates. Each of these three methods perform voxel-wise analyses but it was apparent that the available softwares for the implementation of ALE (GingerALE; www.brainmap.org/ale/) and SDM (www.sdmproject.com/software/) did not currently adequately

control for the risk of false-positives – that is, the risk of finding a significant result, that is false (Eickhoff et al, 2017). Subsequently, a newer software (LocalALE; www.nottingham.ac.uk/research/groups/clinicalneurology/neuroi.aspx) that uses an improved FWHM algorithm and an improved method of multiple-test correction known as false cluster discovery rate (FCDR) presented as a robust method with which to conduct a subsequent CBMA (Tench et al., 2013, Tench et al., 2014)[2].

Previous meta-analyses have been conducted investigating pain neuroimaging of which the first two published examples did not use coordinate based meta-analysis statistical methods and as such they collated how many times each region was reported finding consistent reporting of the bilateral somatosensory areas, insula cortices, anterior cingulate cortex (ACC), and the thalami in healthy subjects during painful stimulation (Apkarian et al., 2005, Peyron et al., 2000). Although these studies were mostly qualitative, the findings were already suggestive that subjects with chronic pain displayed differences in brain activity however specific findings across meta-analyses were themselves discrepant with increased activity initially reported in the thalami, insula and second somatosensory areas (Peyron et al., 2000) and subsequently regions implicated in cognitive and emotional processing not seen in healthy nociception (Apkarian et al., 2005). Subsequent meta-analyses utilised the new ALE technique to investigate neural activation related to: painful stimulation of the upper limb (Farrell et al., 2005),

[2] I am co-author on one of these two manuscripts: Tench, C. R., et al., *Coordinate based meta-analysis of functional neuroimaging data using activation likelihood estimation; full width half max and group comparisons.* PloS one, 2014. 9, e106735. They both came about from our initial desire as a group to perform CBMA but we were finding that there were too many false-positives arising from the available software. I was involved in the testing of the improved algorithms and giving feedback for the second manuscript. I reviewed and approved of the final manuscript.

comparisons between healthy and neuropathic subjects (Friebel et al., 2011), the experience of and empathy for pain (Lamm et al., 2011), comparisons of normalgesia hyperalgesia and allodynia (Lanz et al., 2011), placebo (Amanzio et al., 2013), hot and cold noxious stimuli (Duerden and Albanese, 2013) and amygdala sub-region activation during painful stimulation (Simons et al., 2014). Other meta-analyses of pain also investigated pain anticipation (Palermo et al., 2015), and the shared mechanisms of pain with other networks reporting that overlap in the bilateral anterior insula and anterior cingulate representative of the salience network which is a resting-state network related to attention orientation (Seeley et al., 2007). These previous studies commonly introduced heterogeneity into their data by including mixed stimulus types (cutaneous, subcutaneous and visceral), imaging modalities (BOLD MRI, ASL MRI and PET) and predominantly used a software (GingerALE versions 1-2.3.1) that have been shown to have an increased risk of false positives due to an incorrectly implemented FDR algorithm whilst another software (SDM) has also been shown to also have an increased risk of false positives (Eickhoff et al., 2017, Tanasescu et al., 2015, Tench et al., 2016). With this in mind, new studies should seek to improve on these points.

Although there have been several previous pain meta-analyses, with the exception of Friebel et al (2011), they have all investigated aspects of pain processing or pain states. In this study, we investigated the hypothesis that chronic pain patients and healthy volunteers exhibit differentiated neural activity related to pain, specifically, their response to evoked pain and the anticipation of it. To investigate this in a manner improving on those studies before, the improved LocalALE algorithm was used to collate studies of cutaneous evoked pain as imaged via BOLD fMRI. By following this reasoning, we strove to extract the most homogeneous possible groups of

data which will allow for the most sensitive comparisons. LocalALE utilises a newly developed ALE algorithm that reduces the risk of false positives (Type 1 errors) by employing a false cluster discovery rate (FCDR) multiple-test correction which works in a similar manner to false discovery rate multiple-test correction but for clusters (Tench et al., 2013). The false discovery rate works by ranking results by their respective p-value and subsequently rejecting a set proportion of the results (dependent on the accepted false discovery rate). Ordinarily, in coordinate-based meta-analysis this test is performed at the level of reported foci (or coordinate), this is problematic considering that neighbouring voxels are not independent of one another and that it is clusters of these voxels that should be controlled (Tench et al., 2013). Subsequently, to solve the problem of independence, LocalALE performs this correction at the cluster level.

Cutaneous pain studies will be used as they number the majority of experimental pain studies and they limit the presence of secondary aspects of the pain experience that could be found in incision studies (inflammation) or visceral pain studies for example (which tend to include a greater affective aspect). Additionally, studies investigating the neural correlates of pain intensity were assessed and models of chronic pain in healthy subjects such as experimental hyperalgesia and induced low mood will be compared with evoked pain in healthy subjects to investigate their applicability in modelling the disease-state.

6.2 Methods

6.2.1 Literature search and inclusion criteria

The literature search was carried out according to PRISMA guidelines for the reporting of meta-analyses and systematic reviews (Moher et al., 2009). In all

cases these resources were last accessed: 15.2.2015. BOLD fMRI studies of experimental pain evoked by cutaneous stimuli were collated by searching the following online databases: PubMed, Web of Science and NeuroSynth. NeuroSynth (Neurosynth.org) is an online meta-analytic toolbox and fMRI data repository that allows for automated synthesis of fMRI data via search terms. PubMed and Web of Science were searched using the following strings: (“MRI” or “magnetic resonance imaging”) AND (“functional” or “brain activation” or “neural activity” or “BOLD”) AND (“pain” or “noxious” or “nociception” or “hyperalgesia” or “allodynia” or “low mood” or “emotion”), (“MRI” or “magnetic resonance imaging”) AND (“functional” or “brain activation” or “neural activity” or “BOLD”) AND (“pain” or “noxious” or “nociception” or “hyperalgesia” or “allodynia”) AND (“low mood” or “emotion”) AND (“MRI” or “magnetic resonance imaging”) AND (“functional” or “brain activation” or “neural activity” or “BOLD”) AND (“pain” or “noxious” or “nociception”) AND (“patients” or “neuropathic” or “chronic pain” or “hyperalgesia” or “allodynia”). Additional search strings of (“MRI” or “magnetic resonance imaging”) AND (“functional” or “brain activation” or “neural activity” or “BOLD”) AND (“pain”) AND (“anticipation”), ““pain” and “intensity processing” or “intensity encoding” and “imaging”” were used to find any additional anticipatory or intensity related studies that weren’t found using the initial search strings. NeuroSynth was searched using the terms, “pain” and “chronic pain”. Additional to this primary search, reference lists of the collated articles were also searched for additional articles. Initially, articles were searched via their abstract for those that had studied noxious stimulation via functional MRI. Those that were searched in their entirety were only included if they met criteria 1 and either or both of 2 and 3:

1. They reported their results in either the Montreal Neurological Institute (MNI) (Evans et al., 1993) or the Talairach & Tournoux (Talairach, 1988) standard imaging reference spaces.

2. They reported the main effect of painful cutaneous stimuli. This could be contrasted either via a one sample t-test or by contrast with either innocuous stimuli or rest. Studies that included additional tasks could be included but only if the main effect data as specified previously was reported.

3. They reported the main effect of pain anticipation. This could be any type of painful stimulation (not limited to cutaneous stimulation) contrasted either via a one sample t-test or by contrast with baseline or rest. Studies that included additional tasks could be included but only if the main effect data as specified previously was reported.

In addition to retrieving the main effect results, contrast data will also be extracted where possible e.g. for hyperalgesia vs. normalgesia and patients vs. healthy volunteers.

6.2.2 Extraction and preparation of the data for statistical analysis

Positive and negative activation coordinates were extracted from the included articles. Positive coordinates for all but the anticipation and intensity data were checked individually by three separate people (W. Cottam, R. Tanasescu and C. Tench) as this data has been written up for publication (Tanasescu et al., 2016). W. Cottam was responsible for data extraction in all cases (including for the data used in the published manuscript). Demographic data was also extracted alongside the coordinates including: author lists, year of publication, cohort type (patient or healthy volunteer), sample size, mean age, stimulus type, anatomical site and laterality of stimulation and in which standard space the coordinates were reported in (see appendix 11.2.3).

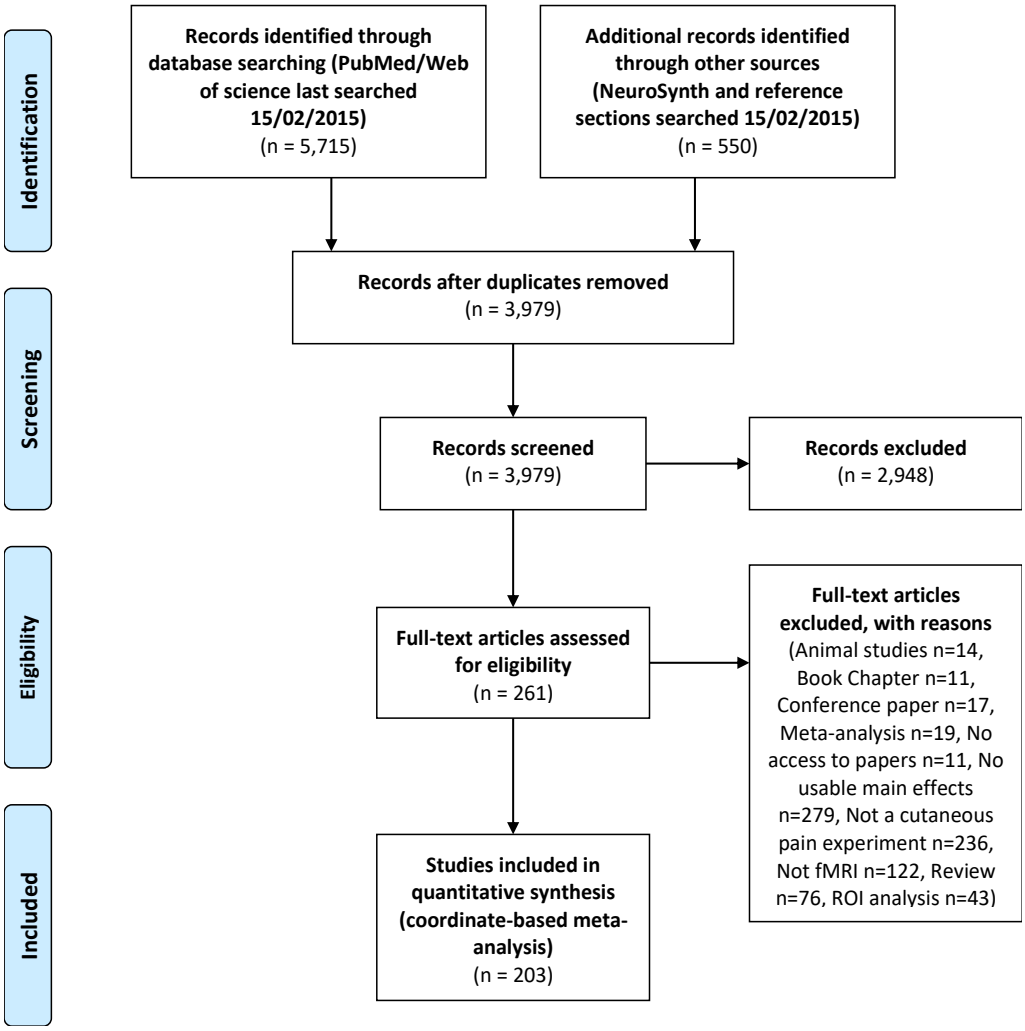


Figure 6.1. PRISMA flowchart of the meta-analytic search.

Data once extracted and grouped were examined for sets of coordinates that were reported in different articles but represented previously published data. When found, duplicated data was excluded to minimise the risk of false positives. A second measure of merging studies was also employed to reduce the risk of false positives. An example of this would be if a study reported two separate tables of coordinates that originated from one single experiment on the same group of subjects e.g. an early and late phase BOLD response analysis. Merging was only performed in cases where the reason for the differentiation between the tables was a point of no interest. This included,

early/late phase analyses, stimulus modality (in the large healthy volunteer vs. chronic pain subjects groups). Results from independent samples were not merged.

Errors in data extraction were also searched for by using the procedure outlined by Tench et al. (2013). By testing how alike the results of all the included studies were, any obviously different studies could be double-checked for wrong entry of data or that they had been reported in the wrong standard space. This process was not used as an exclusion criteria but as a quality control, to ensure that the data had been entered correctly and was of high quality.

6.2.3 Coordinate based meta-analysis

In this study, a recently developed ALE algorithm (LocalALE; www.nottingham.ac.uk/research/groups/clinicalneurology/neuroi.aspx) was used. This algorithm is based upon the previously used ALE algorithm that utilises a specified full width half max (FWHM) and Gaussian to model the activation likelihood per coordinate extracted (Turkeltaub et al., 2002). LocalALE improves on these previous methods by displaying a reduced level of false positive results, attained by adjusting the FWHM based upon the number of studies included in the analysis and not the sample size of the analysis and by employing an improved method of multiple-test correction (Tench et al., 2013, Tench et al., 2014). This FWHM approach is more principled in that the number of studies included will dictate the FWHM used (e.g. the more studies included, the smaller the FWHM). This improves the ability of the meta-analysis to localise regions of commonly reported activity, whereas previously, a generic FWHM of 10mm was proposed to be a best-fit approach (Eickhoff et al., 2009). LocalALE has also taken steps to improve contrast meta-analyses (an approach that compares the common activation

pattern between two groups) by reducing the total number of statistical tests (permutations) performed and using the improved FCDR multiple-test correction. In addition to this contrast meta-analysis, an omnibus test is also employed to test for differences (Tench et al., 2014). While the contrast meta-analysis (aka. A comparison between two collated CBMA datasets) is used to search for significant focal differences between the two groups (which must be very significant to survive multiple-test correction), the omnibus test is more sensitive to more diffuse differences between groups and it performs 1000 random permutations of foci in order to estimate a single p-value of difference which does not need correcting for multiple tests (as it is only a single test). This data can be utilised when contrast meta-analysis is ambiguous but does not reveal the spatial locations of any ensuing differences, only revealing that there are differences.

All single group statistical tests were carried out using a statistical threshold of P<0.05 FCDR while comparison tests were set to a threshold of P>0.1 FCDR. This higher threshold for comparisons is representative that this is a less sensitive test than in a single group. Omnibus tests were considered as significant when a p-value of 0.05 or lower was reported.

6.2.4 Factors that may affect the reported brain activity during painful stimulation

As contrast meta-analyses are the least sensitive tests, it was vital that statistical power was maximised when possible. To test for factors that could affect the neural response to pain in the extracted studies we performed sub-group comparisons to ensure that the large groups were as homogeneous as possible when compared.

Arguments have been made for the lateralisation of pain processing with the most recent coming from another coordinate based meta-analysis that found regardless of stimulus laterality there was significantly more right-hemispheric activity during pain (Duerden and Albanese, 2013). As previous reports have also flipped imaging data to try and minimise the differences caused by the laterality of stimulation (Lanz et al., 2011), we investigated the effect of carrying out this flipping or not. By separating healthy volunteer data into right and left lateralised stimuli, we performed two comparisons. The first being of the left and right stimulations and then comparing flipped left data (in theory to mirror right stimulation) with right stimulation.

Healthy volunteer data was next subgrouped by modality (mechanical, thermal and electrical stimulation), baseline comparisons (whether the main effect data was compared to an innocuous stimulus, rest or simply a main effect) and whether the stimulus had been cued (potentially causing anticipatory effects such as anxiety or catastrophizing). The appropriate subgroups were then contrasted to investigate any differences.

Chronic pain patient data was also subgrouped to test for experimental effects. As certain areas of the body may be affected by their disease state, these studies were grouped by the: anatomical site of stimulation (clinically affected or remote), type of stimulus (noxious or allodynic) and their type of disease (fibromyalgia, neuropathic, musculoskeletal).

6.3 Results

A total of 203 papers were included in the final analyses (see figure 6.1 for PRISMA flow-chart of the search results) combining to give over 3,519 coordinates from 242 fMRI studies of cutaneous pain in 2870 subjects. These included 168 studies of healthy volunteers, 39 of chronic pain patients, 11 of

hyperalgesia and 5 of induced low mood (see table 6.1 for more details). Contrast data was obtained from 24 fMRI studies of patients vs. healthy controls and hyperalgesia vs. normalgesia.

Chronic pain patient studies that were matched the inclusion criteria included those with musculoskeletal (osteoarthritis, n=2; chronic back pain, n=7), fibromyalgia (n=10) and neuropathic disorders (vulvar vestibulitis syndrome, n=1; headache, n=3; peripheral neuropathies, n=3; postherpetic neuralgia, n=2; syringomyelia, n=1; burning mouth disorder, n=1; trigeminal neuralgia, n=1, chronic regional pain syndrome, n=4).

A total of 24 fMRI papers of pain anticipation were included in the final analyses reporting over 500 coordinates from 28 experiments in 516 subjects. These included studies using: thermal (12), electrical (5), mechanical (1) and visceral (6) painful stimulations. Only 1 study reported usable anticipation data from patients and as such no CBMA of pain anticipation in chronic pain patients was performed.

A total of 9 fMRI papers assessing pain intensity in healthy controls were included in the final analyses resulting in over 60 coordinates from 10 experiments in 143 subjects.

Table 6.1.
Study groups and subgroups included within the meta-analysis (main interest groups in bold).

Group	Detail	Population	Papers	Studies Extracted (before merging)	Median sample size of included studies	Range of sample size	Coordinates Extracted	Subjects (no.)
A	All HC	HC	142	168	12	4-61	2603	2036
A1	Mechanical	HC	25	30	12	6-30	429	338
A2	Thermal	HC	97	112	12	4-61	1730	1418
A3	Electrical	HC	23	26	13.5	6-51	444	308
A4	Right Stimulus	HC	61	72	13	5-61	1070	873
A5	Left Stimulus	HC	70	77	13	6-57	1107	1029
A6	Pain vs rest	HC	76	93	12.5	6-57	1334	1120
A7	Pain vs innocuous	HC	65	74	12	5-61	1241	899
A8	Cued	HC	31	33	15	7-61	544	552
A9	Non-cued	HC	110	133	12	4-57	2051	1471
B	All CPP	CPP	30	39	12	5-83	521	474
B1	Neuropathic (not FM)	CPP	15	20	10.5	6-27	307	163
B2	MSK	CPP	8	10	14	5-28	138	109
B3	FM	CPP	8	10	16	9-83	90	202
B4	CS	CPP	15	18	11	5-28	314	183
B5	RS	CPP	17	22	16	8-83	207	329
B6	AL	CPP	10	11	11	6-27	184	154
B7	Noxious	CPP	22	28	14	5-83	396	364
C	Hyperalgesia	HC	9	11	12	11-16	188	116
D	Low Mood	HC	5	5	20	12-40	46	114
E	MAC	P vs HC	8	9	11	6-23	99	85
E1	MAC	Hyper – Stim	13	15	12	6-18	208	159
F	Decreased activity (baseline vs. pain)	HC	30	31	12	7-61	205	496
G	Anticipation increase	HC	24	28	17.5	8-48	402	501
G1	Anticipation decrease	HC	6	7	21	10-32	114	119
H	Pain intensity	HC	9	10	24	6-24	67	143

Abbreviations: HC = Healthy controls, CPP – Chronic pain patients, FM – Fibromyalgia, MSK – Musculoskeletal, CS – Clinically affected site stimulated, RS – Remote site stimulated, AL – Allodynic, MAC – Meta-analysis of contrasts.

6.3.1 Factors that may affect the reported brain activity during painful stimulation

Subgroups looking at the effect of stimulus lateralisation were compared (right vs. left stimulation and right vs. flipped left stimulation) using both the contrast meta-analysis and omnibus test. Comparison of left vs. right stimulation found a single cluster that was more significant within the right stimulation group (cingulate gyrus) (omnibus test p=0.026). The flipped comparison however, displayed 5 significant clusters (omnibus test p=0.000000) which suggests that lateralisation of brain activity should not be altered during analysis whilst lateralisation of the stimulus can be viewed as a point of no interest for the larger group comparisons.

Comparisons of the three stimulus modalities in the healthy volunteer group (thermal, mechanical and electrical), displayed mostly similar spatial patterns but there were subtle differences as displayed via the omnibus test (mechanical vs. electrical p=0.04; thermal vs. mechanical p=0.029). The omnibus test failed to find differences in those studies reporting main effects compared against either rest or innocuous stimuli (p=0.618) or when the stimulus was cued or not (0.147).

Subgroups of the chronic pain patient studies were compared to assess heterogeneity and comparisons of the site of stimulation (remote vs. clinically affected) found significant differences within the clinically affected studies (omnibus test p=0.027). These significant differences were found in the left lentiform nucleus (putamen) and middle frontal gyrus (BA9) as well as the right posterior insula (BA13). Comparisons of stimulus type and disease types however found no differences (omnibus test; noxious vs. allodynic p=0.503; musculoskeletal vs. neuropathic p=0.606; fibromyalgia vs. musculoskeletal p=0.591; fibromyalgia vs. neuropathic p=0.147).As obtaining the largest and

most homogeneous groups possible for the contrast meta-analysis was the primary objective, modalities within the healthy control group were combined into a single group as were all of the chronic pain studies. It was noted however that stimulation modality and site of stimulation within the chronic pain cohorts could be a potential source of heterogeneity.

6.3.2 Brain activity related to painful cutaneous stimulation in healthy volunteers and chronic pain patients

Meta-analysis of the reported coordinates of increased BOLD activity whilst studying painful cutaneous stimulation in healthy volunteers (HC) displayed widespread bilateral activity within all classic pain-related regions including the: insula, thalami, anterior cingulate, lentiform nuclei, prefrontal cortices and the parahippocampal gyrus. The bilateral insula were the most commonly reported regions with approximately 65% of studies with bilateral thalami, inferior parietal lobules, left cingulate gyrus and the right claustrum all also being reported in at least 30% of all studies (Figure 6.2 - blue, Table 6.2).

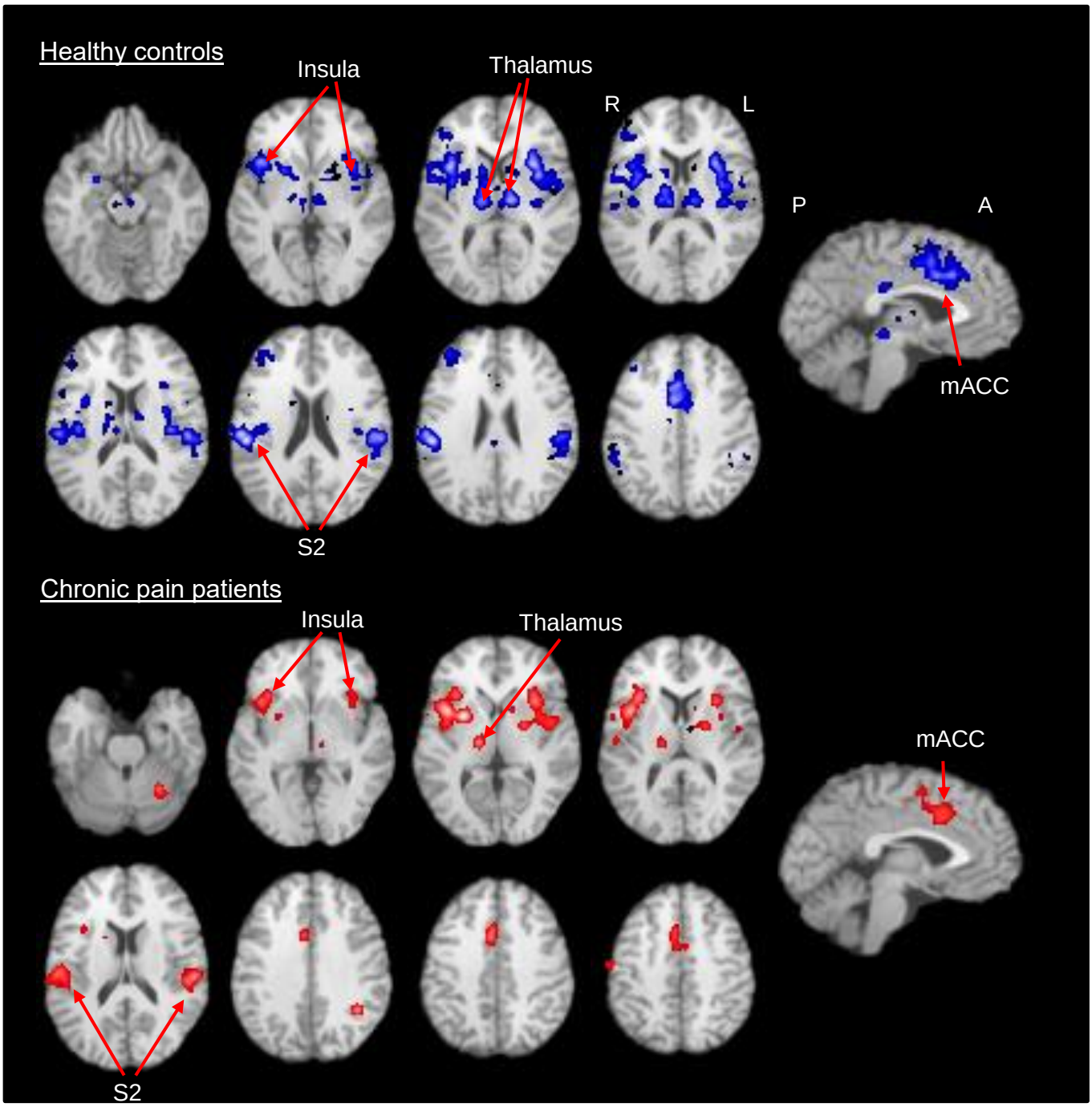


Figure 6.2. Coordinate based meta-analysis results of brain activity in healthy controls (in blue) and chronic pain patients (in red) during painful cutaneous stimulation. All results are significant at P<0.05 false cluster discovery rate (FCDR). Key: R – right, L – left, mACC – mid-anterior cingulate, S2 – secondary somatosensory area.

Table 6.2.
Significant clusters from experimental pain studies in healthy volunteers

Anatomical region (Brodmann Area)	Centroid Coordinates			P-value	Number of studies contributing
	X	Y	Z		
R Postcentral Gyrus (40)	51.6	-25.1	21.2	0	79
R Insula (13)	36.1	12.9	4.6	0	88
L Claustrum	-32.4	14.4	7.0	0	70
L Thalamus – Ventral Posterior Lateral Nucleus	-12.5	-16.3	7.3	0	54
R Cingulate Gyrus (24)	2.1	4.3	40.0	0	59
L Postcentral Gyrus (40)	-55.3	-24.2	19.3	0	59
L Insula (13)	-36.9	1.4	7.6	0	55
L Cingulate Gyrus (32)	-0.1	17.8	35.2	0	48
L Insula (13)	-37.8	-17.6	13.1	0	38
R Thalamus – Medial Dorsal Nucleus	9.6	-15.8	8.6	0	72
R Claustrum	33.3	0.0	11.3	0	39
R Medial Frontal Gyrus (6)	3.9	15.8	47.1	0	27
R Lentiform Nucleus	19.8	7.4	3.1	0	34
R Insula (13)	36.4	-18.0	15.6	0	30
L Inferior Parietal Lobule (40)	-56.1	-34.7	23.0	0	32
R Middle Frontal Gyrus (10)	33.8	43.8	23.4	0.000003	21
R Caudate	10.2	6.7	9.8	0.000004	15
R Parahippocampal Gyrus/Amygdala	20.6	-1.1	-12.1	0.000004	12
R Precentral Gyrus (44)	49.4	0.4	9.1	0.000008	21
R Thalamus	8.8	-1.6	5.3	0.000009	16
L Cingulate Gyrus (23)	-1.2	-28.3	27.2	0.000011	15
L Cingulate Gyrus (24)	-7.5	1.4	35.6	0.000012	23
L Precentral Gyrus (6)	-51.3	-3.5	8.2	0.000034	19
R Midbrain	0.9	-29.1	-5.2	0.000037	12
R Precentral Gyrus (44)	50.2	11.0	6.3	0.000046	15
L Inferior Parietal Lobule (40)	-42.0	-40.4	39.2	0.000048	9
R Inferior Frontal Gyrus (46)	38.8	34.9	9.6	0.000055	15
R Middle Frontal Gyrus (9)	37.1	30.8	33.1	0.000063	8
L Insula (13)	-47.4	4.1	4.2	0.000077	18
R Inferior Parietal Lobule (40)	51.1	-42.8	31.7	0.000081	24
L Lentiform Nucleus	-15.8	3.1	4.0	0.00011	15
L Medial Frontal Gyrus (6)	-5.0	5.4	48.4	0.000114	19
R Inferior Parietal Lobule (40)	47.4	-37.1	40.3	0.000127	15
R Middle Frontal Gyrus (9)	42.9	16.2	31.9	0.000139	9
R Midbrain	7.5	-21.3	-10.2	0.000151	13
L Postcentral Gyrus (3)	-39.1	-27.2	61.9	0.000377	7
L Thalamus	-12.4	-7.2	15.8	0.00052	12
L Precentral Gyrus (6)	-47.8	-0.9	31.2	0.000606	6
R Middle Frontal Gyrus (9)	33.3	36.7	26.4	0.000668	13
R Inferior Parietal Lobule (40)	40.5	-52.3	46.4	0.000699	7
L Midbrain	-7.0	-17.6	-9.5	0.000937	14
R Culmen	22.2	-49.0	-22.1	0.00096	9
L Supramarginal Gyrus (40)	-55.0	-39.9	32.9	0.001411	8
L Insula (13)	-38.6	-7.1	0.9	0.001472	8
R Middle Frontal Gyrus (6)	40.5	4.2	45.0	0.001489	6
R Middle Frontal Gyrus (10)	40.6	46.1	12.2	0.001579	10
R Postcentral Gyrus (43)	60.7	-17.1	20.0	0.001591	7
R Middle Frontal Gyrus (46)	42.2	34.9	15.8	0.001591	12

All clusters significant at FCDR $p<0.05$. Centroid coordinates reported in Talairach space. R – right, L – left. Adapted from (Tanasescu et al., 2016).

Meta-analysis of reported coordinates studying painful cutaneous stimulation in chronic pain patients (CPP) also found activity within many of the classic pain-related brain regions such as the bilateral insula, cingulate gyrus (BA32), prefrontal areas and bilateral thalami. Activity was also reported within the right caudate, precentral and bilateral postcentral gyri as well as the left culmen and claustrum (Figure 6.2 - red, Table 6.3). Of the 6 patient studies reporting deactivations, no significant commonalties were found.

Table 6.3.
Significant clusters from experimental pain studies in chronic pain cohorts

Anatomical region (Brodmann Area)	Centroid Coordinates			P-value	Number of studies contributing
	X	Y	Z		
R Postcentral Gyrus (40)	52.0	-26.9	19.7	0	23
R Precentral Gyrus (44)	41.4	5.8	6.9	0	23
L Postcentral Gyrus (40)	-53.4	-25.0	20.6	0	21
R Lentiform Nucleus	23.6	4.2	3.1	0	11
R Thalamus – Mammillary Body	12.2	-18.4	5.1	0	9
R Insula (13)	33.3	20.2	2.3	0.000002	15
L Cingulate Gyrus (32)	0.3	7.7	38.2	0.000012	18
L Supramarginal Gyrus (40)	-41.8	-49.4	35.1	0.000014	8
L Claustrum	-35.0	2.5	5.4	0.000014	7
L Insula (13)	-33.0	17.7	4.4	0.000057	16
L Precentral Gyrus (6)	-46.7	-3.2	4.8	0.000067	14
L Lentiform Nucleus	-23.3	-3.9	7.1	0.00007	9
R Medial Frontal Gyrus (6)	2.0	-3.4	53.5	0.000084	11
L Culmen	-27.8	-56.5	-21.7	0.002581	5
L Thalamus	-10.4	-8.3	9.8	0.002733	8

All clusters significant at FCDR $p<0.05$. Centroid coordinates reported in Talairach space. R – right, L – left. Adapted from (Tanasescu et al., 2016).

Meta-analysis of the reported coordinates of decreased BOLD activity whilst studying painful cutaneous stimulation in healthy volunteers (HC) displayed widespread deactivation of areas commonly associated with the default mode network such as cuneus and posterior cingulate cortices as well as the subgenual anterior cingulate/ventromedial prefrontal cortices (Figure 6.3, Table 6.4). Further clusters were observed within the bilateral postcentral gyri.

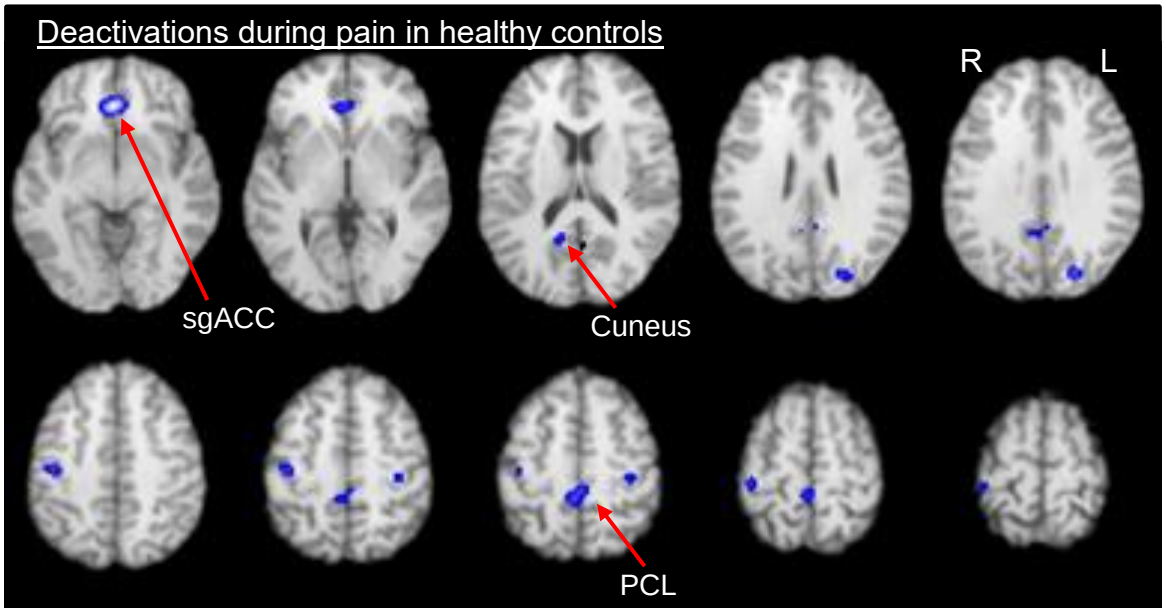


Figure 6.3. Coordinate based meta-analysis results of decreased brain activity during acute experimental pain in healthy controls. Results are significant at P<0.05 false cluster discovery rate (FCDR). Key: R – right, L – left, PCL – paracentral lobule.

Table 6.4.
Significant deactivation clusters from experimental pain studies in healthy volunteers

Anatomical region (Brodmann Area)	Centroid Coordinates			P-value	Number of studies contributing
	X	Y	Z		
L Anterior Cingulate (13)	-0.9	32.3	-4.5	0	11
L Paracentral Lobule (5)	-0.3	-38.3	53.8	0	8
R Postcentral Gyrus (3)	40.1	-19.3	46.3	0.000039	6
L Cuneus (19)	-24.5	-79.2	26.9	0.000161	7
R Posterior Cingulate (23)	9.3	-55.5	17.3	0.000471	4
R Postcentral Gyrus (3)	36.5	-30.6	59.6	0.000522	3
L Precentral Gyrus (4)	-35.7	-26.5	52.5	0.003032	7
L Cingulate Gyrus (31)	-0.8	-49.4	28.3	0.003176	4

All clusters significant at FCDR p<0.05. Centroid coordinates reported in Talairach space. R – right, L – left.

6.3.3 Comparison of the neural representation of pain in healthy volunteers and chronic pain patients

Single group coordinate based meta-analysis displayed mostly overlapping spatial patterns of cutaneous pain in either cohort (Figure 6.2). No significant spatial differences were seen using contrast meta-analysis but the result from the omnibus test suggests that there may be subtle differences between the

two groups that this spatial meta-analysis was not sensitive enough to find (p=0.03). Although visually the ALE maps presented in figure 6.2 look like there might be differences. This is due to those images representing the most significant clusters within either group. When compared, it is not these single-group maps that are compared but all of the reported foci underneath. Thus, even if there appears to be differences when reported separately, the uncorrected data might show overlap that's common to both groups but only shows a significant cluster in one group due to factors such as FWHM sizes (which vary according to how many studies are included per group).

As the deactivations from the 6 chronic pain studies showed no single group commonalities no comparison of deactivations was performed. By also extracting existing contrasts of healthy controls and patients from within studies a second test of this hypothesis was available. Nine such experiments were included within the analysis but no significant results were found.

Due to the possible heterogeneity being introduced within the data having combined data from different stimulus modalities, a comparison of only mechanical stimuli in both groups was performed. No differences between groups were found even via the sensitive omnibus test (p=0.842). Heterogeneity may have also been introduced in regards to the site of stimulus location within the chronic pain cohorts. With this in mind, both subgroups of clinically affected site stimulation (CS) and remote site stimulation (RS) were additionally compared against the HC group. Comparison of CS vs. HC found increased likelihood of activity within the left putamen and the right insula (Figure 6.4, Table 6.5) whilst the second comparison of RS vs. HC found no significant spatial differences but the omnibus test suggests that there may be more diffuse differences present (p=0.004).

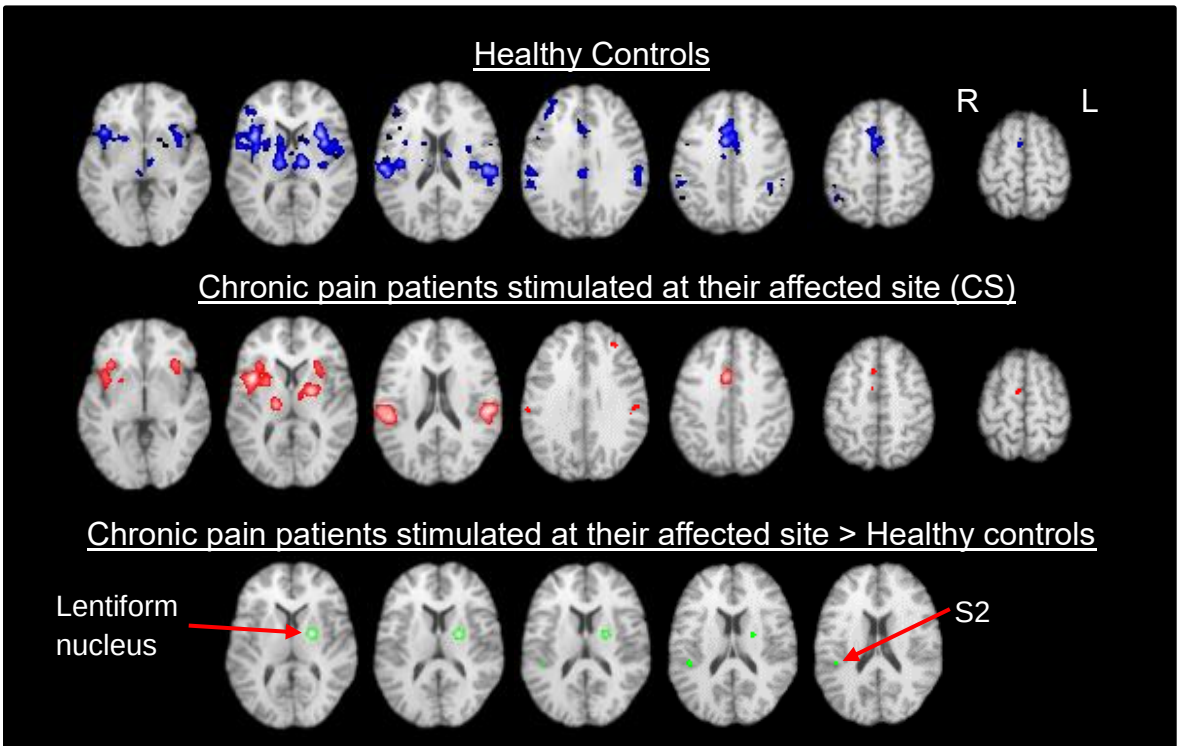


Figure 6.4. Coordinate based meta-analysis results of brain activity in healthy controls (in blue) and chronic pain patients who were stimulated at their clinically affected site (CS - in red) during painful cutaneous stimulation. Areas that were significantly more likely in the chronic pain cohort are displayed in green. Single-group results (for healthy volunteers and chronic pain patients stimulated at their affected site) are significant at P<0.05 false cluster discovery rate (FCDR). Contrast meta-analysis results of chronic pain patients stimulated at their affected site > healthy controls are significant at P<0.1 FCDR. Key: R – right, L – left.

Table 6.5.
Significant clusters from clinically affected site stimulated (CS) and remotely stimulated site (RS) groups and their comparisons.

Anatomical region (Brodmann Area)	Centroid Coordinates			P-value	Number of studies contributing
	X	Y	Z		
CS					
R Insula (13)	40.4	5.1	7.9	0	14
L Postcentral Gyrus (40)	-54.4	-26.1	20.6	0	13
L Lentiform Nucleus	-22.6	-7.0	8.7	0	12
R Lentiform Nucleus	21.6	4.8	4.8	0	7
R Thalamus	12.6	-18.2	5.8	0.000002	6
R Insula (13)	50.5	-28.5	20.8	0.000002	14
L Cingulate Gyrus (32)	-0.2	9.2	38.4	0.000006	15
R Insula (13)	32.3	21.6	2.4	0.000012	8
L Insula	-35.1	16.5	2.8	0.000022	11
R Medial Frontal Gyrus (6)	2.4	-5.4	54.6	0.000741	7
L Middle Frontal Gyrus (10)	-35.2	38.8	24.4	0.002319	7
RS					
L Insula (13)	-45.3	-2.9	5.7	0.000006	10
R Insula (13)	37.6	14.1	3.7	0.000084	12
L Postcentral Gyrus (40)	-52.1	-25.2	22.2	0.000113	8
R Inferior Parietal Lobule (40)	56.1	-31.1	22.7	0.000132	5
R Precentral Gyrus (13)	49.2	-14.1	13.4	0.000589	6
L Insula (13)	-34.9	17.2	6.2	0.002576	7
CS > RS					
L Lentiform Nucleus	-22.4	-5.3	9.3	0.0016	10
R Insula (13)	45.0	-32.6	19.5	0.0019	10
L Middle Frontal Gyrus (9)	-32.7	40.9	26.8	0.0021	7
R Insula (13)	40.1	4.5	10.3	0.0041	11
RS > CS					
L Precentral Gyrus (43)	-49.7	-7.1	9.9	0.001	10

All clusters significant at FCDR p<0.05. Centroid coordinates reported in Talairach space. R – right, L – left, CS – Clinically affected site stimulated, RS – Remote site stimulated. Adapted from (Tanasescu et al., 2016).

6.3.4 Does hyperalgesia present as a model of chronic pain in healthy volunteers?

Results from the coordinate based meta-analysis of hyperalgesia studies (all one-sample t-tests of the main effect of noxious stimulation during evoked hyperalgesia) found high activation likelihoods in regions including the bilateral insula, the right cingulate gyrus, the left thalamus, right superior frontal gyrus and the left lentiform nucleus (Figure 6.5, blue, Table 6.6). The results of the meta-analysis of contrasts (hyperalgesia vs. normalgesia) displays almost identical results with significant activation likelihood within the bilateral insula, cingulate gyri, right superior frontal gyrus, left lentiform

nucleus and additionally in the right inferior parietal lobule (Figure 6.5, red, Table 6.7).

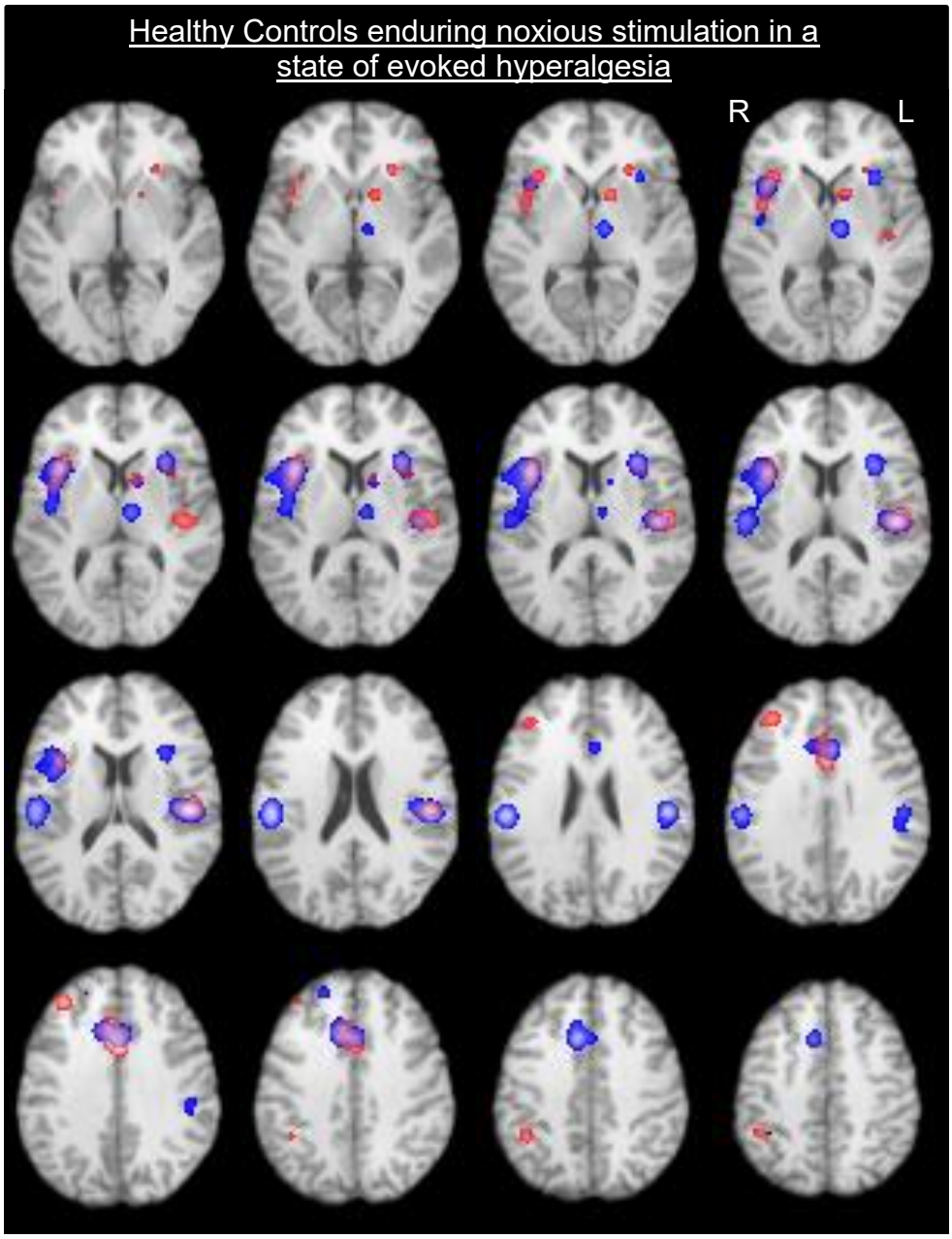


Figure 6.5. Coordinate based meta-analysis results of brain activity in healthy controls in a state of experimental hyperalgesia (in blue) and results of a meta-analysis of contrasts collating reported comparisons of hyperalgesia vs. normalgesia (in red). All results are significant at P<0.05 false cluster discovery rate (FCDR). Key: R – right, L – left.

Table 6.6.
Significant clusters from hyperalgesia group.

Anatomical region (Brodmann Area)	Centroid Coordinates			P-value	Number of studies contributing
	X	Y	Z		
L Insula (13)	-48.0	-24.2	21.4	0	7
R Insula (13)	48.0	-23.9	21.0	0	7
R Insula (13)	39.1	10.1	11.7	0.000001	9
R Cingulate Gyrus (32)	1.5	17.6	35.1	0.000013	8
L Insula (13)	-36.3	16.8	10.7	0.000021	8
L Thalamus	-10.7	-15.0	6.1	0.000241	4
R Superior Frontal Gyrus (8)	17.9	45.7	35.7	0.00209	4
L Lentiform Nucleus	-14.7	4.7	9.9	0.003973	4

All clusters significant at FCDR p<0.05. Centroid coordinates reported in Talairach space. R – right, L – left. Adapted from (Tanasescu et al., 2016).

Performing contrast meta-analysis between the hyperalgesic studies and those of HC no significant differences spatially or via the omnibus test (p=0.711).

Table 6.7.
Significant clusters from the meta-analysis of contrasts (MAC) hyperalgesia vs. normalgesia.

Anatomical region (Brodmann Area)	Centroid Coordinates			P-value	Number of studies contributing
	X	Y	Z		
R Insula (13)	38.7	9.8	7.8	0.000009	6
L Insula (40)	-48.5	-20.1	14.0	0.000396	7
R Middle Frontal Gyrus (9)	31.8	37.1	27.7	0.000526	4
L Lentiform Nucleus	-14.4	5.8	6.5	0.000747	4
L Cingulate Gyrus (32)	0.5	17.9	32.0	0.001317	5
R Inferior Parietal Lobule (40)	41.3	-45.2	40.9	0.002026	4
L Insula (13)	-38.3	12.1	10.4	0.002065	6

All clusters significant at FCDR p<0.05. Centroid coordinates reported in Talairach space. R – right, L – left. Adapted from (Tanasescu et al., 2016).

6.3.5 Does induced low mood in healthy volunteers model chronic pain?

Coordinate based meta-analysis of experiments using induced low mood to model chronic pain in healthy subjects found no consistent patterns of activation.

6.3.6 Brain activity associated with pain anticipation in healthy subjects

Meta-analysis of the reported coordinates of increased BOLD activity whilst studying the anticipation of painful stimuli found significant clusters within the mid-anterior cingulate cortex, right anterior insula and the left mid-insula. Additional clusters were also reported in the right supplementary motor area and middle frontal gyrus (Figure 6.6, Table 6.8).

Table 6.8.
Significant clusters from experimental pain studies of pain anticipation in healthy controls.

Anatomical region (Brodmann Area)	Centroid Coordinates			P-value	Number of studies contributing
	X	Y	Z		
R. Insula (BA 13)	39.3	15.2	-0.8	0	6
Anterior CC (BA 32)	-0.4	9.9	38.7	0	6
L. Insula	-37.8	3.1	-1.3	0.001291	4
R. S1 / Postcentral Gyrus (BA 2)	46.0	-28.0	40.5	0.003373	2
R. Insula	39.8	-5.8	11.1	0.004343	4
R. Thalamus	2.0	-17.7	5.9	0.00559	3

All clusters significant at FCDR p<0.05. Centroid coordinates reported in Talairach space. R – right, L – left.

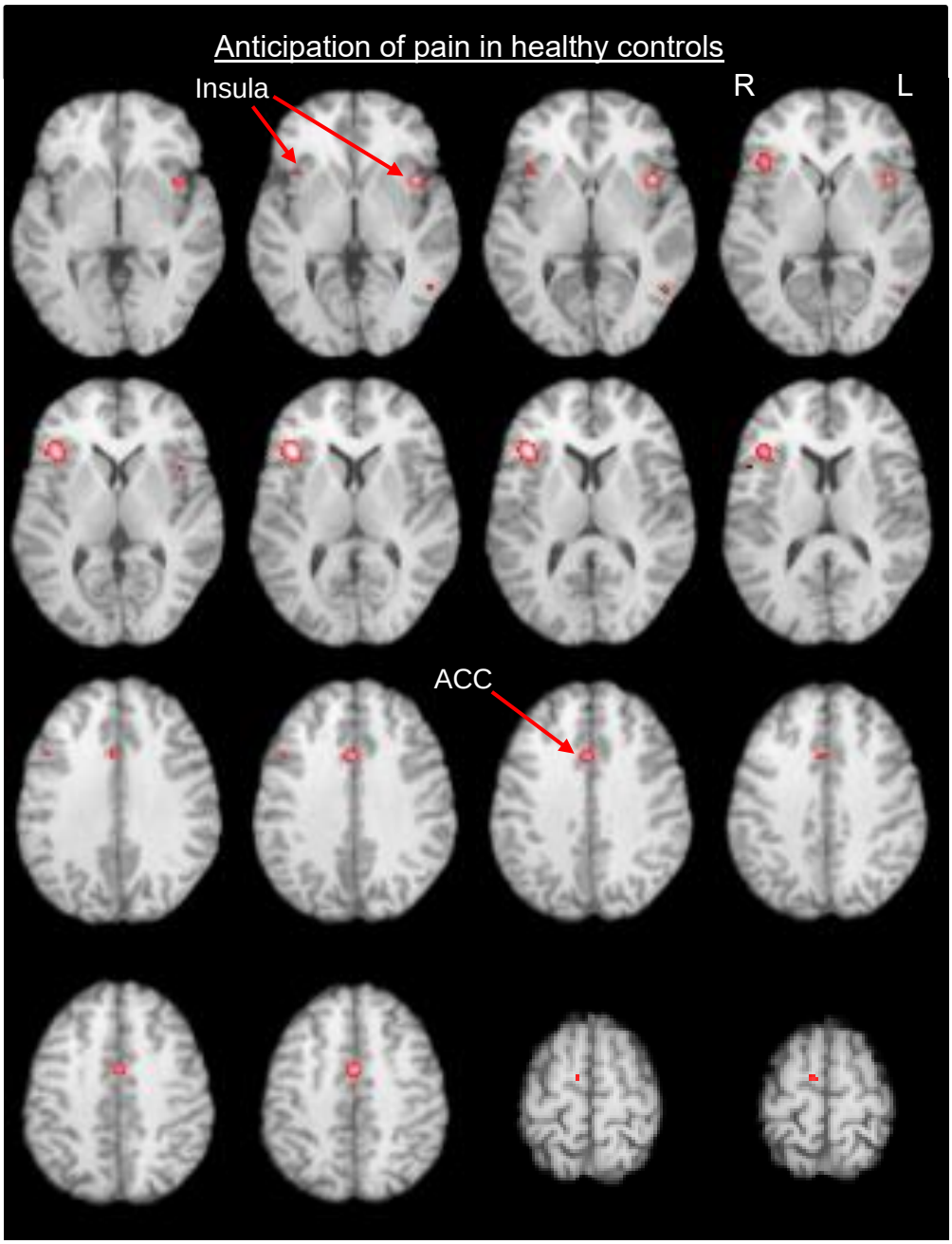


Figure 6.6. Coordinate based meta-analysis results of brain activity in healthy controls during the anticipation of acute experimental pain. Results are significant at P<0.05 false cluster discovery rate (FCDR). Key: R – right, L – left, ACC – anterior cingulate cortex.

6.3.7 Brain activity associated with pain intensity encoding in healthy subjects

Meta-analysis of reported coordinates where BOLD activity was found to be correlated with perceived pain intensity found significant clusters within the bilateral anterior insula, anterior cingulate cortex and the right sensory network (primary somatosensory cortex (S1) / postcentral gyrus, right thalamus), (Figure 6.7, Table 6.9).

Table 6.9.
Significant clusters from experimental pain studies of pain intensity in healthy controls.

Anatomical region (Brodmann Area)	Centroid Coordinates			P-value	Number of studies contributing
	X	Y	Z		
L Anterior Cingulate (24)	-0.9	32.3	-4.5	0	11
L Paracentral Lobule (5)	-0.3	-38.3	53.8	0	8
R Postcentral Gyrus (3)	40.1	-19.3	46.3	0.000039	6
L Cuneus (19)	-24.5	-79.2	26.9	0.000161	7
R Posterior Cingulate (23)	9.3	-55.5	17.3	0.000471	4
R Postcentral Gyrus (3)	36.5	-30.6	59.6	0.000522	3
L Precentral Gyrus (4)	-35.7	-26.5	52.5	0.003032	7
L Cingulate Gyrus (31)	-0.8	-49.4	28.3	0.003176	4

All clusters significant at FCDR p<0.05. Centroid coordinates reported in Talairach space. R – right, L – left.

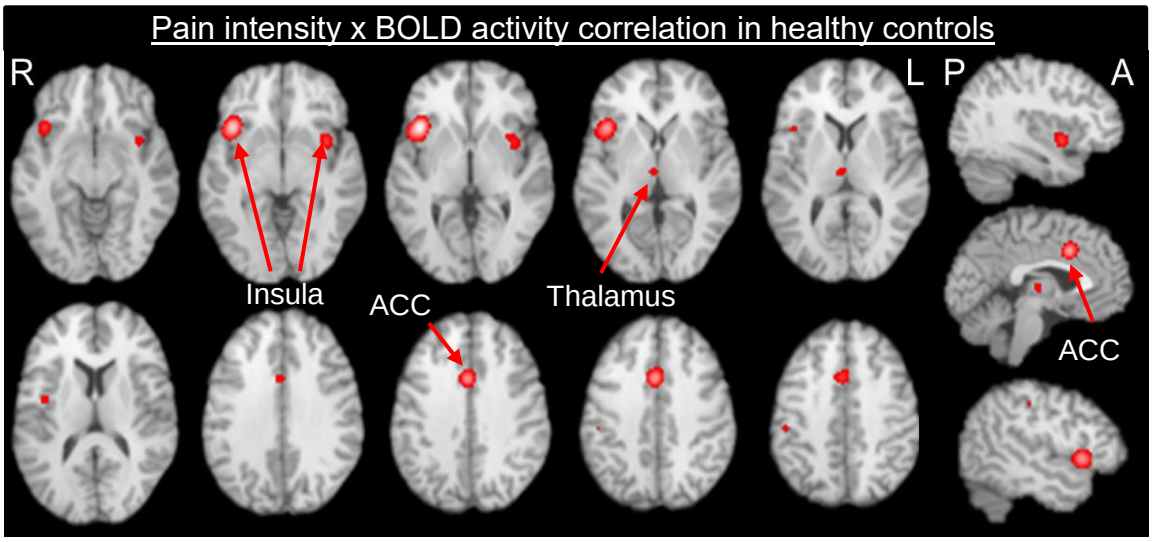


Figure 6.7. Coordinate based meta-analysis of nine functional imaging studies correlating pain intensity with brain activation in healthy controls. Results are significant at P<0.05 false cluster discovery rate (FCDR). Key: R – right, L – left, P – posterior, A – anterior.

6.4 Discussion

This study has used an improved ALE algorithm to investigate the differentiation in neural pain processing between healthy subjects and chronic pain patients based upon previously published data. Individual group analyses found that both healthy and chronic pain subjects display common patterns of brain activity during the perception of noxious stimuli including increased activity in those regions most commonly associated with pain (thalami, insula, anterior cingulate inferior parietal lobule etc) and decreased activity in those regions commonly linked with the default mode network (posterior cingulate and medial prefrontal cortex/subgenual cingulate) (Wager et al., 2013, Raichle et al., 2001). Spatial comparison of these two groups was inconclusive whilst there were signs of subtle differences according to the omnibus test as implemented in LocalALE (Tench et al., 2014). Upon scrutiny of factors that may have introduced heterogeneity into the chronic pain group, differences caused by the anatomical site of stimulation in the patients was investigated. Patients that were stimulated at their clinically affected site (e.g. pressure

applied to an osteoarthritic knee) displayed increased likelihood of neural activity in the left lentiform nucleus and the right insula when compared to healthy volunteers. Conversely, patients whom had been stimulated at a remote site (e.g. pressure applied to a thumbnail in a patient with fibromyalgia) displayed no significant spatial differences when compared with healthy volunteers. This suggests that manipulation of the clinically affected area and subsequent provocation of the clinical pain state is a particularly promising approach in the effort to understand the neural mechanisms underlying chronic pain. Particularly more so than stimulating a remote site.

Having found no spatial difference between studies of cutaneous pain in healthy volunteers and chronic pain patients is not wholly unexpected as previous studies of acute experimental pain in chronic pain patients and healthy subjects have also displayed little to no differences in neural activity when compared (Kulkarni et al., 2007, Parks et al., 2011). Interestingly, both of these studies also looked at ongoing clinical pain in comparison to acute pain in healthy volunteers and found distinct differences, predominantly with the chronic pain patients displaying increased emotion-related processing in regions such as the amygdala, subgenual cingulate and the nucleus accumbens. These results do not definitively prove that there is no difference as the omnibus test suggests that there are diffuse differences. It could however be suggestive that this approach of studying chronic pain by evoking pain in patients might not be the most sensitive approach. Studies of spontaneous or ongoing pain in chronic pain cohorts has to date proved a promising area of research with articles commonly reporting differences between patients and healthy subjects at rest with no need for further stimulation (Liu et al., 2013, Baliki et al., 2008b, Howard et al., 2012).

Hyperalgesia is a commonly used experimental model of the sensitisation observed in chronic pain in which experimenters use capsaicin cream or other approaches to induce increased sensitivity to noxious stimuli (Maihofner and Handwerker, 2005). Results from the meta-analysis of contrasts (reported hyperalgesia vs. normalgesia contrasts) and studies of hyperalgesia both reported commensurate spatial patterns of brain activity including bilateral insula, cingulate, superior frontal gyri, thalamus and left lentiform gyrus. When compared to results in the healthy control group however, there are no significant differences at all.

Experimental hyperalgesia presents as a model of pain sensitisation such as that seen in chronic pain cohorts (potentially underlined by peripheral/central sensitisation). Those with osteoarthritis for instance, may display peripheral sensitisation at their affected joint due to factors such as inflammation. Modelling increased nociceptive drive however is not enough to model the perception of chronic pain. This is most likely related to the personal context in which the pain is perceived. Subjects across the hyperalgesia studies included within this analysis (whom are all healthy volunteers) had a median age of 26.5 years old (one study didn't report the average age). In in comparison to the chronic pain cohorts (median age of 45.5 years old) they potentially lack as many painful life experiences (such as breaking bones, big falls etc) as well as definitely lacking the aversive experience of living with persistent pain for any particular duration. Therefore, although experimental hyperalgesia does seemingly model a state of peripheral sensitisation it cannot reflect the personal multidimensional experience of chronic persistent pain. Factors such as anxiety (Ploghaus et al., 2001), depression (Giesecke et al., 2005), and catastrophizing (Wood et al., 2013) that are known to contribute to the chronic pain experience are absent.

Finding increased neural activity within those patients stimulated at their clinically affected site suggests that noxiously stimulating a patient anywhere whilst suffering with chronic pain is not necessarily the right approach. If the actual clinical pain state is being studied, it is at least logical to evoke pain by manipulating a subject's clinical state. Gwilym et al. (2009) for example, utilised punctate stimulation of the referred hip pain area to assess activity of the periaqueductal grey (PAG), a key region in the descending pain pathway (previously outlined in section 2.1.1.2). Activity within the putamen has previously been shown to be linked with collating sensory-motor responses to pain but also engaging with regions that participate in memory and affect (Starr et al., 2011). The insula however, specifically the posterior insula/S2 region which was found here is commonly associated with intensity processing in healthy subjects as well as being strongly linked to the somatosensory cortices and also not necessary for the evaluation of pain itself (Starr et al., 2009, Segerdahl et al., 2015b, Wiech et al., 2014a). These results could then be suggestive of an increased sensory sensitivity (akin to hyperalgesia) to the noxious stimuli. The putamen however, is also known to play a part in aversive learning (Gramsch et al., 2014) and thus potentially, this result could be reflective of the subjective nature of chronic pain which is being evoked by stimulating each subjects clinically affected anatomical site. It should be noted however, that previous studies have found that not only the clinically affected site can display brain changes relating to sensitisation. For instance, early work assessing cortical EEG responses to tactile stimulation of the index finger and back in chronic back pain patients and controls reported an increased cortical response at both sites of stimulation (Flor et al., 1997). Flor et al. (1997) additionally found that the cortical response to back stimulation in patients had shifted medially (compared to controls) and was potentially representative of pain-related cortical reorganisation.

Previous studies that have compared clinical pain to evoked pain however have noted stark differences in neural activity in the clinical state. Kulkarni et al. (2007) for example, reported that arthritic pain was related with increased activity in emotional processing areas such as the bilateral amygdala, subgenual ACC and the caudate where evoked pain was strongly linked with sensory activity in areas such as S1 and S2. Similar results were noted in another osteoarthritic cohort with clinical pain related to activity in the amygdala, basal ganglia and lateral prefrontal cortex as opposed to evoked painful activity in the somatosensory areas and insula (Parks et al., 2011). The differences observed in these studies are likely reflective of the increased emotional and cognitive burden associated with chronic pain, subjective aspects of the pain experience that acute painful stimuli are unable to evoke. Conversely, the reduced somatosensory activity related with the clinical pain is likely reflective of reduced sensory input and suggestive of an increased central component to the chronic pain compared with evoked pain.

Only a small percentage (~25%) of the included healthy volunteer studies reported reduced brain activity during painful stimulations. This was however enough data to display results that include regions known to be involved in the medial default mode network (DMN) such as the posterior and subgenual anterior cingulate (Raichle et al., 2001). Taken together, the DMN is thought of as a baseline neural network that is engaged when subjects are allowed to rest and think in the absence of a given task. It has also been shown to be anti-correlated with the onset of tasks and commonly the ‘task-positive’ resting state network which is associated with concentration on a particular task (Fox and Raichle, 2007). Considering this, it is understandable that these regions might be seen to be deactivated during the onset of acute experimental pain in healthy subjects. As these deactivations are of interest, it is noteworthy that

Kong et al. (2010a) found that higher levels of deactivation were found during a low pain condition in comparison to a high pain condition. This is contradictory to evidence from other studies such as that by Iannetti et al. (2005) in which increased deactivation during experimental pain was found in capsaicin-induced hyperalgesic subjects compared to their non-hyperalgesic state. There may be some explanation for this; Kong et al describe a hypothesis related to the DMN named the 'internal mentation hypothesis'. This hypothesis states that the DMN is involved in internal thoughts unrelated to the external environment such as memories, thoughts of the future and the imagining of alternative scenarios (Buckner et al., 2008). This would potentially help explain higher deactivation during the lower pain stimulus as this would be a) less salient than a high pain stimulus and would therefore be less attentionally demanding, b) harder to evaluate than a stronger stimulus and therefore be more cognitively demanding on the subject to internally evaluate the perception (Kong et al., 2006). In addition to the contradictory study by Iannetti et al. (2005), another study also found that the DMN only displayed deactivation during the anticipation of pain but actually displayed increased activity during the perception of acute pain (Ter Minassian et al., 2013b). Ter Minassian et al postulate that DMN activity is proportional to pain intensity and that this relationship can also be enhanced via the context of the pain (via cue's for example). It is interesting to note that chronic pain patient studies of the DMN have reported a loss of anticorrelation between the DMN and the 'task-positive' networks (Baliki et al., 2008a) or a less connected DMN (Cauda et al., 2009b) which are both plausible reasons as to why there were no consistent deactivations detected within the patient cohorts. Taken together, these findings point to a more complex relationship between the DMN and other networks in chronic pain cohorts. Additionally of interest is the deactivation within the paracentral lobule, a region known to be involved in

motor coordination of the leg and foot. Motor cortex responses during acute experimental pain is a relatively small area of research and so it can only be postulated that this deactivation may relate to an inhibition of motor response during the acute pain (and has been found to persist post-pain) that is thought to be a mechanism of defence against the threat of further pain and/or injury but further research is needed (Burns et al., 2016, Hodges and Tucker, 2011).

Neural activity during the anticipation as assessed by CBMA revealed bilateral anterior insula activity alongside the anterior cingulate. These regions are collectively referred to as the salience network (Seeley et al., 2007). As a network it is implicated in the response to salient stimuli such as uncertainty and pain which it has been found to 'encode ongoing fluctuations in the salience of pain' (Mouraux et al., 2011, Kucyi et al., 2013). In regards to anticipation, this network ensures awareness of the impending stimulus. For example, the anterior cingulate is known to part of the monitoring attentional system (Posner, 1994) as well as being implicated in action monitoring (Holroyd et al., 2004) both of which are important in regards to actions that may cause bodily harm. Several of the reported regions have also been implicated in the central processing of sympathetic control, namely the anterior cingulate and right anterior insula (Beissner et al., 2013). The right insula specifically is thought to act as a sympathetic response hub. Taken together with the cluster found within the supplementary motor area (SMA), it is likely that the reported neural anticipatory response acts together in order to orient attention (salience network), monitor performance and environmental cues needed for changes in action (ACC) alongside potential motor preparatory activity (SMA) and sympathetic responses (ACC and right anterior insula). These findings correspond quite closely with what was reported by Palermo et al. (2015) although they find more clusters. This difference most

likely is due to the more conservative approach to the inclusion/exclusion criteria set out within this thesis but also to the use of a version of GingerALE that was subsequently found to have a bug in its multiple-test correction code (FDR) which they used. However, it is reassuring that the basis of our results overlap.

Chronic pain patient studies of anticipation have been slow to accrue (and as such no analysis was performed here) but those published provide evidence of altered neural responses to cued painful stimuli. A study of fibromyalgia patients using fMRI found that the patients displayed reduced activity in areas such as the middle cingulate, PAG and SMA suggesting the previously mentioned motor and performance monitoring processes (as well as descending inhibitory pathways via the PAG) are altered compared to healthy controls (Loggia et al., 2014). A separate study of fibromyalgia patients also saw differentiated anticipatory activity in patients vs. healthy subjects (Burgmer et al., 2010).

Pain intensity was found to commonly be associated with regions that strongly overlapped also with pain anticipation, namely the bilateral insulae and the anterior cingulate. These structures form the core of the salience network which as discussed is involved in orienting attention and allocating neural resources. As such, these results could be interpreted to then simply show the salience network activity associating with the salience (or relative pain) of the stimuli presented. It presents the question however that if the same brain regions are both associated with the anticipation of and the subsequent intensity encoding of a stimulus (in healthy participants at least), then what impact might changes to the connectivity within and to this network affect pain sensitivity?

The strength of this study lies in the quality control procedures and homogeneous choice of studies that were included. Duplications were removed or merged to reduce any inflation of the ALE, whilst an improved ALE algorithm was utilised to reduce the possibilities of false positives and to correct appropriately for multiple-test comparisons. Most of the limitations of this study are inherent within the technique; coordinates extracted from studies are not weighted (i.e. they do not contain extra data about the statistical weight of a particular coordinate) and also potential variances between studies cannot be controlled for such as pain intensity, age or field strength of the magnet use to image the subjects.

6.5 Summary

This study provides strong evidence that cutaneous experimental pain in healthy and chronic pain subjects evokes similar spatial patterns of neural activity that in both cohorts, displays activity within classic pain-related brain regions. Differences between these groups were non-significant via coordinate based meta-analysis. This result provides the motivation for study 2 in which the use of arterial spin labelling (an imaging technique more sensitive than BOLD fMRI to tonic stimuli) will be used to assess ongoing chronic knee osteoarthritis pain without any overt stimuli being administered. Additionally, results of the deactivations observed during pain, activity during anticipation and intensity coding of pain point to resting-state networks (i.e. the default mode and salience network) as playing major roles in the experience of pain and provide motivation for study 3 in which the activity of each network and their interaction between will be assessed in chronic knee osteoarthritis patients.

7 Imaging to Understand Pain in Osteoarthritis: the ImPOA study

7.1 Introduction

The ImPOA study (funded as part of the Arthritis Research UK Pain Centre at the University of Nottingham - Grant 18769), begun as a multimodal imaging study to try and better understand how chronic OA pain was reflected in the structure and function of patients in comparison with age- and sex-matched healthy volunteers. This thesis will only concentrate on the functional MRI data that was collected as part of this study. Other PhD candidates have used the structural (Alshuft, 2015), microstructural and metabolic (Reckziegel, 2017) data collected as part of that study.

Chronic knee OA pain was chosen as the focus for the study due to the discrepancy between the prevalence of knee OA pain in the general population and the lack of knowledge about central vs. peripheral aspects of chronic knee OA pain. OA incidence increases with age and is more likely in women than men with large surveys suggesting that knee OA is perhaps more frequent than hip OA (Breivik et al., 2006). The relationships between reported pain and clinical features in OA have been previously investigated finding that factors such as knee injury, diabetes, and serum hyaluronic acid predict the structural progression of OA (including joint space narrowing and Kellgren-Lawrence (KL) grade) (Eymard et al., 2015, Sasaki et al., 2015, Driban et al.,

2014). The larger problem, is that reported pain does not consistently relate with the structural damage to the knee joint as discussed in chapter 1. Thus, there is a need to study the central and peripheral drivers of the OA pain and this is what the ImPOA study was designed to do.

This chapter will describe how the study subjects were recruited and what specific measures were acquired from them. This chapter will be referred to in the methods sections of the subsequent study chapters.

This study (from which the two subsequent study chapters take their data) was carried out in accordance with the declaration of Helsinki and was approved by Nottingham Research Ethics Committee 2 (ref: 10/H0408/115).

7.2 Methods

7.2.1 Recruitment pathways

Subjects were recruited via research coordinators employed within the larger ARUK Pain Centre (Maggie Wheeler and Nadia Frowd). They performed mainly recruitment and data acquisition duties (including questionnaires and quantitative sensory testing). Age- and sex-matching of the patients and healthy controls was carried out by a previous PhD student (H. Alshuft) together with the research coordinators.

My role in the study recruitment and data acquisition was that I took over meeting the patients, taking consent and carrying out questionnaires and QST after M. Wheeler retired. I therefore performed this duty on roughly a quarter of the recruited participants. I was also involved in the wider project administration in regards to the everyday project management and governance. For example, playing a key role in the submission of ethical

amendments and completing annual reports for linked funding and administrative bodies.

Patients with osteoarthritis were recruited via several routes: GP letters (working in concert with the clinical research network to screen and find participants with diagnosed knee OA), OA hip and knee pathway within Nottingham University Hospitals, and previous participation in University of Nottingham studies (in which they'd agreed to be contacted regarding future studies). Healthy volunteers were recruited mainly via posters or having previously participated in University of Nottingham research and consented to be contacted again regarding future studies (see appendix 11.2.1).

7.2.1.1 Eligibility criteria

Patients were considered eligible if they fulfilled the following criteria:

1. **Had radiologically defined knee OA.**
2. **Had chronic knee OA pain defined as 'pain for most of the day and on most days of the week' for at least 3 months.**
3. **Pre-operative clinical status.**
4. **Un-medicated in regards to strong painkillers or non-steroidal anti-inflammatory drugs with the exception of aspirin or paracetamol (taken as needed).**
5. **Aged 18 or over.**
6. **Able to give informed consent.**

Healthy volunteers were considered eligible if they fulfilled the following criteria:

1. **Able to give informed consent.**
2. **Free from major medical, neurological and psychiatric co-morbidities.**

3. **Aged 18 or over.**

Participants from either group were excluded if:

1. **Aged under 18 years old.**
2. **Pregnant or possibly pregnant.**
3. **Diagnosed with major medical, neurological or psychiatric co-morbidities.**
4. **Presenting with other significant medical condition.**
5. **MRI unsafe. E.g. presenting with metallic or electrical agents embedded within the body (e.g. shrapnel, aneurism clips, cardiac pacemaker) that were not specifically known to be MRI compatible.**

7.2.2 MRI scanning protocol

The ImPOA study utilised multimodal MRI to study chronic pain and as such, T1-weighted, BOLD fMRI, ASL, magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) data were acquired. This thesis will focus on BOLD fMRI and ASL data only whilst utilising T1-weighted structural data for registration and tissue segmentation purposes only. Acquisition parameters will be outlined within each of the relevant chapters (Chapter 5 – ASL; Chapter 6 – BOLD fMRI). All subject underwent MRI at 3T (MR750 Discovery, GE Healthcare) using a 32-channel head coil. Scanning was carried out in the Sir Peter Mansfield Imaging Centre, Queen's Medical Centre, Nottingham (previously known as the Medical Imaging Unit, Queen's Medical Centre).

Participants were always screened via a safety questionnaire that they would counter-sign (appendix 11.2.1) to ensure that they were safe to be scanned.

7.2.3 Phenotypical and demographic subject data

In order to best phenotype and control for potential confounding variables, a battery of questionnaires was carried out in all participants. The included questionnaires were chosen by the colleagues that initiated the ImPOA study (I joined the team mid-way through the study) and were chosen to reflect the chosen research questions and appropriately guided by the relevant literature. Additional points taken into account were ease of administration, interpretation and taking advantage of self-report when appropriate. Importantly, these were questionnaires generally used and reported within the arthritis pain literature. Questionnaires were marked and scored by previous colleagues (including Hamza Alshuft and Diane Reckziegel) but were checked by myself before use. Copies of the questionnaires used are included within the appendix. Although other questionnaires were collected, only those focusing on core demographic (education, handedness) or pain- and negative affect related details (depression, anxiety, pain catastrophizing, neuropathic-like pain) are utilised within this thesis.

Specifically, the questionnaires used and analysed within this thesis include the (see appendix 11.2.2):

Edinburgh handedness inventory (Oldfield, 1971)

Educational level (Egerton and Mullan, 2008)

Beck's Depression Inventory (Beck et al., 1996)

McGill Pain Questionnaire (Melzack, 1980)

State-Trait Anxiety Inventory (Spielberger et al., 1983)

Pain Catastrophizing Scale (Sullivan et al., 1995)

PainDETECT (Freynhagen et al., 2006)

Patients reported their subjective OA pain using a 10cm visual analogue scale (VAS scale 0-100; 0 meaning no pain and 100 meaning worst imaginable pain) (McCormack et al., 1988).

7.2.4 Quantitative Sensory Testing

Quantitative sensory testing is used in the pain field in order characterise psychophysics of both normal and chronic pain participants. There are several different approaches available including pin-prick stimulation, thermal stimulation (hot and cold) and pressure stimulation. Within this study, pressure pain thresholds (PPT's) were recorded to assess for sensitisation but were not included for analysis within this thesis.

Data were acquired by applying three repetitions to the: nailbed of the index finger (non-dominant hand), sternum (3cm inferior of the sternal notch), medial tibia, and the medial and lateral joint lines of the most painful knee. Each participant was read the following instructions –

"The idea of these tests is to look at pain thresholds in people with OA. We aren't looking at how much pain you can tolerate, simply at what point you start to feel pain. The pain you feel will only be fleeting, as the test will be stopped as soon as you indicate that you have started to feel pain. You will hold this push button and I will start to apply a graded pressure on your finger nail bed. You will feel pressure as the probe is pressed down and the pressure will be gradually increased. As soon as the pressure starts to change to pain, you should press the button and I will withdraw the probe. The first test is on the finger nail and is really just a practice to let you know how it feels. Then I will do the same on other parts of your body, specifically the sternum, around the knee joint and on the lower leg. At each site I will take 3

readings with a few seconds in between. Between each site there will be a 2 minute break."

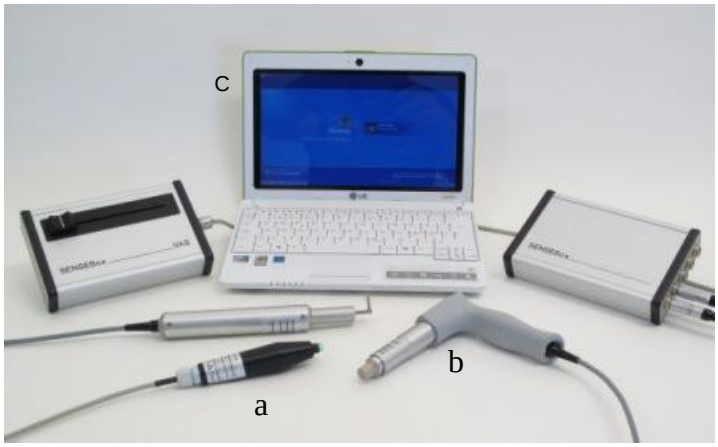


Figure 7.1. Pressure pain threshold equipment including the (a) button-press, (b) digital algometer and (c) laptop. Image was adapted from the SOMEDIC website (www.somedic.com).

Measurements were taken using a digital algometer (Somedic AB, Sweden) (fig 7.1). The average of the last two readings for the three non-local PPT sites (index finger, sternum and medial tibia) were taken to use as non-knee PPT's and the average of the last two readings for the two knee joint lines were taken to use as knee PPT's.

7.2.5 Data storage and conversion from DICOM

Study data are stored within the department at the University of Nottingham in accordance with good clinical practice and ethical regulations.

All data was converted from DICOM using an in-house program. The program 'dtoa' was written by Professor Paul Morgan and is available on his website (http://www.nottingham.ac.uk/~msapm1/software/dtoa.html).

7.2.6 Power calculation

The main studies that were calculated for power in the overall ImPOA study were the structural studies (presented previously in both a paper and thesis by

Hamza Alshuft (Alshuft, 2015, Alshuft et al., 2016). The second study that was calculated for power was that of functional connectivity using resting-state fMRI. This was powered based upon results published previously by (Napadow et al., 2010). In table 2 of the study the authors present between group differences between patients with fibromyalgia and healthy controls. To power the study contained within this thesis (chapter 9), the average z-score and standard deviation from each significant cluster was averaged for each group (patients and controls). The results values were then entered into G*Power 3.1.9.2, a statistical software specifically designed to perform power calculations for statistical tests (Faul et al., 2007). Having calculated the group means ± SD from the table (fibromyalgia - 1.4725 ± 0.92; volunteers - 0.3925 ± 0.855), a power calculation was performed to be able to find the appropriate sample-size for a two-sample t-test (two-tailed) with a type-one error rate of 0.05 and a power of 0.95. The calculated effect size (d) was 1.2160863. This calculated that the required sample-size to detect a difference between groups would be 19 vs. 19 for a comparison of functional connectivity. For the ASL study in chapter 8, there was no explicit sample-size calculated for the main statistical test (the CBF x pain intensity correlation) and as such, a *post hoc* sample-size calculation will be carried out assessing the correlation between reported pain severity and cerebral blood flow in the anterior cingulate (as this was the region most commonly covarying with pain intensity as assessed by coordinate based meta-analysis [section 6.3.7]). If a significant cluster is found to covary within the anterior cingulate within the study these values will be used to calculate the correlation. If no significant cluster is found, then the coordinates from the meta-analysis (section 6.3.7) will be used as the basis for a 6mm spherical ROI. This will be assessed by using the R^2 value under the following options: as a *post hoc* power analysis

of a two-tail t-test correlation analysis (point biserial model) with a sample size of 26 and an α error probability of 0.05.

7.3 Summary

This chapter explained the base study from which data for the next two chapters was derived. Details of the studied cohorts will be outlined per study but briefly, study 2 will utilise arterial spin labelling data will be used to assess the neural correlates of ongoing chronic knee osteoarthritis pain (n=26) and comparing cerebral blood flow at rest with age and sex matched healthy volunteers (n=27), study 3 will utilise resting-state BOLD fMRI to assess both within- and between-network functional connectivity in chronic knee osteoarthritis patients (n=25) vs. age- and sex-matched healthy controls (n=19) in regards to the default mode, salience and central executive network.

8 Associations between brain activity and severity of ongoing chronic osteoarthritis pain as measured by arterial spin labelling[3]

8.1 Introduction

Arterial spin labelling is a functional MRI technique that has been available for over twenty years (Detre et al., 1992, Williams et al., 1992), but has only begun to be used regularly in studies of pain within the last decade (Howard et al., 2012, Kato et al., 2010, Owen et al., 2008). As reviewed previously in section 3, studies using ASL imaging have added to the pain functional imaging literature. ASL not only provides a more sensitive technique for the study of tonic pain, but also quantifiable differences between chronic pain

[3] This work has been previously published: Cottam, W.J., et al. *Associations of limbic-affective brain activity and severity of ongoing chronic arthritis pain are explained by trait anxiety.* Neuroimage Clin, 2016. 12, 269-76. My role in this manuscript was as lead author, I acquired data, conducted all analyses and wrote the manuscript. Other contibutors to the study were Professor Dorothee Auer (concept and design), Dr Laura Condon, Dr Diane Reckziegel and Dr Hamza Alshuft who helped acquire data. All authors reviewed and commented on the final manuscript.

cohorts and healthy controls. This type of imaging has grown (although total papers still number under 40 within the field) due to its increased sensitivity (thanks in large part to the new pCASL sequence type) and it's applicability in studying chronic pain. This is due to it being more sensitive to long-lasting tonic stimuli which chronic pain commonly presents as. This sensitivity over the period of minutes or longer is a by-product of the way in which ASL images are obtained - as the subtraction of sequential image pairs. This subtraction both flattens the associated frequency spectra of the data and removes temporal autocorrelation, providing a technique that is sensitive to slow and continuous changes (Aguirre et al., 2002). BOLD fMRI images, sampled once every repetition time (TR; usually in the order of 3 seconds or less), are susceptible to slow signal "drifts" which can affect signal comparisons made over more than a minute apart, whereas previous research has shown that ASL is sensitive to changes in CBF over the course of minutes and hours (at which point BOLD signal displayed significantly reduced signal-to-noise ratio) (Wang et al., 2003).

Neuroimaging studies of chronic osteoarthritis pain to date have proven discrepant with brain responses to acute experimental pain displaying both significant differences in some, and then no difference in others (Gwilym et al., 2009, Hiramatsu et al., 2014b, Parks et al., 2011, Sofat et al., 2011). Taken together with the results of the meta-analysis carried out in chapter 6, these results of evoked pain studies evidence the need for a more appropriate approach to the study of chronic osteoarthritis pain. Additionally, it is likely that simply no differences would be seen due to cutaneously evoked pain not being able to reproduce the subjective experience of chronic osteoarthritis knee pain with all of its aversive components such as individualised fears and memories. Examples of contextually relevant stimulations in chronic pain are

present however, such as the use of tactile stimulation in peripheral neuropathy (Schweinhardt et al., 2006) or using a functionally relevant grip task in patients with OA of the first carpometacarpal joint (Sanders et al., 2015). Subsequently, it seems that an approach like that taken by Segerdahl et al. (2015b) in which perceived ongoing pain was correlated with cerebral blood flow as measured by ASL MRI could be utilised to assess ongoing OA pain. Although that particular experiment was carried out in healthy controls, it presents as a particularly good approach for the study of chronic pain in which a) no external stimuli is needed and b) allows for the study of the actual clinical pain and its related neural activity for which it has already been discussed that ASL displays an increased sensitivity towards (see section 3.2.1).

With this proven usefulness in studying pain and ease of applicability, this study aimed to locate and characterise neural activity associated with clinical knee OA pain by correlating pain scores recorded prior to scanning with ASL imaging data. We hypothesised that brain activity associated with ongoing pain intensity would include limbic regions (including the amygdala, anterior cingulate and insula) and that this activity could be partly explained by negative affect. This hypothesis was predicated on the previous work that had evidenced increased limbic/emotional activity (Kulkarni et al., 2007, Parks et al., 2011, Howard et al., 2012), as well as increased levels of negative affect such as anxiety and depression during arthritis pain (Creamer et al., 1999, Eckhoff et al., 2017, Keefe et al., 2000).

In order to test these hypotheses, we utilised arterial spin labelling to measure regional CBF (as a measure of neural activity) and its covariance with subjective rating of ongoing pain in chronic knee OA patients with and without controlling for markers of negative affect (trait anxiety, BDI). Limbic brain

regions that displayed significant covariation between CBF and ongoing pain scores were assessed *post hoc* for potential mediation via recorded affective scores.

8.2 Methods

8.2.1 Subjects and Materials

As discussed in chapter 7, this cohort was recruited as part of the ImPOA study. Specifically, 43 patients with chronic knee osteoarthritis pain (median age 64.5 years, range 45-84 years, range of pain duration 12-456 months, 19 males) were recruited alongside 30 healthy volunteers (median age 64.5 years, age range 43-80 years, 11 males). All patients and healthy volunteers passed all the studies inclusion/exclusion criteria and were found to be safe to scan. All participants gave informed, written consent to participate. Patients reported their subjective OA pain using a visual analogue scale (VAS scale 0-100; 0 meaning no pain and 100 meaning worst imaginable pain).

8.2.2 MRI data acquisition

Only whole-brain ASL and high-resolution T_1 3D-FSPGR anatomical data (used for registration) is reported (Flip angle=12°, echo time [TE]=3.172 ms, repetition time [TR]=8.148ms, inversion time [TI]=450ms, field of view [FOV]=256mm, slice thickness=1mm, matrix=256x256). The ASL sequence combines pulsed-continuous ASL (pCASL) labelling with a 3D fast spin echo (FSE) spiral read-out (Flip angle=111°, TE =10.5ms, TR=4632ms , labelling duration=1450ms, post-labelling duration=1525ms, FOV=240mm, slice thickness=4mm, slice gap=4mm, number of slices=36, echo train length=1, number of excitations=3, matrix=128x128, no. of volumes=72, scan length=5mins 33s) (Dai et al., 2008b). Background suppression was used and an M_0 image collected also for image quantification. T1 images were acquired

using a gradient echo sequence (TE/TR=3.324/8.492ms, TI=450ms, slice gap=1mm, field of view=256, matrix=256x256, flip angle=12°) parallel to the AC-PC line whilst the bottom of the acquired ASL image was positioned just below the cerebellum to allow whole-brain CBF imaging. The excitation slab was positioned 10mm below the imaging slab and was 33.4mm thick.

8.2.3 Data quality assurance

ASL datasets were excluded upon the presence of poor quality due to either image artefacts or high levels of movement. Several datasets were excluded due to this (patients=8, controls=3). Figure 8.1 displays examples of the movement artefact seen in some of the images, usually seen upon a sagittal view of the central sulcus appearing in a finger-like or striped fashion (example in the top left image). Additionally, the bottom left image displays a subject showing abnormally low perfusion in the left posterior quadrant potentially due to anatomical variation with a prolonged transit time or a potential stenosis of the left posterior cerebral artery. This could be due to having used an insensitive inversion time (TI=1525ms) as the recent ASL white paper recommends that patient cohorts should be imaged using a TI of 2000ms to allow for perfusion in participants with potentially tortuous vessel pathways or slow perfusion (Alsop et al., 2015). Additional causes of low image quality could have been due to issues with labelling inefficiency or possibly due to metal dental work (such as fillings or crowns) that could have caused localised field distortions and reduced the available signal.

All images were checked visually, particular scrutiny was applied to those whose mean raw image value was below 30 ml/100g/min as this is a particularly low value considering that the average CBF in healthy individual is usually between 40-80 ml/100g/min as measured by ASL MRI (Madsen et al., 1993). Those images with average values below 30 ml/100g/min were usually

also found to be of low quality. Lastly, patients that reported no pain on the day of scanning were excluded (n=9) as we were primarily interested in those currently experiencing their OA pain.

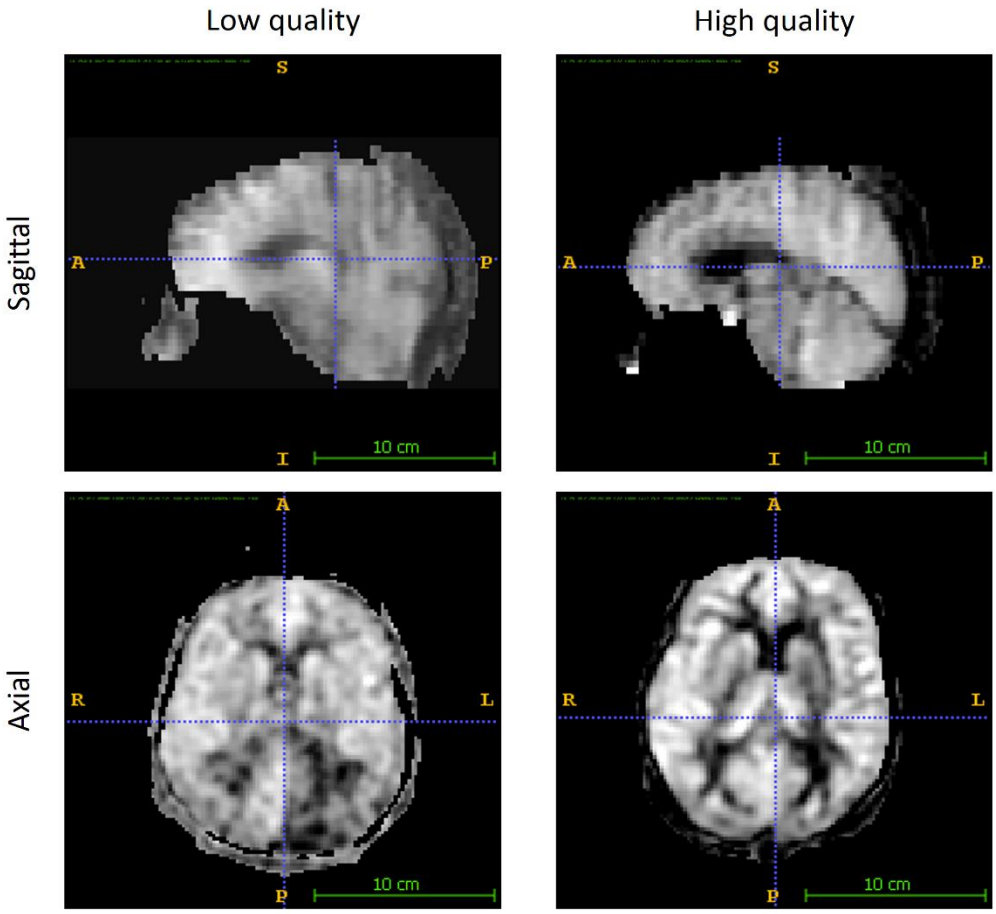


Figure 8.1. Example of non-brain extracted low and high quality ASL images displaying both high and low levels of perfusion. All four images are from separate individuals.

8.2.4 Image Processing

An automatic reconstruction script was used to generate quantitative CBF maps (ml/100g/minute) as reported previously by Zaharchuk et al (2010). These data were then manually brain extracted using an in-house software (NeuROI; http://www.nottingham.ac.uk/scs/divisions/clinicalneurology/software/neuroi.aspx). Images were then registered linearly (12 DOF) to MNI-space using FSL-FLIRT v6.0 (FMRIB software library) (Jenkinson et al., 2002) and smoothed to

8mm FWHM in SPM8 (http//:www.fil.ion.ucl.ac.uk/spm). Linear registration was utilised over non-linear registration as it proved more robust with the acquired images. To ensure that only grey matter CBF was being analysed, a dual-tissue probability mask was applied (excluding ≤20% grey matter and ≥30% cerebrospinal fluid) based on modified International Consortium for Brain Mapping (ICBM) tissue-probability maps provided in SPM8 (Rex et al., 2003).

8.2.5 Statistical Analysis

To test the main hypothesis, a whole-brain grey matter perfusion correlation with reported pain intensity (VAS) scores was performed in OA subjects. Secondary tests included: an independent samples t-test between OA patients and healthy controls, a subgroup independent samples t-test of OA patients with either left- or right-lateralised knee OA, repeat correlation analyses with reported pain intensity scores using data flipped in the x-axis (only data from patients with left-sided knee OA were flipped to theoretically make them also 'right' knee affected) and controlling for affective scores found to be significantly correlated with reported pain intensities. All whole-grey matter analyses were corrected for age, sex, and mean global CBF (to control for differences of no interest in inter-subject CBF levels) by including de-meaned versions of these measures as nuisance covariates within the analysis design. Image analysis was carried out using voxel-wise non-parametric permutation testing using FSL-randomise to correct for multiple comparisons (5000 permutations). Permutation testing was utilised in the knowledge that the relationship between reported pain severity and cerebral blood flow might not be linear in all (or any brain regions). This approach therefore maximised sensitivity across the brain. Significance was set at P <

0.05 Family-Wise Error (FWE) corrected using threshold-free cluster enhancement (TFCE) (Nichols and Holmes, 2002, Smith and Nichols, 2009).

Further tests in line with our hypothesis of an increased limbic-affective component of OA pain were carried out by extracting mean CBF values from ROI's that displayed significant CBF-VAS relationships in the main regression analysis. These values were used for *post-hoc* analyses to assess interrelations with patient reported negative affect including depression, trait anxiety and pain catastrophizing scores. These scores underwent Rasch conversion so that they could be used within linear statistical tests. Rasch conversions were used courtesy of Bryan Moreton and Nadina Lincoln from the ARUK Pain Centre, University of Nottingham. Conversion tables can be found in the thesis appendices (11.2.4). Any of these psychometric scores of negative affect that displayed correlations at either significant or trend levels ($P<0.1$) with VAS and regional CBF values were tested via mediation analysis using the Process macros for SPSS (Hayes, 2015). Each mediation test carried out used reported VAS as the independent (X) variable and regional CBF values as the dependent (Y) variable. VAS scores were treated as a continuous variable. Psychometric scores of negative affect were included as the mediating variable in each case (M). Each test used 5000 bootstrap samples (bias corrected), measured total and indirect effects of X on Y through M, and were considered significant only when the 95% confidence interval did not pass through zero. All tests of demographic variables were compared using independent samples *t*-tests and were performed using SPSS 22 (IBM).

A *post hoc* power analysis will be carried out to assess whether the study was adequately powered as outlined previously in section 7.2.6.

8.3 Results

8.3.1 Overall findings

No significant differences between groups were found when comparing age or sex (see table 8.1 overleaf for demographic data). Patients were found to have significantly lower mood and educational levels. This low mood (as measured by BDI-II) did not in any case score highly enough that it could fulfil the criteria of clinical depression as the highest scores still only classified as 'mild' low mood (Beck et al., 1996). Patients were also found to score significantly higher in state and trait anxiety levels but not pain catastrophizing.

Average whole grey matter CBF scores were not significantly different (P = 0.52, age and sex corrected) between OA (44.0 ± 7.8 ml/100g/min) and HC (45.8 ± 10.5 ml/100g/min) groups. When assessing correlations between demographic scores and whole grey matter CBF neither educational levels, reported VAS, BDI, PCS, nor STAI scores significantly correlated (Educational, P=0.809; VAS, P=0.573; BDI, P=0.203; PCS, P=0.449; State anxiety, P=0.386; Trait anxiety, P=0.963; controlled for age and sex). Assessing for interrelations between negative affect scores, trait anxiety and pain catastrophizing scores significantly correlated with reported VAS (Trait anxiety –R=0.643, P<0.001; PCS – R=0.564, P=0.003) whilst Rasch converted BDI and state anxiety scores did not (BDI - R=0.116, P=0.573; State anxiety – R=0.333, P=0.104).

Table 8.1
Patient Demographics and group differences

Data	Knee OA patients	Healthy Controls	P-value
N.	26	27	-
Median age (range)	67.5 (54-84)	65.0 (57-80)	0.076
N. Males	12	9	0.35
Laterality of affected knee	12 left / 14 right	-	-
N. Right-handed	24	23	-
Median Educational Scores	6**	3	**0.023**
VAS 0-100	40.2 (10-80)	-	-
PainDETECT[#]	12.5 (0-25)	-	-
BDI (range)[#]	7.8 (0-19)	2.5 (0-12)	**0.0003**
STAI-S	14.0 (10-26)*	12.4 (10-23)*	0.174
STAI-T	19.6 (11-37)*	16.2 (11-23)*	**0.044**
PCS	13.6 (1-34)	11.7 (0-29)	0.438
PCS: Helplessness	5.6 (1-14)	4.2 (0-13)	0.203
PCS: Magnification	2.4 (0-6)	2.3 (0-7)	0.903
PCS: Rumination	5.6 (0-15)	5.2 (0-20)	0.749

Displayed are the mean (range) values unless elsewise specified. BDI – Beck's Depression Index, STAI-S – State Anxiety, STAI-T – Trait Anxiety, PCS – Pain Catastrophizing Scale. *1 subject score missing, **2 subjects were missing, [#]scores reported are the raw questionnaire scores. Adapted from Cottam et al. (2016).

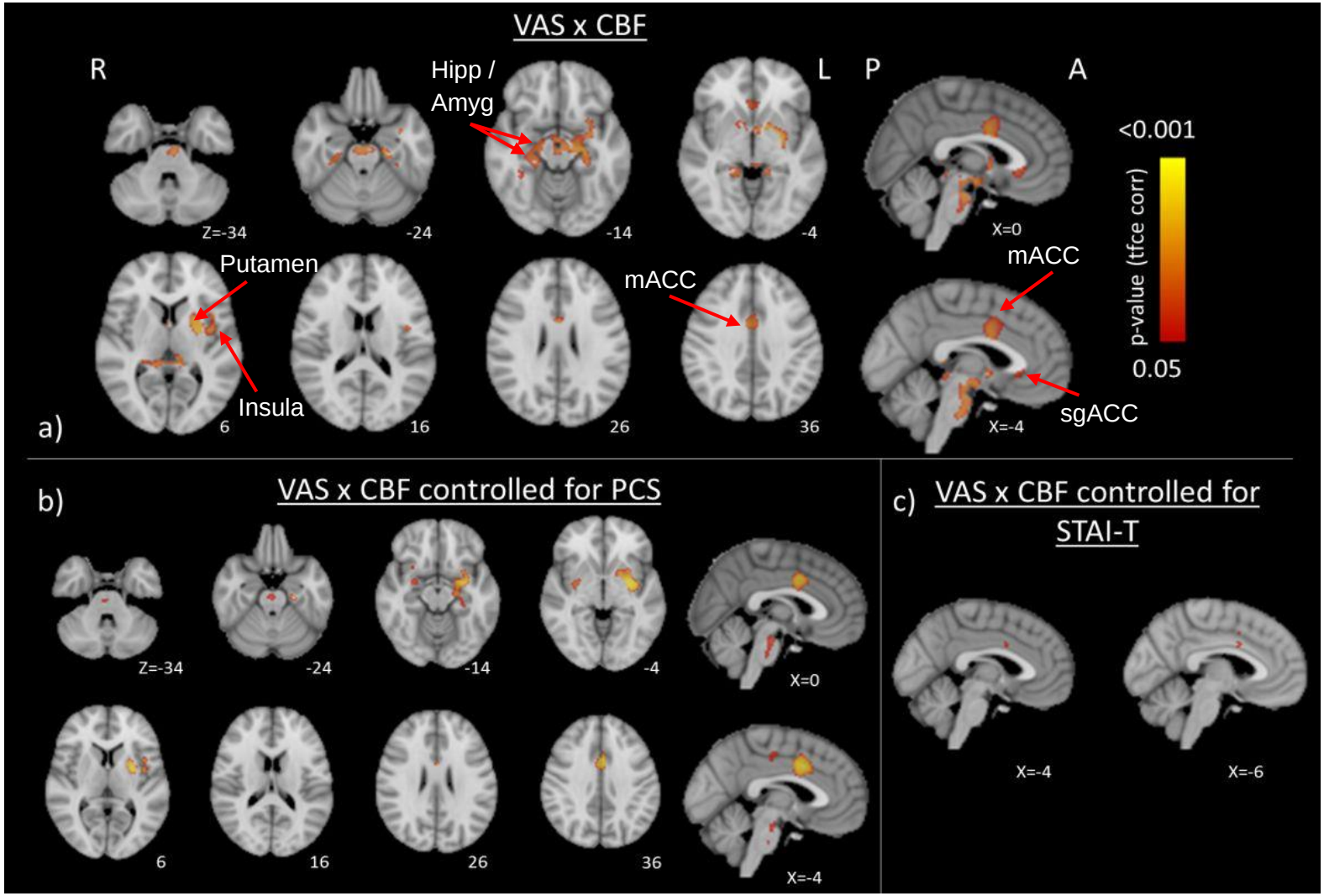


Figure 8.2. Brain regions where CBF correlates positively (FWE p<0.05) with reported VAS scores after a) correcting for age, sex, and mean CBF and additionally for b) pain catastrophizing and c) trait anxiety scores. All images are shown in radiological format (right hemisphere is displayed on the left of the figure). Figure adapted from (Cottam et al., 2016). Key: mACC – mid-anterior cingulate cortex, sgACC – subgenual anterior cingulate cortex, Hipp / Amyg – Hippocampus / Amygdala

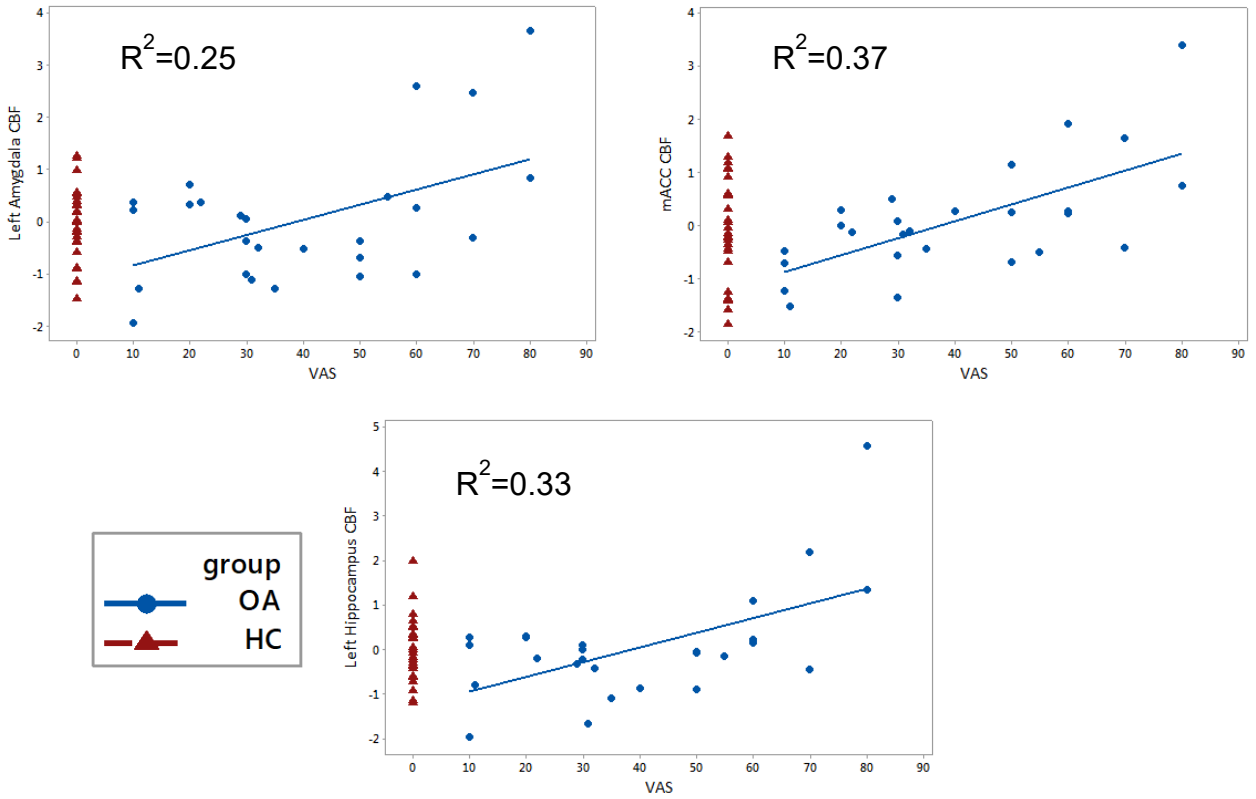


Figure 8.3. Scatter plots displaying partial correlations of reported pain intensity (VAS) and cerebral blood flow in healthy controls (HC; red) and chronic OA pain patients (OA; blue) in the left amygdala, hippocampus and the anterior mid-cingulate cortex (aMCC) controlled for age, sex and mean grey matter CBF. R^2 values display the amount of variance explained in the OA group only. CBF of healthy controls is plotted to provide context for the values observed in patients. Figure adapted from (Cottam et al., 2016)

8.3.2 Relationship of CBF with reported pain intensity in OA patients

When performing voxel-wise correlation in grey matter CBF, reported pain intensity was found to significantly positively correlate in few areas commonly reported in experimentally induced nociception as evidenced by previous literature (e.g. Wager et al. (2013)). The main region found to overlap with previous reports was the anterior mid-cingulate (aMCC). Of significant interest was that positive covariance between CBF and reported VAS in limbic regions commonly associated with fear and emotion. Covariance was found within the subgenual ACC (sgACC), bilateral hippocampi, left putamen and the bilateral amygdala (Figure 8.2 and table 8.2). Illustrative scatter plots of the CBF x reported VAS correlations are displayed in figure 8.3. No significant negative correlations were observed.

Table 8.2
Areas with significant associations between CBF and reported ongoing OA pain intensity

Anatomical regions	Cluster extent	X	Y	Z	T-score
Positive Correlations					
L. Central Operculum	2983	-42	0	12	5.05
L. Putamen		-24	4	8	4.5
L. Brain Stem		-4	-34	-4	4.76
L. Posterior Thalamus		-10	-32	6	4.24
L. Hippocampus		-28	-24	-12	4.08
R. Hippocampus		28	-26	-10	3.77
L. Mid-Insula		-40	-2	2	3.43
L. Amygdala		-22	-6	-12	3.62
R. Amygdala		18	-10	-14	3.24
aMCC	253	2	2	34	5.49
R. Subgenual ACC	79	4	26	-6	5.04
L. Subgenual ACC		-2	26	-6	4.22
R. TOF	68	38	-40	-12	3.73

All results at FWE corrected P<0.05, reported in MNI152 standard space. L. – Left, R. – Right, aMCC – Anterior Mid-Cingulate Cortex, TOF – Temporal Occipital Fusiform, Cluster extent – the number of voxels within a cluster. Adapted from Cottam et al. (2016).

A subgroup analysis of patients with left and right affected OA knees was performed as the results from the main analysis displayed predominantly left sided lateralisation. A Kruskal-Wallis *t*-test was performed to test whether this might be due to a biased level of pain from one affected knee side (left knee n=12; right knee n=14). A Kruskal-Wallis test was used due to its non-parametric properties as linearity could not be assumed. Reported pain was not found to differ significantly between these subgroups (P=0.411; controlled for age and sex). Additional whole grey matter tests of left- versus right-lateralised knee OA were also non-significant when corrected for multiple-comparisons (FWE, P>0.05). To further test the effect of OA laterality I flipped the data along the x-axis (only left-sided OA patients had data flipped) such that all patients were theoretically 'right side affected'. The main correlation analysis was then re-computed. The results in this case were mainly based around the midline with clusters presenting once again in the mACC, sgACC, left hippocampus and the right hippocampal/amygdala complex. Upon flipping the data, no clusters remained significant within the insulae but there were still two small clusters found within the left putamen (figure 8.4).

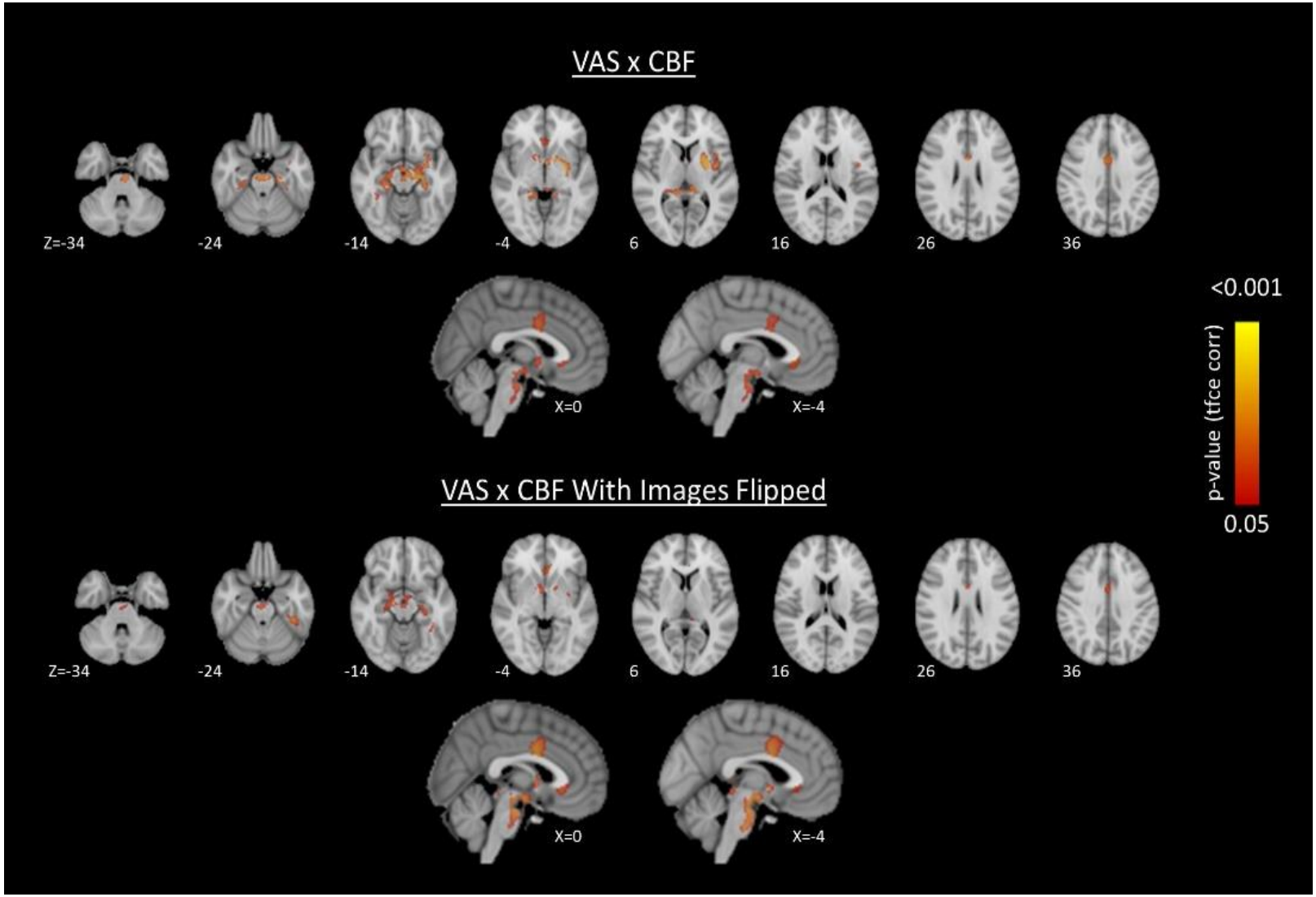


Figure 8.4. Brain regions where CBF correlates positively (FWE p<0.05) with reported VAS scores before and after flipping all image data in those patients with osteoarthritis in their left knee (correcting for age, sex, and mean CBF). All images are shown in radiological format (right hemisphere is displayed on the left of the figure). Figure adapted from (Cottam et al., 2016).

Catastrophizing and trait anxiety scores were found to significantly correlate with reported pain scores and as such we repeated the whole grey matter correlation analysis and in separate tests, controlled for trait anxiety and PCS scores (n=25 for these tests as one subject was found to be missing questionnaire data) to test for confounding or mediating covariance with CBF. When controlling for trait anxiety, the majority of the previously significant clusters were removed with only 2 clusters within the aMCC remaining significant (figure 8.2c, table 8.3). Controlling for PCS separately however did not affect the previous results in a large way. Only the cluster in the sgACC was lost whilst other clusters were additionally found in the posterior cingulate gyrus, the right central operculum and the right putamen (figure 8.2b, table 8.3).

Table 8.3
Areas with significant associations between CBF and reported ongoing OA pain intensity additionally controlled for pain catastrophizing and trait-anxiety scores.

Anatomical regions	Cluster extent	X	Y	Z	T-score
VAS x CBF controlled for STAI-T					
aMCC	11	-4	6	32	5.84
aMCC	2	-4	6	44	5.84
VAS x CBF controlled for PCS					
L. Putamen	1261	-30	-6	-4	6.63
L. Amygdala		-24	-6	-14	4.72
L. Hippocampus		-22	-16	-16	3.82
L. Central Operculum		-42	-2	12	3.99
L. Insular Cortex		-40	-4	4	3.93
aMCC	331	-2	8	38	7.4
R. Putamen	195	32	-6	-2	4.87
R. Amygdala		26	-6	-14	3.70
Brain Stem	100	0	-20	-22	4.14
PCC	19	-2	-20	46	4.83
R. Anterior Insular Cortex	17	28	14	-14	4.38
R. Central Operculum	6	44	-2	10	3.91

All results at FWE corrected P<0.05, reported in MNI152 standard space. L. – Left, R. – Right, aMCC – Anterior Mid-Cingulate Cortex, S2 – Secondary Somatosensory Cortex, PCC – Posterior Cingulate Cortex, STAI-T – Trait Anxiety, PCS – Pain Catastrophizing Scale, Cluster extent – the number of voxels within a cluster.

8.3.3 Correlations between psychometrics of negative affect and CBF

In order to further disentangle the relationships between CBF, reported VAS and negative affect, *post-hoc* tests were carried out using CBF from those regions found to significantly covary with reported VAS. As was previously outlined, only PCS and trait anxiety significantly associated with reported VAS. All variables displayed were suitable being continuous variables and displaying reasonable variance. No significant correlations were found between regional CBF and psychometric scores. Borderline associations were found between PCS and sgACC CBF (P<0.1) and BDI and bilateral amygdala CBF (P<0.1, table 8.4). Due to its borderline association with sgACC, PCS was assessed for mediation effect but was found to be non-significant (95% confidence interval lower limit -0.0596, upper limit 0.1946).

Table 8.4
Bivariate Pearson correlation scores between psychometric scores and CBF in regions of interest.

	BDI	PCS	aMCC	sgACC	L. Amyg	R. Amyg	L. Hipp	R. Hipp
Trait	0.359 (0.078)	0.649 (0.000)	0.171 (0.415)	0.120 (0.568)	0.169 (0.419)	0.225 (0.281)	0.169 (0.420)	0.083 (0.693)
BDI		0.359 (0.078)	0.234 (0.250)	0.293 (0.147)	0.336 (0.093)	0.335 (0.095)	0.327 (0.103)	0.312 (0.120)
PCS			0.239 (0.250)	0.390 (0.054)	0.073 (0.729)	0.245 (0.239)	0.317 (0.123)	0.298 (0.148)

All values are reported r-correlation values (P-value) from between variables carried out in SPSS 22. Abbreviations: L – Left, R – Right, Trait – STAI Trait anxiety score, BDI – Rasch-converted BDI-II scores, PCS – Pain Catastrophizing Scale, sgACC – subgenual Anterior Cingulate Cortex, Amyg – Amygdala, Hipp - Hippocampus.

8.3.4 Comparisons of whole brain CBF between OA and HC groups

No significant differences in CBF was found between OA patients and healthy controls (FWE, P>0.05).

8.3.5 *Post hoc* power calculation

As a significant cluster was found (as outlined in section 7.2.6), the statistical power of the experiment was assessed *post hoc*. The correlation value of the

significant aMCC cluster CBF with the reported pain intensity (R^2=0.37) was entered into G*Power 3.1.9.2. The reported power was 0.96 suggesting that the correlation analysis was adequately powered.

8.4 Discussion

This study utilised arterial spin labelling MRI to assess the neural correlates of clinical pain in knee OA. The results present evidence that a network of limbic, paralimbic, and subcortical structures underlie chronic pain perception. This is in keeping with the large affective component of chronic pain that these patients report. Additionally, secondary tests show that the relationship between CBF and reported VAS in OA patients in both limbic and paralimbic regions was modified by trait anxiety.

Assessing the correlation between reported pain intensity in chronic OA pain patients and their cerebral blood flow revealed a covarying network of nociceptive (aMCC, insula), limbic and paralimbic (bilateral amygdala, sgACC, and hippocampus), and subcortical regions (left putamen and brainstem). The aMCC alongside the insula (specifically the anterior insula) are core hubs of the salience network (as mentioned previously in chapter 3) and are typically activated within experimental pain studies (see chapter 5) and have been thought to be an integral part of the 'signature of pain' (Wager et al., 2013). Recent studies however have challenged the specificity of this signature of pain or 'pain matrix' (as it used to be known) and demonstrate salience network activity in many non-painful sensory stimulation tasks and also suggest a functional lateralisation of the salience network with a role of the right anterior insula and mACC in processing the salience of outcome (Iannetti et al., 2013, Spati et al., 2014). Previous studies of experimental nociception in healthy volunteers have also identified activity in overlapping regions of the insula (usually bilateral), thalami, S2 and aMCC as evidenced by the

coordinate based meta-analysis of pain intensity encoding in healthy participants carried out in chapter 6 (Boly et al., 2007, Christmann et al., 2007, Coghill et al., 1999, Peyron et al., 2007, Straube et al., 2009, Favilla et al., 2014a). The aMCC has also been found to have a sub-region containing a large number of neurons that respond specifically to nociception (Lenz et al., 1998, Sikes and Vogt, 1992, Vogt, 2005). Further to this, this was the only region that was found to show a significant CBFxVAS relationship after correcting for trait anxiety. Specifically within this cohort, this finding links to parallel work (also carried out as part of the multimodal ImPOA study) in which we found that reported OA pain intensity anticorrelated with GABA within the aMCC suggesting potential neurochemical changes underlying OA pain (Reckziegel et al., 2016).

Other than the aMCC, the results presented here suggest a dissociation between the neural activity related to the reported pain intensity in chronic pain and that seen in healthy controls undergoing experimental nociception. This study did not find for example, associations between pain intensity and CBF in regions such as S1, S2, thalami, or anterior insulae which are regularly reported in studies of healthy volunteers, whilst additional limbic structures were found in this study which are not commonly reported in these healthy volunteer studies (Baliki et al., 2006, Boly et al., 2007, Christmann et al., 2007, Coghill et al., 1999, Moulton et al., 2012). For example, we report amygdala CBF to relate to perceived pain intensity in chronic pain but very few healthy volunteer studies also report the amygdala, and those that do are not consistent in their reported laterality (Atlas et al., 2014, Oertel et al., 2012, Peyron et al., 2007).

The approach of performing whole grey matter CBF regression with reported pain intensity gave rise to a network of regions such as the sgACC,

hippocampi, amygdala, and left putamen. These are regions not previously reported as consistently encoding pain intensity in studies of healthy volunteers (Apkarian et al., 2005, Duerden and Albanese, 2013). Several of these regions have, however, been reported in previous studies of chronic pain patients such as OA and chronic back pain such as the sgACC (Baliki et al., 2008b, Howard et al., 2012, Kulkarni et al., 2007, Parks et al., 2011). The sgACC is reported as being a key region involved in affective disorders such as depression in which it has been reported as displaying atrophy and functional hyperactivity in comparison to that in age- and sex-matched individuals (Connolly et al., 2013, Niida et al., 2014, Rodriguez-Cano et al., 2014). In addition, when trait anxiety or pain catastrophizing scores were used as covariates of no interest the sgACC no longer displayed a significant relationship with reported pain. Additional *post-hoc* analysis of the PCSxCBFxVAS relationship was not significant.

Bilateral hippocampal CBF was found to significantly correlate with reported pain intensity. Furthermore, the left hippocampus correlation was found to be independent of catastrophizing whilst the correlation found within the right hippocampus was no longer significant after controlling for patients' catastrophizing. The hippocampi are generally well known for their contribution in memory but have also been seen to display reduced neuronal plasticity and nerve growth in pre-clinical chronic pain models (Terada et al., 2008, Mutso et al., 2012). On top of this, human neuroimaging studies have shown increased hippocampal activity during OA pain (Howard et al., 2012, Parks et al., 2011) and when comparing chronic pain patients with healthy controls (Mutso et al., 2014). The combination of these previous studies with the currently presented results strongly suggest that the hippocampi are involved with chronic pain and its percept. Additionally, previous studies have

displayed longitudinal evidence of hippocampus plasticity in the transition of back pain state from subacute to persistent pain (Mutso et al., 2014) and increases in regional grey matter after participating in an 11-week cognitive behavioural therapy (Seminowicz et al., 2013).

As discussed briefly in chapter 1, pain is known to be a summative percept including overlapping sensory and affective components. These affective components are known to be increased in chronic pain, most commonly reported as increased levels of stress, distress, depressive thoughts and/or anxiety. One brain region that has been reported as being involved at the interaction of pain and emotion is the amygdala (Neugebauer et al., 2004). Studies in rodent models of pain have shown examples of this, reporting that the persistence of pain in a neuropathic pain model could be “significantly inhibited” by lesioning the amygdala (Li et al., 2013) or that applying corticotropin-releasing factor (CRF) to the amygdala was enough to produce pain-related behaviour (Ji et al., 2013). Imaging studies of human brains have also produced evidence that the amygdala is involved with the perception of chronic pain (Hashmi et al., 2013, Liu et al., 2013, Neugebauer et al., 2004). Furthermore, the concurrent finding of both the amygdala and sgACC together related to reported OA pain corresponds with previous reports of known functional and structural connectivity between these two regions (Kellermann et al., 2013, Robinson et al., 2010, Simons et al., 2014), and with previous PET and ASL/BOLD fMRI studies showing increased neural metabolism within the left amygdala and sgACC in OA patients compared to less painful states or against healthy controls (Howard et al., 2012, Kulkarni et al., 2007, Parks et al., 2011). Most convincingly, a longitudinal MRI study of patients reporting with back pain demonstrated a shift of pain processing away from mostly sensory brain regions towards more regions more commonly related to

emotion-processing (including the amygdala) in those patients who progressed from subacute to persistent back pain (Hashmi et al., 2013, Vachon-Presseau et al., 2016). Taken together with these previous findings, the finding of the amygdala encoding chronic OA pain presents as further concurrent evidence of the role of the amygdala in chronic pain and reinforces the idea of amygdala maladaptation as a contributing mechanism to ongoing pain.

Activity within the putamen has previously been reported in ASL studies of ongoing pain states such as fibromyalgia, postherpetic neuralgia, subcutaneous evoked pain, and post-surgical tooth pain (Liu et al., 2013, Owen et al., 2012, Shokouhi et al., 2015, Howard et al., 2011). Structurally, there is also evidence of enlarged putaminal volumes in chronic pain (Desouza et al., 2013, Schmidt-Wilcke et al., 2006). The basal ganglia is structurally connected to a number of regions involved in nociception, attention and sensory-motor processing which together support the role of the putamen in pain perception – working together with other regions to enable motivational shift and response selection (Starr et al., 2011). A previous study of pain catastrophizing in fibromyalgia patients observed increased putaminal and anterior cingulate activity in high catastrophizers compared to low catastrophizers (Gracely et al., 2004). This is interesting to compare with our finding of a positive relationship between reported pain intensity and blood flow in these same regions, a relationship that was not significantly impacted on by further controlling for pain catastrophizing scores. One potential interpretation of this putaminal activity is that this represents a learning and memory of prior aversive pain experiences, an idea supported by the co-activity reported in the amygdala-hippocampal complex and sgACC (Gramsch et al., 2014, Kattoor et al., 2014, Vogt, 2005). This supposed link to learnt pain

sensitivity would also concur with the reported independence of the putaminal CBFxVAS relationship and the negative affective scores (catastrophizing and trait anxiety). Together, the reported observation of putaminal activity related to clinical OA pain could likely be related to a learned aversive response to the repeated experience of chronic pain. Interestingly, this finding and interpretation fit with the findings of the CBMA performed in chapter 5 in which it was found that patients displayed increased reports of putaminal activity compared to healthy controls when receiving noxious stimulation at their clinically affected site. It is interesting to postulate whether stimulation of the affected site might be enough (in some cases) to evoke neural activity more encompassing of the affective components related to the chronic pain state. Alternatively, it could simply be due to a state of hyperalgesia at the affected site but these questions are beyond the scope of the current thesis to answer.

The relationship between anxiety and chronic pain has been strongly evidenced and in line with this literature, we report a significant increase in anxiety in OA patients (compared with age and sex matched healthy controls) and a positive correlation between trait anxiety and reported pain intensity (Axford et al., 2010, Marks, 2009). We also report that trait anxiety and pain catastrophizing scores were correlated however when controlled for individually, only the trait anxiety scores accounted for the majority of the VASxCBF relationship. This suggests that self-reported measures of trait anxiety substantially related to the involvement of the limbic brain regions in clinical OA pain perception. Of note, the reported activity within the amygdala in relation to perceived pain was only abolished when controlling for trait anxiety and not catastrophizing. Trait anxiety was not found to mediate this relationship but it is plausible that the effect of trait anxiety on amygdala

activity in pain perception could play a role in the inconsistent reports of amygdala activity in pain imaging literature.

No difference in brain activity was observed in this study between groups which is contradictory to prior studies in OA (Gwilym et al., 2009, Howard et al., 2012). Similar reports of null comparisons have also been published in OA patients experiencing acute experimental pain and in fibromyalgia patients at rest compared to healthy volunteers (Kulkarni et al., 2007, Parks et al., 2011, Shokouhi et al., 2015). One interpretation of this finding is that all of the regions are nonspecific to pain and subsequently, may be carrying out other processes (such as interoceptive, physiological and cognitive) in the healthy volunteers which could well have confounded our comparison. Building upon this line of thought, the fact that the reported CBFxVAS association was not independent of trait anxiety suggests that prior reports of group differences may have been due to a greater difference between patient and volunteer reported anxiety. The study was also potentially hampered by the fact that most of the studied patient cohort were only experiencing mild pain (below three or four out of ten) and anxiety and had been thoroughly prepared to reduce anxiety and discomfort during scanning. This may have again reduced potential differences between groups. Statistical power may also have been low for a group comparison in that only one ASL image was acquired per participant in comparison to the study by Howard et al. (2012), in which four ASL images were acquired per subject (two per session over two sessions).

This study had limitations. Firstly, to minimise the issue of low signal-to-noise ratio (SNR) associated with ASL imaging we utilised a 3D pCASL sequence with background suppression which is known to improve SNR (Dai et al., 2008a). This sequence is however known to be sensitive to motion artifacts and subsequently the conservative quality assurance checking should have

helped avoid these confounding results. Additionally, the 3D acquisition did not allow for concurrent recording of pain scores whilst the cross-sectional design of the study limits the study to observational findings only. Pain (VAS) scores were only recorded prior to scanning and lastly, without a larger sample population, the secondary tests of pain catastrophizing and trait anxiety on VASxCBF interrelation should be considered preliminary but of interest for further validation.

8.4.1 Summary

This study reports that ongoing chronic knee osteoarthritis pain is characterised by increased limbic brain activity in line with prior evidence that there is a strong emotional component of arthritis pain. This observation is further supported by comparison to the results of the pain intensity CBMA carried out in chapter 6 which did not evidence the extent of limbic activity in healthy controls as is seen here related to chronic OA pain. The subsequent finding that controlling for trait anxiety (and to a lesser extent pain catastrophizing) modulated the CBFxVAS relationship also supports this finding.

Whilst the findings here further evidence that ASL (implemented in this fashion) is a sensitive way to look at the activity state of the brain but not the cross-talk or the connectivity between regions in the brain. Although these results present an interesting static ‘snapshot’ of brain activity related to chronic pain, the fact that the pattern of covarying activity with CBF and reported pain is qualitatively altered compared to healthy volunteers (e.g. the pain intensity encoding CBMA in chapter 6) and the brain activity related to acute pain previously found using ASL (discussed in chapter 3) there is evidence enough to suggest the presence of an altered brain state or indeed maladaption due to chronic pain. This evidence of an altered state provides

motivation for the study in chapter 9 in which connectivity between networks in the brain will be investigated to better understand the ‘state’ of the brain in chronic pain and how it has altered in comparison to healthy volunteers.

9 Functional connectivity of the right anterior insula in chronic knee osteoarthritis: a resting-state fMRI study[4]

9.1 Introduction

There has been considerable interest in using neuroimaging to investigate the neural underpinnings of chronic pain. Interestingly, studies focusing on brain responses to evoked pain failed to consistently distinguish patients from healthy volunteers (Parks et al., 2011, Tanasescu et al., 2016). By contrast, resting state fMRI studies regularly report altered functional connectivity (FC) in the default mode network (DMN), thought to relate to interoception and mind wandering, in patients with chronic pain. DMN changes in chronic pain were mainly reported as increased connectivity (Baliki et al., 2011, Baliki et al., 2008a, Baliki et al., 2014, Cauda et al., 2009b, Ceko et al., 2015, Hemington et al., 2016, Kucyi et al., 2014, Loggia et al., 2013, Napadow et al., 2010), while others find the opposite (Baliki et al., 2014, Hemington et al., 2016). The

[4] The work presented in this chapter been published as Cottam, W.J., et al. *Altered connectivity of the right anterior insula drives the pain connectome changes in chronic knee osteoarthritis*. PAIN, 2018, In press (DOI: 10.1097/j.pain.0000000000001209). My role in the manuscript was as lead author, to acquire data, design and performance of all analysis and write the manuscript. Other contributors to the manuscript were Professor Dorothee Auer (concept and design), Dr Sarina Iwabuchi (technical help with analysis and interpretation), Dr Diane Reckziegel and Marianne Drabek (data acquisition). All authors reviewed and commented on the final manuscript.

most common region showing increased FC with the DMN in chronic pain is the insula (Baliki et al., 2011, Baliki et al., 2014, Cauda et al., 2009b, Ceko et al., 2015, Loggia et al., 2013, Otti et al., 2013a) suggesting increased binding between the salience network and DMN. There are, however, surprisingly few studies reporting salience network changes in chronic pain with two studies reporting increased connectivity (Becerra et al., 2014, Hemington et al., 2016), and one no difference compared to controls (Baliki et al., 2014).

Attention to the external world is driven by the salience of perceived stimuli, which is particularly relevant for threatening and painful stimuli. There is a mutual link between, and interdependence of, perception and attention to pain known from everyday life experience and demonstrated at the neural level (Wiech, 2016). A brain network (previously mentioned in chapter 3) that has been implicated in this process has been named the 'salience network' (Seeley et al., 2007). The core salience network (SN) is formed by the bilateral anterior insula and the dorsal anterior cingulate cortex supporting the integration of external information, prior experience, and concurrent homeostatic state, to orient attention (Menon and Uddin, 2010). Coordinate based meta-analysis also found these regions amongst the most commonly activated areas in response to experimental pain, during pain anticipation and relating to pain intensity encoding further emphasising their importance in pain perception (as evidenced by the findings of bilateral insula and ACC activity during pain anticipation and pain intensity encoding in healthy volunteers (see chapter 5)). Therefore, the SN is expected to play a dominant role in chronic pain, a condition thought to represent a maladaptive state of heightened arousal and pain anticipation linked to aversive learning in which the sufferer might continually re-learn the salient value of stimuli (Baliki and Apkarian, 2015, Borsook et al., 2013).

A wide body of functional imaging literature has investigated and discussed the brain networks known as the resting-state networks. These intrinsically organised networks, are proposed to underlie a large body of functions ranging from basic sensory-motor, to higher-order cognitive capabilities (van den Heuvel and Hulshoff Pol, 2010). Three such networks that are particularly well studied are the default-mode network (DMN), the salience network (SN) and the central-executive network (CEN). These networks form a particularly interesting relationship as the DMN is thought to anticorrelate with the CEN (although recent studies throw this simple view into doubt (Dixon et al., 2017, Kucyi et al., 2016) reflecting the underlying neural processes at rest (DMN) and when attending to a task (CEN) whilst the SN coordinates spontaneous switching between the two (Sridharan et al., 2008).

The ability to oscillate between these networks (or to combine them) is increasingly of interest in studying the brain in health and disease. Within the context of the three aforementioned networks, the SN is the only one that responds to the relative salience of a given stimulus be it extrinsic, intrinsic, emotional or cognitive (Craig, 2002, Critchley et al., 2004, Seeley et al., 2007). It is therefore not surprising that this network has been suggested to initiate the spontaneous switching between the two networks during tasks and at rest (Sridharan et al., 2008). This has been further supported by subsequent neuromodulation and dynamic causal modelling studies of fMRI data (Chen et al., 2013, Goulden et al., 2014). Specifically, Chen et al. (2013) employed transcranial magnetic stimulation to either inhibit or excite accessible nodes of the CEN or SN and subsequently measured the effects of actively altering connectivity between these networks and the DMN. They reported that they were able to influence downstream DMN activity by altering the activity of the CEN/SN via targetable cortical hubs. Goulden et al. (2014) then used dynamic

causal modelling (a model-based approach to testing causal/directional information flow) to repeat and reproduce the findings of Sridharan et al (2008) in two separate datasets that the salience network drives the switching between default mode and central executive networks. Specifically, evidence has pointed to the right anterior insula (rAI) – a major hub of the SN - as being important in the coordination of these two brain networks (Menon and Uddin, 2010, Sridharan et al., 2008).

The CEN is postulated to be involved in the preservation and handling of information in working memory and decision making (Sridharan et al., 2008). In chronic pain patients the CEN has been found to show altered functional connectivity with amygdalar and insular regions compared with healthy controls (Napadow et al., 2010, Jiang et al., 2016). CEN-insula connectivity was found to correlate significantly with reported pain intensities whilst amygdalar-CEN connectivity was correlated positively with pain catastrophizing scores (Jiang et al., 2016, Napadow et al., 2010).

Given the importance of the SN in orienting attention, and the primacy of the rAI we hypothesised that chronic pain is characterised by altered rAI functional connectivity which causally alters depending network function (e.g. the DMN and CEN). To test this hypothesis, we utilised seed-to-brain connectivity analysis to assess resting-state networks in subjects with chronic knee osteoarthritis pain compared with age- and sex-matched healthy controls. Comprehensive analysis was then undertaken to assess inter-network connectivity, effective and dynamic connectivity changes and their interrelation with pain characteristics, structural and cerebral blood flow data using available multi-modal data from this cohort (Cottam et al., 2016, Drabek et al., 2017). BOLD fMRI data was utilised for this analysis due to the higher signal-to-noise ratio, temporal and spatial resolution than the acquired ASL data.

9.2 Methods

9.2.1 Participants

Thirty-nine patients with radiographically defined unilateral chronic knee osteoarthritis (15 males; median age 65 years; range 48-84 years; range of pain duration 1-38 years) and twenty-five healthy subjects (8 males; median age 65.5 years; range 51-80 years). None of the recruited subjects had a history or current diagnosis of any psychiatric or neurological illness.

The study was run in accordance with the Declaration of Helsinki and ethical approval was given by the Nottingham Research Ethics Committee 2 (Ref: 10/H0408/115). Signed and informed consent was obtained from all participants before enrolling in the study.

9.2.2 Demographic and questionnaire data

Directly before the scan session, all subjects undertook a battery of psychometric questionnaires including measures of: education (N.B. the lower the score, the higher the level of education), low mood (Beck's Depression Index; BDI), anxiety (State-Trait Anxiety; STAI), pain state (McGill Pain Questionnaire; MPQ) and pain catastrophizing (Pain Catastrophizing Scale; PCS) (Beck et al., 1996, Egerton and Mullan, 2008, Melzack, 1975, Spielberger et al., 1983, Sullivan et al., 1995). Patients also reported their subjective OA pain using a visual analogue scale (VAS scale 0-100; 0 meaning no pain and 100 meaning worst imaginable pain).

9.2.3 MRI Data acquisition

All subjects underwent multimodal MRI at 3T (Discovery MR750, GE Healthcare) using a 32-channel head coil at the Sir Peter Mansfield Imaging Centre (Queen's Medical Centre, University of Nottingham). BOLD fMRI resting-state data is reported here alongside a T1-weighted anatomical image

used for registration purposes. Arterial spin labelling, structural, and magnetic resonance spectroscopy data from this study have been reported separately (Alshuft et al., 2016, Cottam et al., 2016, Reckziegel et al., 2016). Resting-state data consisted of 165 single-echo echo-planar (EPI) volumes acquired over 5 minutes 30 seconds whilst participants were asked to keep their eyes closed and relax (TE/TR=32/2000ms, interleaved acquisition, slice thickness=3.6mm, 35 axial slices parallel to anterior-posterior commissure plane, flip angle=90°, matrix=64x64, field of view=240). This particular scan length of 5 minutes 30 seconds was chosen as a standard minimum needed data length in order to see reproducible fMRI connectivity results (Birn et al., 2013). Although the reliability of subject-level connectivity estimates as you increase scan length (up to a peak of approximately 30 minutes acquisition) (Gordon et al., 2017), this need for reliable observations was also balanced against the overall studies multimodal approach (to allow appropriate time for other MRI acquisitions) and also to minimise participant burden. High resolution 1mm isotropic anatomical images were acquired using a gradient echo sequence (TE/TR=3.324/8.492ms, TI=450ms, slice gap=1mm, field of view=256, matrix=256x256, flip angle=12°).

9.2.4 Data quality assurance

Imaging data underwent a two-step quality checking method (examples can be seen in figure 9.1). Firstly, using an in-house pipeline following criteria outlined in the Function Biomedical Informatics Research Network (FBIRN) study we assessed raw image quality and found that several datasets displayed low quality (e.g. excessive noise in the frequency spectra) (Friedman and Glover, 2006). Secondly, data were excluded if it was of poor quality due to movement (a threshold of =>1mm absolute relative motion). In

total, 20 datasets were discarded (patients=14, controls=6). Group demographics after exclusions can be found in Table 9.1.

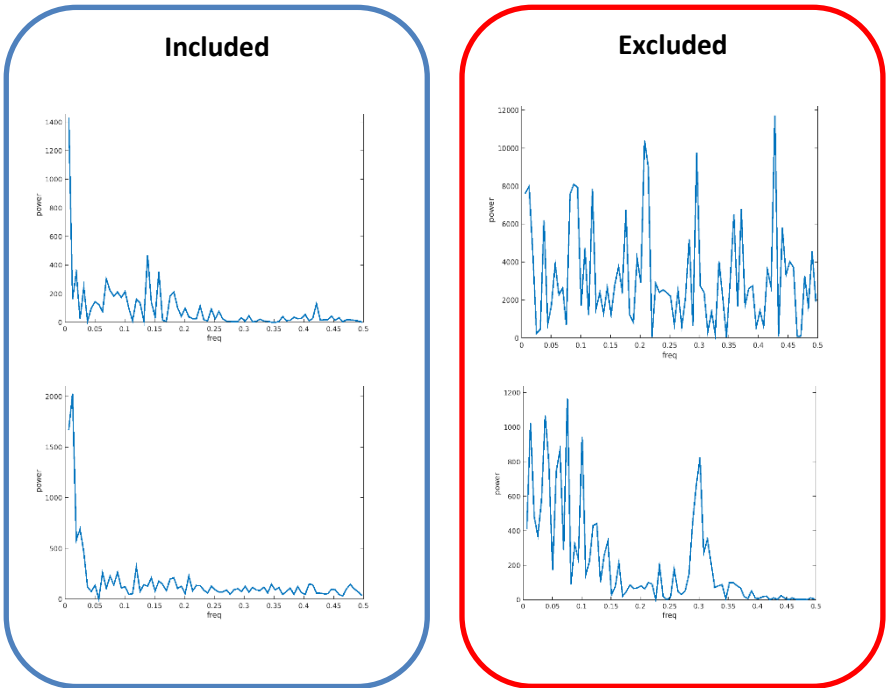


Figure 9.1. Examples of frequency spectra calculated using in-house scripts to assess raw fMRI data quality that led to data being included or excluded from further analysis.

9.2.5 Image preprocessing

Image preprocessing was carried out using FSL 5.0.8 (FMRIB software library) initially performing preprocessing steps including: removal of the first 5 imaging volumes to allow for signal equilibrium effects, high-pass temporal filtering (0.01-Hz cutoff), interleaved slice-timing correction, motion correction (Jenkinson et al., 2002), brain extraction and spatial smoothing (5-mm FWHM). Linear registration (FLIRT) to the T1-weighted image (BBR) and Montreal Neurological Institute standard space (12 degrees of freedom (DOF)) was performed (Jenkinson et al., 2002, Jenkinson and Smith, 2001). Linear registration was utilised over non-linear registration as it proved more robust with the acquired images. All datasets were denoised using ICA+FIX (independent component analysis followed by FMRIB's ICA-based X-noiseifier (Griffanti et al., 2014, Salimi-Khorshidi et al., 2014). To additionally control for

physiological/scanner related noise, time series data were extracted for each subject from cerebrospinal fluid (CSF) and white matter (WM). This was acquired using FMRIB's Automated Segmentation Tool (FAST) to calculate tissue segmentations from the subjects T1-weighted images. The CSF and WM maps were then transformed to fMRI space using the previously calculated transformations and were volume thresholded to retain only the top 20 and 198 cm3 (respectively) to minimise partial volume effects (Chai et al., 2012). Mean CSF and WM time series were then extracted per subject using these masks and regressed out of the data alongside the 6 motion parameters (x, y, z, roll, yaw, and pitch) as part of the subsequent GLM analysis (Bright and Murphy, 2015). Global signal regression was not carried out.

The denoising strategy used was an informed choice based upon testing of different strategies. This work culminated in a poster presented at ISMRM 2017 (of which I was first author) in which I investigated the correlation between global signal, WM and CSF and components from the aCompCor approach (in which the time series from WM and CSF undergoes primary component analysis and the first 5 components time series are used for regression) (Behzadi et al., 2007). There is no best approach for all studies in regards to denoising and regression strategies and as such there will always be disagreement and variations in the field of strategies taken to do this. For instance, two independent papers both made observations similar to that which I found which was the application of the aCompCor approach led to findings which were very similar to those seen when applying global signal regression, an observation also reported by other independent groups (Siegel et al., 2016, Ciric et al., 2017). For this reason, alongside the evidence that global signal regression has been seen to mathematically force the presence

of anticorrelations I chose not to use either of these approaches (Murphy et al., 2009, Murphy and Fox, 2017).

9.2.6 Seed-based connectivity

Seed-based connectivity was calculated using three 6mm spherical regions of interest (ROIs) to investigate the three networks of interest using the: SN - right anterior insula (rAI; MNI coordinates [MNIxyz] = 32, 16, 6), CEN - the left dorsolateral prefrontal cortex (lDLPFC; MNI coordinates [MNIxyz] = -46, 20, 44) and the DMN - posterior cingulate cortex (PCC; MNI coordinates [MNIxyz] = -8, -50, 28) based on previously published coordinates (Hemington et al., 2016, Uddin et al., 2011) (see figure 9.2 for visualisation).

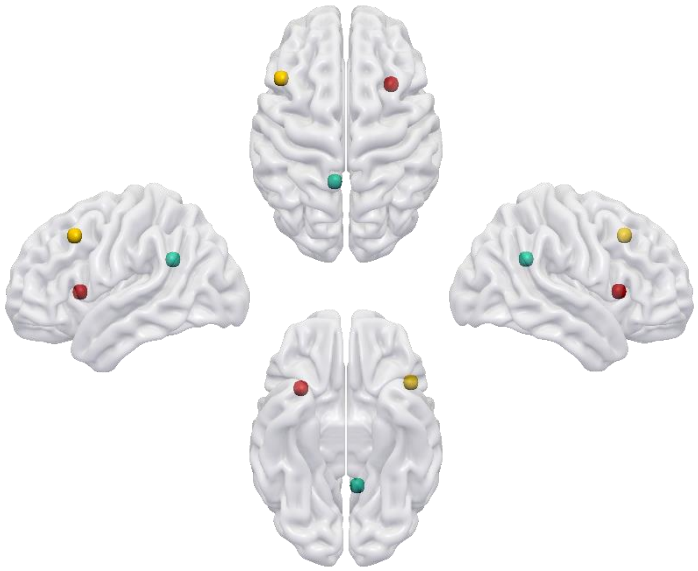


Figure 9.2. Brain maps displaying the three seed regions: the right anterior insula (red), the left dorsolateral prefrontal cortex (yellow) and the posterior cingulate cortex (green).

9.2.7 Inter-network connectivity

Measures of functional connectivity between networks were calculated by means of a) correlative connectivity and b) Granger Causality measures. Correlative connectivity was assessed by using the three extracted timeseries (used as regressors in the seed-based connectivity analysis) for the rAI,

LDLPFC and PCC. Pearson correlation coefficients were calculated between these three timeseries per subject and then the Fisher r-to-z transformation was applied.

Bivariate first-order coefficient-based voxelwise Granger causality analysis (GCA) was calculating using the REST fMRI toolbox (Song et al., 2011). GCA calculates an estimate of the causal effect of a region of interest on each voxel in the brain (X to Y effect) as well as the reverse (Y to X effect). A positive coefficient from X to Y specifies that activity in the region of interest exerts a positive influence on the activity of a specific region. Conversely, a negative coefficient from X to Y indicates that activity in the region of interest exerts a negative influence on the activity of a specific region. Seed-to-whole-brain Granger scores were calculated for each of the three ROI's per subject. For each seed region, mean Z-values were extracted from the remaining two ROIs from the x2y contrast only. ROI values were extracted to focus on the interaction between key network regions as opposed to whole-networks.

9.2.8 Dynamic functional connectivity

To assess intra-network variability, a sliding-window analysis was performed to calculate standard deviation using an in-house Matlab code (courtesy of Dr Xingfeng Li). The three networks were defined by performing group ICA analysis (multi-session temporal concatenation) on all 44 subjects via FSL Melodic (v3.14) limited to 25 components. DMN, CEN and SN components were then visually assessed (see figure 9.3).

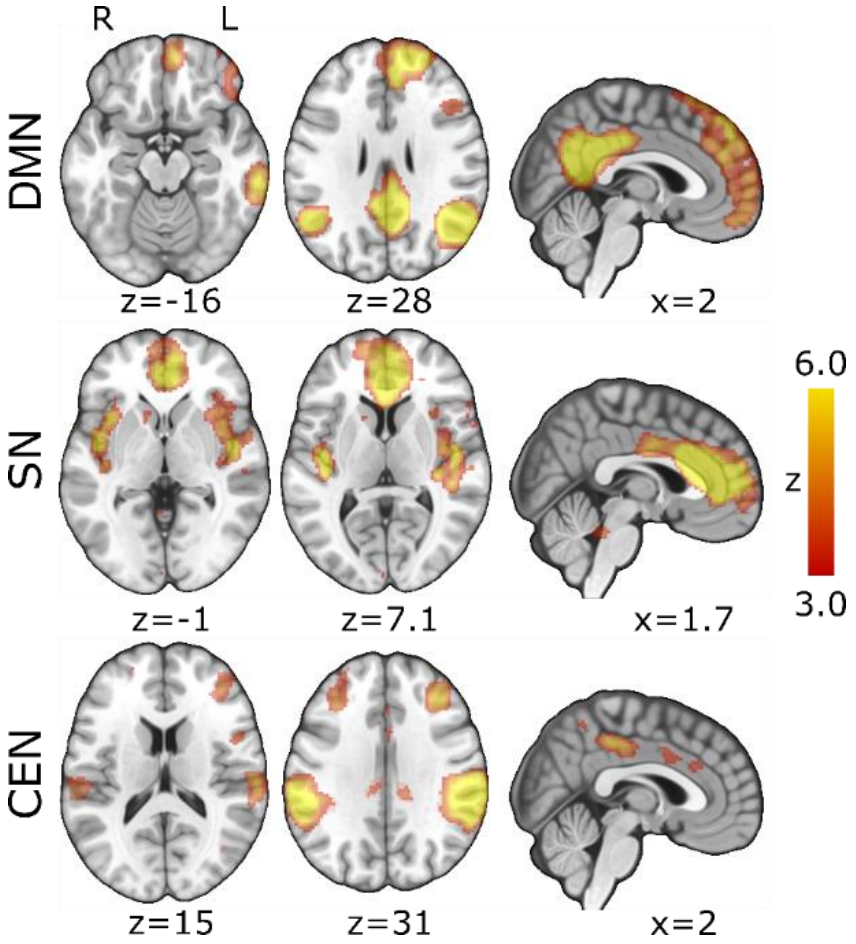


Figure 9.3. Brain maps displaying the default mode, salience and central executive networks resulting from group independent component analysis. Images are shown in radiographic format (right hemisphere is on the left) and thresholded at Z=>3.0 for visualisation.

These components were then thresholded at Z=<2.3 and back-registered into subject space to use as masks in the sliding-window analysis. Intra-network analysis was performed by breaking the networks down into their individual clusters and then extracting time series by using singular value decomposition (to reduce the effect of outlier values on the extracted time series) from the respective clusters. A window of 100 seconds or 50 TR's was used as this corresponds to the frequency of 0.01 Hz - the lowest frequency of interest. Pearson correlation coefficients were then calculated per window and underwent Fishers r-to-z transformation. The standard deviation of these correlation values over all windows was calculated per connection per person.

These standard deviation values were subsequently taken into further analysis.

9.2.9 Multimodal data

To further characterise changes observed from these three seed regions, cerebral blood flow (CBF) and grey matter densities from participants (from which data was available) were extracted. CBF data was taken from previously published material whilst grey matter density was calculated by using the FSL VBM toolbox (Cottam et al., 2016, Drabek et al., 2017). Grey matter density was then extracted by back-registering the seeds into subject space.

9.2.10 Statistical tests

Demographic data (age, gender), questionnaire scores (BDI, PCS, STAI) and levels of mean relative motion recorded during the fMRI scan were compared between groups using independent sample t-tests in Minitab 17.2.1. Measures of inter-network connectivity were also compared using two-sample t-tests within Minitab 17.2.1. Significance for these tests was set at $p<0.05$.

For subject-level image analyses, time series from each of the 3 ROI's were used as predictors in individual regression models including 8 nuisance covariates (CSF, WM & six motion parameters) using FSL FEAT giving a total of 9 event variables included. Whole-brain positive and negative correlations with each network ROI were calculated per subject. Group-level analyses were controlled for mean relative motion (Hlinka et al., 2010), and statistical analysis was carried out using FLAME 1 (a mixed-effects general linear model within FSL; FWE-corrected $Z>2.3$, cluster significance $p<0.05$) comparing connectivity in OA patients vs healthy controls. Four contrasts were ran at the

group level per network: OA group mean, HC group mean, OA > HC and HC > OA.

Relationships between regions where functional connectivity was found to be significantly different between patients and controls were investigated in Minitab 17.2.1 using stepwise linear regression. Z-scores from the brain regions were entered as dependent variables whilst all other reported measures (pain at time of scanning, pain duration, MPQ subscores; sensory, affective and evaluative), neuropathic-like symptoms, anxiety, low mood and catastraphising subscales were entered as independent variables in the model. Holmes-Bonferroni multiple-test correction was employed for these regression analyses.

9.3 Results

9.3.1 Demographics

No significant group differences were found in age, gender, catastraphising or mean relative motion during the fMRI scan (P=0.36) between patients and controls. Educational, low mood and anxiety scores were however significantly different between OA patients and healthy controls. See table 9.1 for details.

Table 9.1
Patient Demographics and group differences

Data	Knee OA patients	Healthy Controls	P-value
N.	25	19	-
Median age (range)	65.0 (54-84)	65.0 (51-80)	0.21
N. Males	12	8	0.697[#]
Laterality of affected knee	12 left / 13 right	-	-
N. Right-handed	24[*]	16	-
Median Educational Scores	5[*]	3	0.014[#]
VAS 0-100	27.8 (0-70)	-	-
PainDETECT	11.9 (1-23)	-	-
PD: Nociceptive	13	-	-
PD: Unclear	10	-	-
PD: Likely-Neuropathic	1	-	-
BDI (range)	7.5 (0-19)	2.5[**] (0-12)	0.002
STAI-S	33.4 (20-55)[**]	27.8 (20-49)[**]	0.082
STAI-T	40.7 (22-70)[*]	31. 8 (22-52)[*]	0.016
PCS	13.3 (1-38)[*]	13.7 (0-29)	0.859
PCS: Helplessness	5.2 (0-14) [*]	5.1 (0-13)	0.905
PCS: Magnification	2.6 (0-9) [*]	2.7 (0-5)	0.828
PCS: Rumination	5.5 (0-15) [*]	6.7 (0-20)	0.390

Displayed are the mean (range) values and p-values from independent samples t-tests unless elsewise specified. BDI – Beck's Depression Index, PD – PainDETECT grouping, STAI-S – State Anxiety, STAI-T – Trait Anxiety, PCS – Pain Catastrophizing Scale. [*]1 subject data missing, [**]2 subjects data missing, [#]Chi-Square test.

9.3.2 Seed-based connectivity of the SN, DMN and CEN

Seed-based functional connectivity of the SN (seeded within the right AI) displayed significant and consistent connectivity in both subject groups within core SN regions such as the bilateral anterior insula, the mid-anterior cingulate cortex (mACC) with further clusters observed within the bilateral putamen, caudate heads, frontal poles, the right amygdala and temporoparietal junction. Patients displayed connectivity with the left temporoparietal junction and the right precentral gyrus (Figure 9.4, Table 9.2). Group comparisons revealed a cluster in the cuneus that displayed increased connectivity in patients compared healthy controls. The reverse contrast (controls>patients) revealed several clusters that were significantly different between groups in a range of areas associated with the DMN including the PCC, bilateral parietal areas and the superior frontal gyrus (FWE P<0.05).

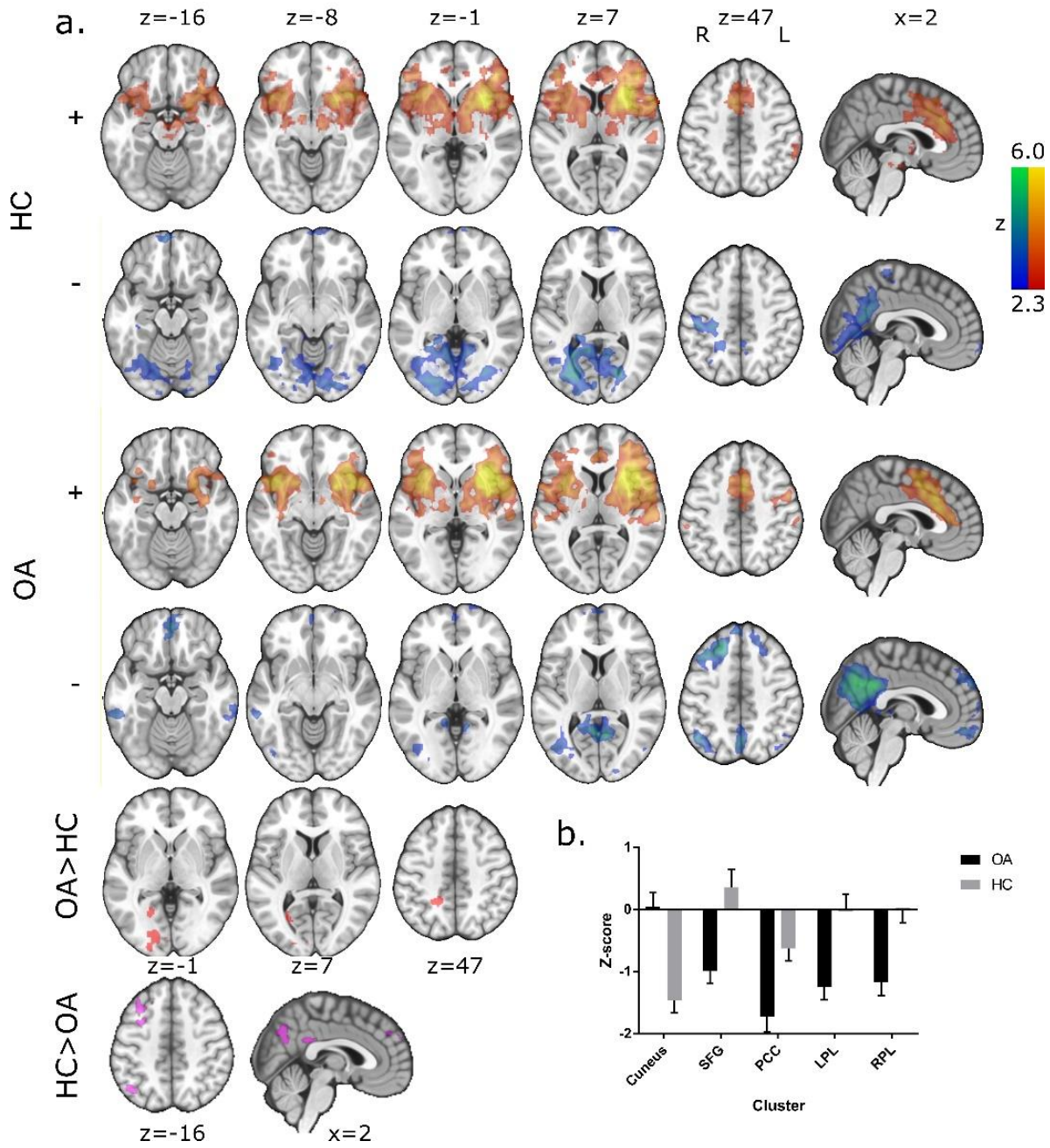


Figure 9.4. Positive and negative (denoted by the symbols + and -) resting-state connectivity of the right anterior insula in a) healthy controls (HC), chronic knee osteoarthritis patients (OA) and differences between these groups (FWE $p<0.05$) and b) mean (+SEM) z values of those clusters displaying a significant group difference are displayed on a bar graph to visualise the anticorrelations observed in chronic knee osteoarthritis patients. All images in a. are displayed in radiographic format (right hemisphere is displayed on the left of the figure).

Table 9.2.
Regions of significant seed-based connectivity of the right anterior insula / salience network.

Anatomical regions	Cluster extent	X	Y	Z	Z-score
HC					
R. Putamen	23974	28	14	4	7.54
R. Anterior insula		35	17	3	7.36
R. Middle frontal gyrus		39	46	23	5.08
L. Anterior insula		-32	20	4	4.45
Anterior cingulate		3	25	30	4.86
R. Middle frontal gyrus		-33	48	22	3.78
R. Thalamus		15	-15	4	3.63
L. Putamen		-25	5	8	3.29
L. Thalamus		-6	-15	2	3.26
R. Inferior parietal lobule	1498	64	-30	32	3.97
OA		-22	-6	-12	3.62
R. Anterior insula	16659	34	16	4	8.62
R. Supramarginal gyrus		62	-38	35	4.72
R. Thalamus		6	-12	2	4.24
R. Frontal pole		33	49	28	4.06
L. Anterior insula	8907	-38	12	2	5.9
L. Frontal pole		-32	42	26	3.74
L. Supramarginal gyrus		-64	-33	28	2.99
L. Thalamus		-10	-16	2	2.74
Juxtapositional lobule	5049	0	2	56	5.66
OA>HC					
L. Lingual gyrus	467	-18	-80	2	3.82
L. Precuneus	408	-14	-52	52	4.14
HC>OA					
L. Medial frontal gyrus	1197	-8	50	34	3.57
L. Posterior cingulate	876	-10	-46	28	3.87
R. Lateral occipital gyrus	724	48	-68	30	3.44
L. Angular gyrus	428	-58	-58	30	3.33

Results are FWE-corrected (Z>2.3, cluster-based threshold of p<0.05) and reported in MNI152 standard space. L. – Left, R. – Right, Cluster extent – the number of voxels within a cluster..

Upon inspection, it was found that rather than the clusters displaying increased (positive) connectivity in controls, the reality was that the connectivity was significantly more negative in all clusters within the patient group and vice versa for the finding in the cuneus (see figure 9.4b for graphical representation).

Seed-based functional connectivity of the DMN (seeded within the PCC) displayed significant consistent connectivity across both subject groups within the core DMN regions such as the PCC/precuneus, the medial prefrontal cortex and the lateral parietal regions. Additional connectivity was observed within the bilateral thalami, hippocampi and the lateral frontal cortex (Figure 9.5, Table 9.3). Comparisons between patients and healthy control groups revealed no significant differences.

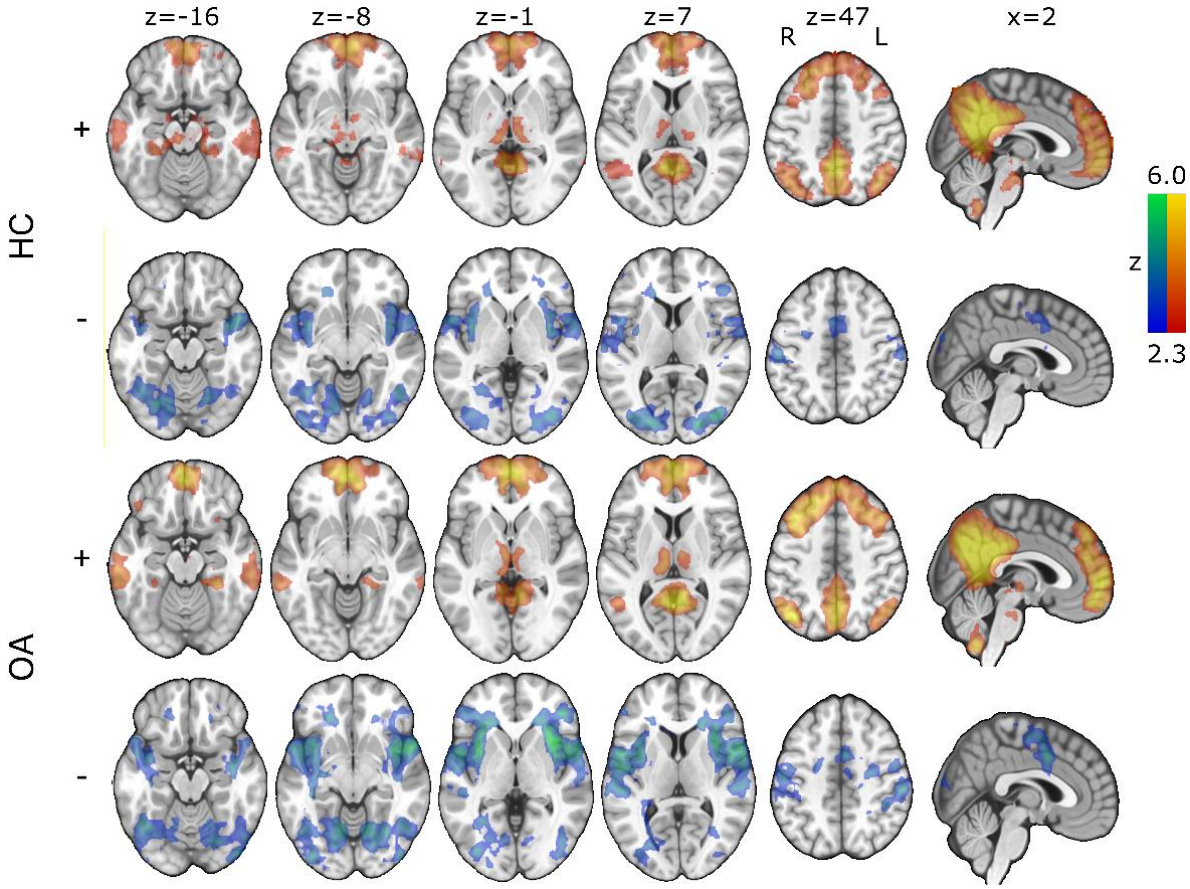


Figure 9.5. Positive and negative (denoted by the symbols + and -) resting-state connectivity of the posterior cingulate cortex in a) healthy controls (HC), chronic knee osteoarthritis patients (OA; FWE $p<0.05$). All images are displayed in radiographic format (right hemisphere is displayed on the left of the figure).

Table 9.3.
Regions of significant seed-based connectivity of the posterior cingulate / default mode network.

Anatomical regions	Cluster extent	X	Y	Z	Z-score
HC					
L. Posterior cingulate	17042	-8	-54	28	8.01
L. Lateral occipital gyrus		-52	-66	32	5.94
L. Superior frontal gyrus	14099	-4	58	28	5.66
L. Medial frontal gyrus		-4	57	9	5.34
R. Lateral occipital gyrus	3877	48	-60	26	5.9
R. Middle temporal gyrus	1764	56	2	-37	4.8
L. Middle temporal gyrus	1740	-56	-4	-28	5.39
R. Cerebellum	1642	26	-82	-44	5.0
L. Cerebellum	1013	-35	-72	-54	3.82
R. Cerebellum	627	4	-54	-50	4.27
OA		-22	-6	-12	3.62
L. Superior frontal gyrus	17827	-20	28	40	6.93
R. Medial frontal gyrus		3	59	0	6.43
R. Superior frontal gyrus		16	24	57	5.29
L. Middle frontal gyrus		-40	18	53	5.19
R. Middle frontal gyrus		37	17	57	4.26
L. Posterior cingulate gyrus	16478	-6	-48	30	9.25
L. Angular gyrus	4410	-52	-58	22	7.12
L. Middle temporal gyrus	2552	-62	-6	-32	5.47
R. Temporal pole	2007	56	6	-35	4.28
R. Cerebellum	1796	30	-76	-40	5.44
L. Cerebellum	1336	-20	-86	-28	4.60
L. Cerebellum	1172	-2	-56	-52	5.54
Brain stem	747	-2	-22	-30	4.83

Results are FWE-corrected (Z>2.3, cluster-based threshold of p<0.05) and reported in MNI152 standard space. L. – Left, R. – Right, Cluster extent – the number of voxels within a cluster..

Seed-based functional connectivity of the CEN (seeded within the left DLPFC) displayed significant consistent connectivity in both subject groups within the core CEN regions including the bilateral DLPFC and posterior parietal cortices. The clusters within the bilateral DLPFC extended into the medial prefrontal regions whilst additional clusters were also observed in the PCC, the bilateral middle temporal gyri, cerebellum and the bilateral thalami. Comparisons between patient and healthy control groups revealed a single cluster of significant difference (controls>patients; FWE P<0.05) that extended

superiorly from the right temporal pole and insular cortex into the inferior frontal gyrus (Figure 9.6, Table 9.4).

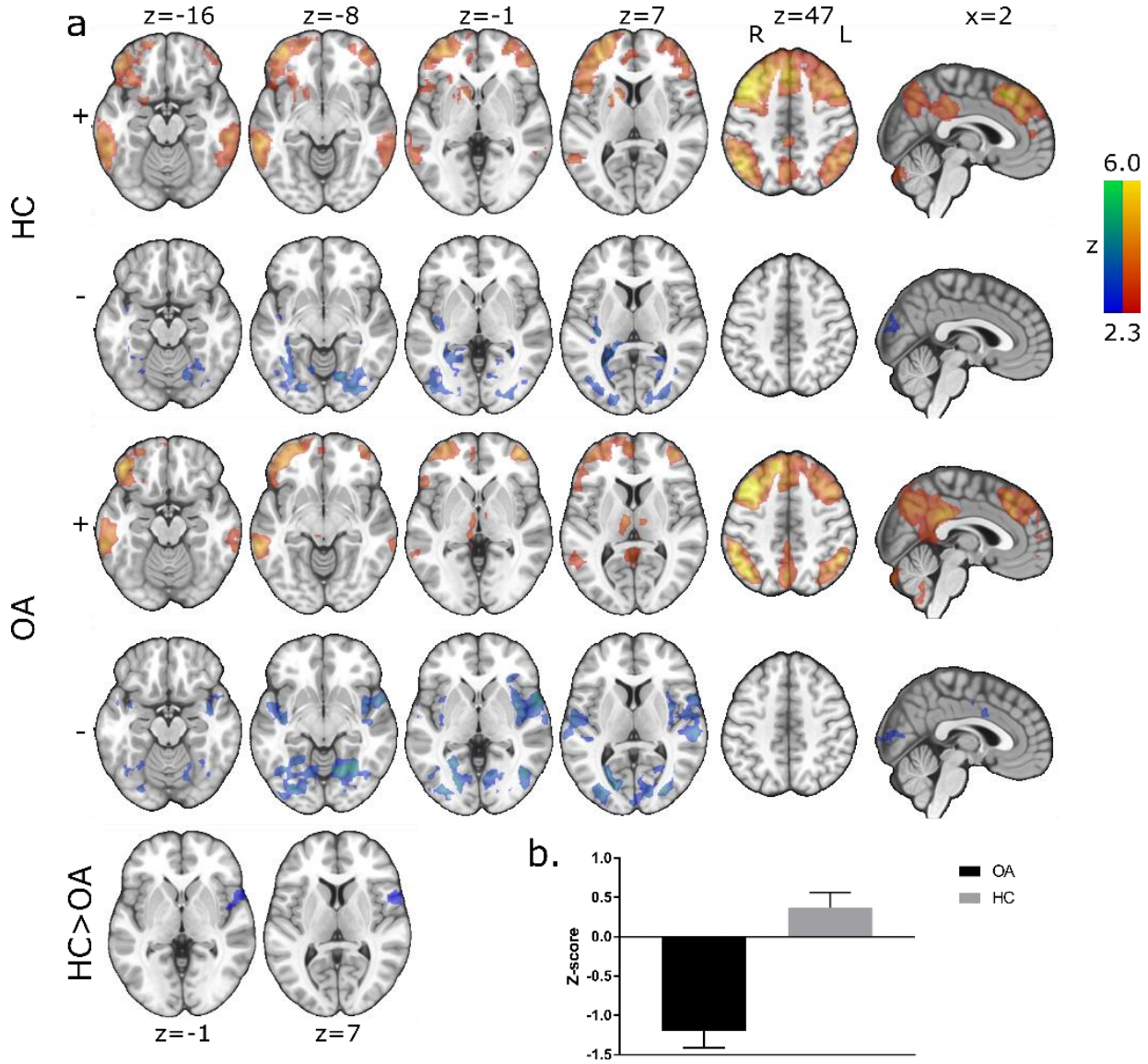


Figure 9.6. Positive and negative (denoted by the symbols + and -) resting-state connectivity of the left dorsolateral prefrontal cortex in a) healthy controls (HC), chronic knee osteoarthritis patients (OA) and differences between these groups (FWE $p<0.05$). B) Mean (+SEM) z values of those clusters displaying a significant group difference are displayed on a bar graph to visualise the anticorrelations observed in chronic knee osteoarthritis patients. All images are displayed in radiographic format (right hemisphere is displayed on the left of the figure).

Table 9.4.
Regions of significant seed-based connectivity of the left dorsolateral prefrontal cortex / central executive network.

Anatomical regions	Cluster extent	X	Y	Z	Z-score
HC					
L. Middle frontal gyrus	23577	-46	20	42	7.81
L. Superior frontal gyrus		3	30	49	5.58
R. Middle frontal gyrus		46	10	42	4.25
L. Caudate		-12	12	1	3.80
L. Putamen		-19	10	3	3.22
L. Anterior insula		30	21	-5	3.26
L. Lateral occipital cortex	14409	-50	-60	46	6.07
R. Angular gyrus		52	-54	50	5.07
L. Precuneus		-6	-62	40	4.90
L. Middle temporal gyrus		-58	-36	-10	4.89
L. Posterior cingulate gyrus		-6	-46	34	4.57
R. Cerebellum	4055	14	-80	-36	5.01
L. Cerebellum		-36	-70	-33	4.40
R. Inferior temporal gyrus	1446	60	-30	-18	4.25
OA					
L. Lateral occipital gyrus	19702	-54	-62	36	7.06
L. Posterior cingulate gyrus		-1	-36	32	5.53
L. Middle temporal gyrus		-64	-36	-12	5.42
L. Thalamus		-8	-12	6	4.90
L. Precuneus		-2	-68	46	4.71
R. Thalamus		6	-16	4	3.81
L. Middle frontal gyrus	19101	-42	22	46	8.53
L. Paracingulate gyrus		-2	34	34	6.41
R. Cerebellum		34	-70	-38	5.84
R. Middle frontal gyrus		46	12	42	5.16
L. Cerebellum		-36	-68	-50	5.15
L. Frontal pole		-2	56	-10	3.32
R. Angular gyrus	3620	52	-50	46	5.74
R. Frontal pole	814	40	54	2	5.72
R. Middle temporal gyrus	665	70	-42	-6	4.14
HC>OA					
R. Temporal pole	501	58	12	-2	4.28
R. Insula		38	-1	-12	2.82

Results are FWE-corrected (Z>2.3, cluster-based threshold of p<0.05) and reported in MNI152 standard space. L. – Left, R. – Right, Cluster extent – the number of voxels within a cluster.

9.3.3 Between-network hub functional and effective connectivity

Seed-to-seed functional connectivity as estimated via Pearsons correlations were calculated and assessed for between group differences. No significant differences were found between patient and healthy control cohorts in connectivity between the rAI-PCC (*t*(41)=-0.06, P=0.95), rAI-lDLPFC (*t*(41)=0.11, P=0.92), or the PCC-lDLPFC (*t*(41)=1.53, P=0.13).

In contrast, effective connectivity between ROI's revealed a significant difference between groups from rAI->PCC (*t*(33)=-2.26, P=0.03). No other calculated Granger coefficients were found to be significantly different between groups: rAI->lDLPFC (*t*(33)=-1.57, P=0.13), lDLPFC->rAI (*t*(33)=-1.31, P=0.20), lDLPFC->PCC (*t*(33)=-0.65, P=0.52), and PCC->rAI (*t*(33)=-1.40, P=0.17) with a trend from PCC->lDLPFC (*t*(33)=1.89, P=0.07) (see figure 9.7 for graphical representation of seed-to-seed information flow [whether positive or negative] as calculated via Granger causality analysis).

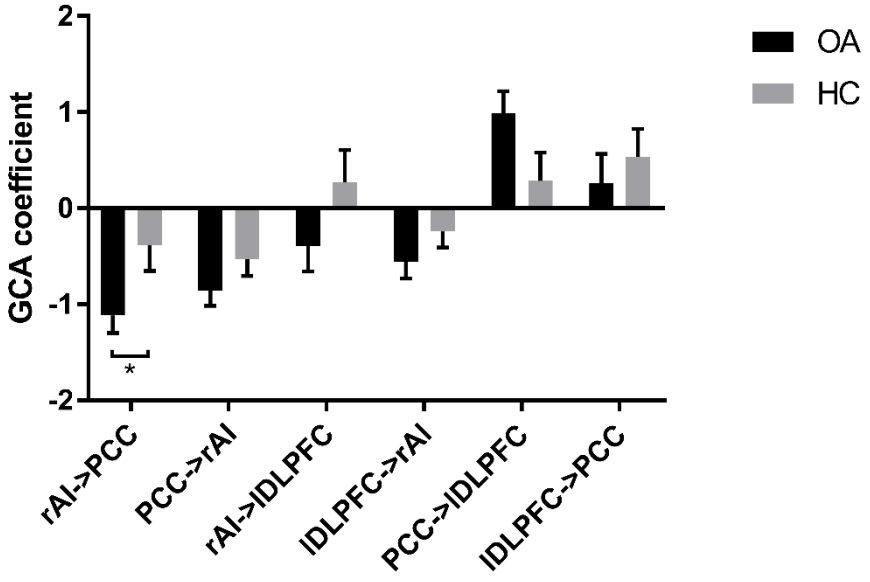


Figure 9.7. Graphical visualisation of mean (+SEM) group values for calculated seed-to-seed Granger Causality coefficients. Key: OA – osteoarthritis patients, HC – healthy controls, rAI – right anterior insula, PCC – posterior cingulate cortex, lDLPFC – left dorsolateral prefrontal cortex, * - significant at p<0.05.

9.3.4 Dynamic connectivity

Intra-network connectivity also displayed significantly reduced variability within the DMN in patients compared to healthy controls ($t(42)=2.873$, P=0.006). SN and CEN networks displayed no significant differences between patients and controls. Post-hoc assessment of different sliding window sizes found that these findings were consistent across sizes from 20-50 TR's (figure 9.8).

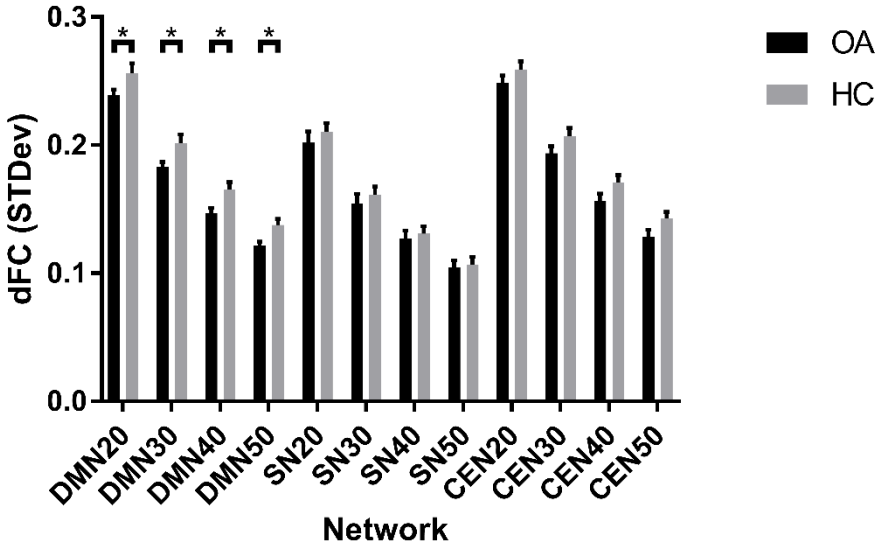


Figure 9.8. A bar graph displaying the group means (+SEM) of calculated dynamic functional connectivity over sliding windows starting from sizes of 20 TR's (40 seconds) up to 50 TR's (100 seconds). Key: dFC – dynamic functional connectivity, STDev – standard deviation, OA – osteoarthritis patients, HC – healthy controls, DMN – default mode network, SN – salience network, CEN – central executive network.

9.3.5 Associations with demographic data

Exploratory analyses of those clusters found to be significantly different between groups revealed several associations between reported pain and psychological scores. Firstly, group differences from the SN network comparison in the PCC and superior frontal gyrus were found to be correlated with reported pain intensities in patients ($t(22)=2.68$, P=0.015 and $t(22)=2.1$, P=0.048 respectively). The difference in CEN connectivity between groups found within the right temporal gyrus also correlated with trait anxiety ($t(22)=$-

2.26, P=0.035). These relationships were not significant after multiple-test correction (see figure 9.9 for visualisations of these three correlations).

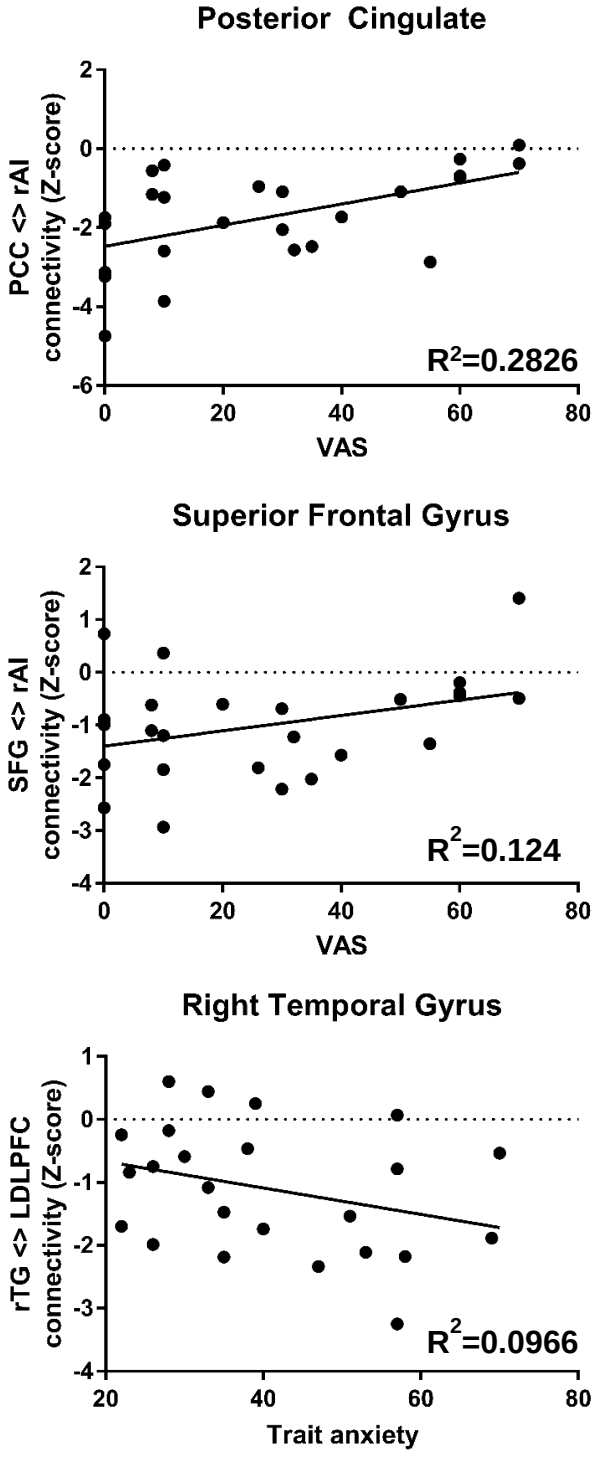


Figure 9.9. Scatter plots displaying correlations of seed-based connectivity (taken from clusters of significant functional connectivity differences between osteoarthritis and healthy control groups) in the posterior cingulate (PCC), the superior frontal gyrus (SFG) and the right temporal gyrus (rTG) with reported pain severity (VAS) and trait anxiety. Key: rAI – right anterior insula, LDLPFC – left dorsolateral prefrontal cortex. NB. These correlations were not significant after multiple-test correction.

9.3.6 Associations with multimodal data

The acquired multimodal dataset allowed further scrutiny of the observed FC and effective FC changes. We were able to assess whether these changes were reflective of an altered state of brain activity (related to the ongoing pain) or morphometry (structure). Subsequently, we assessed the average (mean) CBF from each of the three network hub ROIs hypothesising that the observed FC changes would be mirrored by CBF group differences. These tests observed no significant differences in CBF between OA and HC groups in any of the three network hubs.

Relationships between brain structure and the observed FC changes were assessed via correlation analysis. Average (mean) grey matter density of the three network hub ROIs were correlated with observed FC changes but no significant correlations were found.

9.4 Discussion

In this study, we undertook a comprehensive resting-state connectivity analysis of the static and dynamic pain connectome to investigate a possible key role of the right anterior insula in chronic pain. We found increased anticorrelations between the SN and nodes within the DMN, and between the CEN and the left temporal gyrus/insula in patients with chronic OA knee pain compared to pain-free controls. Importantly, we also found increased negative effective connectivity (as measured by Granger causality analysis) from the rAI to the PCC suggesting an increased negative influence exerted by the SN on the DMN. Moreover, temporal variability of DMN FC was reduced in patients and thus more alike the lower variability seen in SN. Taken together, our findings of static, effective and dynamic FC changes in chronic OA pain suggest that the rAI may play an important role in the altered pain connectome in OA (see figure 9.10 for pictorial example).

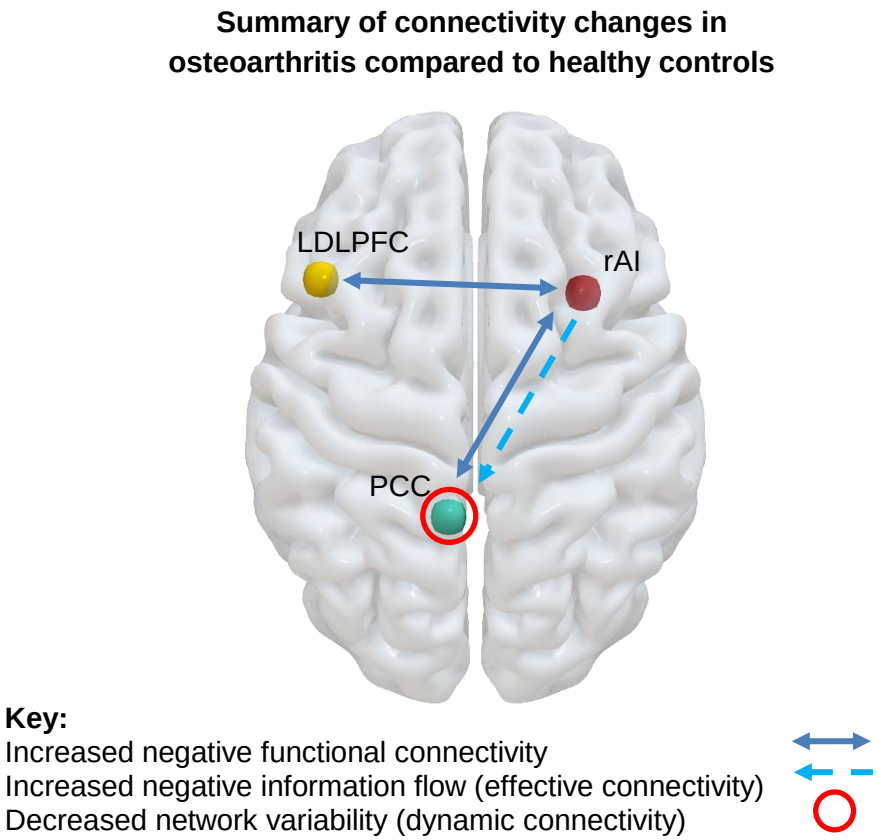


Figure 9.10. Pictorial summary of the differences in connectivity in chronic osteoarthritis pain patients compared to healthy controls. Functional connectivity (solid blue lines) displayed increased anticorrelations between the right anterior insula (rAI; red sphere) and both the posterior cingulate cortex (PCC; green sphere) and left dorsolateral prefrontal cortex (LDLPFC; yellow sphere) in osteoarthritis patients. Effective connectivity analysis (Granger causality analysis) evidenced an increase in negative information flow (dashed blue line) between the rAI and the PCC. Dynamic connectivity analysis found that the default mode network (based upon the PCC within this picture) displayed less variability in osteoarthritis patients compared with healthy controls.

Our study provides evidence that the rAI may drive the altered pain connectome as we found selective effective connectivity changes with an enhanced negative influence of the rAI on the DMN. Patients displayed an increased negative influence of the rAI->PCC which offers a plausible mechanistic explanation for the observed increased negative connectivity found in the seed-based SN network. Previous studies have evidenced the causal influence of the SN onto the DMN using time-lag and Granger causality analyses showing that the rAI displayed the highest number of outflowing causal connections and the lowest number of inflowing causal connections

(Goulden et al., 2014, Sridharan et al., 2008). Further mechanistic evidence was given by a subsequent study using excitatory and inhibitory transcranial magnetic stimulation (TMS) to interrupt these relationships showing that excitation of CEN/SN nodes induced negative between-network connectivity with the DMN whilst inhibitory TMS resulted in disinhibition of the DMN (Chen et al., 2013). Within the context that altered salience may contribute to or form part of the suffering in chronic pain (Borsook et al., 2013), it is then plausible that neuroplasticity changes in the SN caused by the repeated salient and/or painful sensations that characterise chronic pain may underpin observed altered intra-network and inter-network connectivity changes. That is to say, the continual aversive resonance of the internal brain state (measured here as BOLD fMRI connectivity) due to persistent OA pain may be the underlying cause of this observed plasticity. This persistent pain can modulate brain networks for instance, Borsook et al. (2013) present a model in which chronic pain impacts on the salience network creating a negative feedback loop. This negative feedback loop impacts on salience processing by causing it to be innately sensitised to pain-relevant inputs and also maladapted in response to external cues/stimuli. Expanding on this, it has also been theorised that chronic pain and negative affect form a continuum of aversive learning, and considering the importance of the SN and its known connectivity with limbic regions, it is likely that this continuous re-learning may be reflected by changes in the SN (Baliki and Apkarian, 2015). Such a notion is supported by our exploratory findings of both anxiety and pain severity relating to functional SN and CEN connectivity in patients (which did not survive multiple-test correction).

The study of dynamic network changes may be particularly revealing to understand abnormal network architecture characterised by the inability to

switch between states. The neurophysiological basis of network dynamics and the best ways to measure them is an emerging area of active research (Hutchison et al., 2013). This study observed reduced temporal variability (indexed as standard deviation) within the DMN but not the SN or CEN in patients with chronic OA. Impaired temporal fluctuation of the DMN FC has been reported in a number of diseases including major depression (Kaiser et al., 2016) and bipolar disorders (Nguyen et al., 2017). Reduced FC variability has been interpreted to reflect impaired switching between brain states characterised by more segregated subnetworks. Behavioural correlation studies found that reduced variability of FC between networks and/or regions is associated with lower performance in behavioural tasks in healthy controls and with slower processing speed in patients with bipolar disorder compared to controls (Jia et al., 2014, Nguyen et al., 2017). In the context of chronic pain, the observed stronger inhibitory influence of the rAI on the DMN may offer an explanation why within DMN switches may be suppressed. The tonic input of chronic pain could affect the dynamic ability of the brain to switch between networks, leading to the continual re-learning of salience – a hypothesis supported by current data showing altered connectivity between- and within-networks (Borsook et al., 2013). Interestingly, healthy individuals whose cognition was more impacted by a pain distractor, or reported a reduced ability to disengage from pain-related thoughts displayed reduced variability between brain regions (Cheng et al., 2017, Kucyi and Davis, 2015, Kucyi et al., 2013). This suggests that impaired dFC may be an additional important hallmark of the chronic pain connectome that may reflect the inability to detach from clinical pain.

We report here that patients with chronic OA pain display significantly more anticorrelation between the rAI and DMN regions suggesting an altered brain

state at rest characterised by increased inhibitory effect of the SN on the DMN. This is interesting as previous reports of group differential DMN-insular connectivity are not consistent in their direction. For instance, several studies report increased (more positive) connectivity in patients (Baliki et al., 2011, Cauda et al., 2009b, Loggia et al., 2013, Napadow et al., 2010), whilst others report decreased positive connectivity or increased anticorrelations (Baliki et al., 2014, Ceko et al., 2015). Whilst differential DMN-insula connectivity is a consistent finding in the pain literature, the different directions suggest additional factors that modulate the direction of the connectivity alteration. One such influence could be reported pain severity, a factor that we found relates to rAI-PCC connectivity (although not significant after multiple-test correction) which is in-line with previous studies that also report relationships between pain and DMN-insula connectivity in multiple pain cohorts (Baliki et al., 2014, Napadow et al., 2010). Perceived pain severity in general and during scanning may explain the discrepant findings of reduced anticorrelated connectivity of the SN and DMN found in patients with ankylosing spondylitis compared to controls (Hemington et al., 2016), and potentially our finding of no difference in DMN connectivity between groups.

In addition to the major findings within the SN, connectivity of the CEN, specifically in a cluster encompassing the right middle temporal gyrus/inferior frontal gyrus/mid-insula, was found to be negative in patients whilst controls displayed generally positive connectivity. This cluster is placed almost completely within the SN network, further pointing to the importance of the SN network and its altered inter-network connectivity. Additionally, connectivity within this cluster correlated with trait anxiety in patients such that subjects with the highest levels of anxiety displayed the highest anticorrelation. This is interesting in the context that anxiety disorders have previously been related

to hyperactivity of the AI within the SN network (Paulus and Stein, 2006, Seeley et al., 2007). Thus, given the known influence of the SN on the CEN, it is possible that increased anxiety (a common comorbidity of chronic pain) plays a role in the maladaptation of SN-CEN connectivity.

DMN alterations are the most commonly reported network changes in chronic pain yet we found no such group DMN FC difference (Baliki et al., 2008a, Becerra et al., 2014, Cauda et al., 2009b, Kucyi et al., 2014, Loggia et al., 2013, Napadow et al., 2010, Otti et al., 2013a). It is possible that differences could be due to different patient cohort, subgroups (with more severe pathology) or analytical choices. For instance, several of these studies used ICA-based connectivity methods and the majority that did perform seed-based connectivity analyses used ROI's based within the medial prefrontal cortex rather than the PCC. Additionally, this study performed relatively conservative quality assurance on the data which may have also further differentiated findings from previous reports.

The reported altered connectivity between networks is similar to reported inter-network effective connectivity changes that have been reported in mental health disorders such as schizophrenia and major depressive disorder (Iwabuchi et al., 2014, Palaniyappan et al., 2013). Interestingly, neuromodulatory treatment has been shown to impact on these inter-network connections in these conditions and as such could also be applied in the context of chronic pain. For instance, recent work has shown in healthy controls that individually targeted theta-burst TMS (excitatory stimulation) to the DLPFC alters effective connectivity of the anterior insula (Iwabuchi et al., 2017). Thus, the reported altered effective connectivity of the rAI may present as a plausible target for such neuromodulatory treatment.

The present study had some limitations that impact on what can be inferable from the findings. Firstly, the study is limited by its cross-sectional design and as such only allows for observational findings. Secondly, the reported VAS found to correlate with connectivity was only reported prior to the scan and as such we cannot confirm that the same level of pain persisted after the scan session. Lastly, temporal resolution would ideally be higher than 2 seconds when performing effective connectivity analyses such as those carried out in this report. However, recent studies have argued that effective connectivity results from fMRI can be reproduced at much higher resolutions (e.g. using MEG) lending weight to our use of such techniques (Mill et al., 2017, Wang et al., 2014).

9.4.1 Summary

We present novel and comprehensive pain connectome analysis in patients with chronic OA pain and propose the rAI as key region driving static and dynamic network connectivity changes. Whilst complementing theories of altered salience in chronic pain, these findings also present a novel target and network metrics to mechanistically assess efficacy of neuromodulatory treatments.

10 General Discussion

10.1 Summary of the results

The main goals of this thesis were to 1) uncover whether there was a consistent significant difference in acute pain processing between healthy volunteers and chronic pain cohorts, 2) to determine how perceived levels of chronic osteoarthritis pain are represented by neural activity and whether they interrelate with reported negative affect, and 3) to assess whether these osteoarthritis patients displayed differential connectivity in resting-state networks. The findings presented within this thesis, derived from MRI and thorough pain phenotyping, provide new knowledge about the sensitivity of acute experimental pain as an investigative tool into chronic pain, neural activity related to perceived chronic osteoarthritis pain and its interrelation with negative affect, and the relationships between- and within-brain networks and their integrity in chronic pain populations. These findings should stimulate fresh thoughts on the fMRI approaches used to study chronic pain and how to potentially target aberrant neural mechanisms for treatment.

The key findings were:

1) **Using the largest and most homogeneous data to date, we found that acute experimental pain produces a consistent pattern of co-varying brain activity in both healthy volunteers and chronic pain cohorts. Even with this large dataset, no significant difference in brain activity associated with acute experimental pain was observed between healthy volunteers and chronic pain patients. This finding suggests that this experimental approach is not**

sensitive and probably not relevant in the search to understand the neural processes underlying chronic pain. Experimental pain lacks the personal subjective and affective values associated with ongoing chronic pain (although exceptions to this are acknowledged such as mechanical stimulation of brush-evoked allodynia or functional use of joints to evoke joint pain). Subsequent comparison of painful stimulation of the clinically affected site vs. non-affected sites displayed significant differences. This suggested that the site of stimulation was an important experimental factor.

2) **Comparisons of studies of hyperalgesia (as a model of chronic pain) were inconclusive when compared with acute experimental pain in healthy volunteers. This suggests that this approach models increased peripheral input, but is not enough to model the subjective and affective components of chronic pain.**
3) **Coordinate based meta-analysis of low mood models of chronic pain was inconclusive due to a lack of studies.**
4) **Coordinate based meta-analysis of brain activity associated with pain anticipation revealed a co-reported network of brain regions associated with the salience network (bilateral insula and mid-cingulate). Unsurprisingly this revealed a network of brain regions known to be involved in the modulation attention towards salient stimuli e.g. pain. This potentially provides an experimental approach in which the value accorded to pain could be investigated in subsequent experiments.**
5) **Reported pain intensity in chronic osteoarthritis knee pain is associated with increasing brain activity in limbic-affective regions. This relationship was markedly reduced when**

controlling for reported trait anxiety. These results build upon the known interrelation between negative affect and chronic pain and point toward a potential target for treatment.

6) **Seed-based functional connectivity analysis of the salience network revealed increased anticorrelation with the default mode network in patients, a finding paralleled by increased negative information flow from the right anterior insula (salience network hub) to the posterior cingulate cortex (default mode hub). By investigating complementary measures of connectivity (functional (i.e. correlative) and effective (Granger causality analysis) connectivity), reported differences were able to be better interpreted. This finding goes beyond previous reports of simple group differences in functional connectivity and points toward a potential target for neuromodulatory treatment approaches.**
7) **Intra-network dynamic functional connectivity analysis observed reduced variability within the default mode network in patients compared to controls suggesting a downstream effect of the observed aberrant insular connectivity in which the usually lower variability of the salience network was subsequently enforced upon the default mode. This downstream effect could potentially be an example of why so many prior studies find default mode network differences between chronic pain patients and controls.**

All of these findings are novel and significantly advance our understanding of the neural mechanisms underlying chronic osteoarthritis knee pain.

10.2 Limitations and methodological problems

There are several limitations on the reported research that should be appropriately considered. Firstly, the coordinate based meta-analysis (chapter 3) approach is inherently a low-powered approach due to the fact that you are simply clustering points in space with no related statistical weighting. It was this knowledge that led us to take the approach of obtaining the largest and most homogeneous data sample possible. For instance, it would have been simple to include other data such as visceral and chemical stimulations but for the fact that these new sensory pathways introduce increasing heterogeneity into the data sample. Cutaneous stimulation was chosen as it was the most commonly published approach used to try and navigate this limitation. In an ideal world, if all imaging data was available from all studies and image-based meta-analysis would have been carried out but this is not realistic currently. Attempts to make this avoid this in future are underway with resources such as neurovault.org providing a databank to which researchers can upload un-thresholded statistical maps which are what would be used for image-based meta-analysis. Additionally, the author has subsequently published a new method to perform coordinate based meta-analysis in which the approach of 'censored-statistics' are utilised (Tench et al., 2017). In essence, this approach uses data commonly reported in fMRI manuscripts (such as clustering thresholds and cluster peak statistics) to assume a minimum voxel value across the whole-brain and then to perform meta-analysis on these.

Another limitation of this thesis is the study sample sizes. For example, within the arterial spin labelling study (chapter 8) this is in part due to the conservative data quality assessment in light of the knowledge that the sequence was sensitive to motion artefacts. The sample size sits well in comparison to other studies especially considering that the primary hypothesis

was a within-group regression which is statistically stronger at this size than a between-group comparison. It does however leave the secondary findings (including trait anxiety and pain catastrophizing as confounding variables) as preliminary findings and as such they should be replicated and/or further investigated in subsequent experiments. The sample size of the resting-state fMRI study in chapter 9 was above the required number set out originally and is also favourable in comparison to most of the comparative literature in patients but would be strengthened by increased samples. The conservative approach also taken with this dataset in both quality assurance and the preprocessing pipeline should mitigate this argument to some degree. For instance, many of the previous functional connectivity studies in chronic pain do not explicitly report having done quality assurance and denoising steps and as such some of the prior results may be due to poorly controlled motion and physiological confounds. Motion and physiological confounds remain a large topic of research especially in BOLD fMRI and as such the approaches used in this thesis to control for them represent the best approach known at the time of writing. For instance, newer automated approaches such as ICA-AROMA for fMRI motion denoising present very well in comparison to many optional pipelines (see (Siegel et al., 2014, Ciric et al., 2017, Pruim et al., 2015)) and the choice to not perform global signal regression was made in the knowledge that it could potentially force anticorrelation which was unwanted.

10.3 Future directions

A couple of future directions were previously alluded to in this thesis. Here I expand upon those and some other avenues of research that I think would be most fruitful moving forward. Specifically, the use of non-classical pharmacological and neuromodulatory interventions in the treatment of

chronic pain alongside the benefits mechanistic longitudinal studies in which predisposing or causal factors may be found and targeted.

Firstly, the use of pharmacological and neuromodulatory treatments such as opioids and behavioural training have previously shown mixed effects and to date, chronic pain relief remains ineffective on average. However, an example of a possible off-label treatment is duloxetine for the treatment of chronic OA pain. The drug itself is mainly used as an anti-anxiolytic and to a lesser extend an anti-depressive. It is a selective serotonin-norepinephrine reuptake inhibitor (SNRI) that has previously been found to have significant pain relief effects in chronic osteoarthritis but the mechanism of this pain relief is unknown. It is tempting to hypothesise that the drug might reduce the affective components of the pain and that the known interrelation between reported affect and pain severity might lead to a relationship in which treating either pain severity of affect could reduce the other. I have had an ongoing role in a locally run study of duloxetine treatment in osteoarthritis patients based at the University of Nottingham in which this particular line of thinking is being studied (see Reckziegel et al. (2017) for the published study protocol). This study (although not yet completed) has been the basis of one of my colleagues' thesis (D. Reckziegel) and I am involved in the study for data collection and analysis.

Neuromodulatory treatments such as transcranial magnetic stimulation (mentioned in chapter 9) present as non-invasive treatments that could potentially normalise maladaptive brain connectivity (such as that reported in chapter 9) back to a more normal level. Studies of depressed individuals have shown the efficacy of such a treatment and it is of great interest in pain also but the question is whether the correct approaches are being taken. Are we stimulating/correcting the proper brain regions and are we correcting in the right direction by which I describe that the connectivity of one's brain is

variable in relation to many external and internal stimuli. Subsequently, the connective state of a participant at the time of stimulation might be increased or decreased and as such neuromodulatory approaches should take this into account. I acknowledge that both of these approaches are difficult with many peripheral effects that have to be taken into account, the placebo effect for example. Future studies of this kind will need to carefully take this factors into account otherwise null treatment effects will likely be the consequence. We are actively applying for funding for such a project in which I am a co-applicant helping to design the study.

Longitudinal studies remain the gold-standard for attributing predisposing or causal factors to disease progression. A recent example of this published a 3 year follow-up study of back pain patients who present initially with subacute back pain. They were then followed up intermittently over 3 years using questionnaire, MRI and genetic data. One of the main findings from Vachon-Presseau et al (2016) is that connectivity between the prefrontal cortex and the medial temporal cortices was predictive of transition from subacute to persistent back pain. This connection is predominantly a dopaminergic pathway and subsequently that lab are now working on several clinical trials looking to use dopaminergic precursors to try and treat chronic back pain. More locally, I am now involved in two studies building upon the work presented within this thesis and others. One – a longitudinal study of pain progression assessing participants with recent onset of knee pain over two years with the aim to predict pain progression and two, a large-scale observational study aimed at phenotyping patients with chronic knee osteoarthritis pain in order to identify subgroups of patients whom might be treatable via differing mechanisms. Both studies are using multimodal imaging (structural, functional and metabolic imaging) alongside a battery of

phenotyping questionnaires and quantitative sensory testing to characterise these participants. Specifically, I am project managing the phenotyping study whilst being actively involved in the administrative running and data acquisition for both studies.

10.4 Conclusion

This thesis utilises complementary primary and secondary research approaches to investigate the neural underpinning of chronic OA knee pain and chronic pain more broadly. It can be concluded via coordinate based meta-analysis that acute experimental pain is not a sensitive approach to the study of chronic pain in that it lacks that subjective components that are so important to the perception of chronic pain. Subsequent fMRI studies further support this with the finding that a reported relationship between reported OA pain intensity and brain activity was almost completely accounted for when including trait anxiety scores into the statistical model. Additionally, analysis of resting-state fMRI in chronic knee OA patients displayed altered salience network connectivity with the default mode network. This relationship was observed in the absence of overt stimuli (noxious or not) and as such furthers the argument for not using acute experimental pain. From a basic scientific perspective, this thesis reveals changes in brain activity and connectivity related to chronic osteoarthritis pain and supports the view of interrelated pain and affect in chronic pain populations. These findings could subsequently be translated into clinical treatment approaches that might target the reported anxiety or between-network connectivity via pharmacological or neuromodulatory approaches.

11 References and appendices

11.1 References

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11.2 Appendices

11.2.1 Forms used in the ImPOA study

As the ImPOA study is still ongoing under various study extensions, the forms presented here will be of the latest applicable versions used for the cohort studied within this thesis. These forms will be presented in the following order:

Participant information sheet for Knee OA patients

Participant information sheet for healthy controls

Consent form for knee OA patients

Consent form for healthy controls

Recruitment poster

MRI safety questionnaire

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The University of Nottingham

PATIENT INFORMATION SHEET

"Imaging to Understand Pain in Osteoarthritis"

Name of Investigators: *Prof Dorothee Auer, Prof David Walsh, Prof Brigitte Scammell, Prof Michael Doherty, Prof Nadina Lincoln, Dr Laura Condon, Dr Jennifer Dixon, Mr Hamza Alshuft, Ms Anita French, Dr Naranjargal Dashdorj, Ms Maggie Wheeler*

You have been invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish to. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part or not. If you decide to take part you may keep this leaflet. Thank you for reading this.

Background

People with Osteoarthritis (OA) feel pain in their joints, particularly in the knee. This means that they may experience a persisting chronic pain which is processed in a specific way by the brain. By comparing the brains of patients with OA, patients with other musculo-skeletal pain, and healthy volunteers with no pain, we hope to better understand the nature of knee pain in OA.

Why have you been chosen?

You have been asked to take part because you have either:

- Been diagnosed with OA,
- Been diagnosed with musculo-skeletal lower back pain.
- You have previously taken part in research in Academic Rheumatology at The University of Nottingham.
- You have previously taken part in this program of research via questionnaire study (REC reference: 10/H0403/70),

What will happen to me if I take part?

If you volunteer you will be asked to complete some health questionnaires by post and attend the Division of Academic Radiology at the Queen's Medical Centre, or the Sir Peter Mansfield Magnetic Resonance Centre at the University of Nottingham on up to three occasions. During your visits you may be asked to do some or all of the following:

- Undergo an MRI scan of your knee.
- Undergo an MRI scan of your brain
- Undergo a quantitative sensory test (QST) to examine your threshold to different temperature and pressure sensations.
- Fill out some health questionnaires,
- Undergo an MRI scan of your brain as you feel manual pressure applied to your knee.
- You may also need to undergo an x-ray of your knee if there is no recent one available which was taken as part of your routine clinical care.

The MRI scans can take place in up to two or three separate visits. This will be discussed with you by the investigator upon your first visit. If you are taking any strong painkiller

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medications or NSAID's we would like you to stop taking them for 24 hours prior to your MRI scan and take paracetamol instead. Also, on the morning of your visit we may ask you to take a sample of your saliva in a container which we will provide for you and bring it along to your appointment.

Do you have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. Your level of ongoing care will not be affected should you choose to take part, or not to take part. If you do decide to take part, we would like to seek your permission to contact you again in the future regarding other research studies taking place at The University of Nottingham.

What will happen to any samples I give?

The samples will be analysed for levels of the hormone, cortisol, which is associated with stress. The samples will not become part of a human tissue bank and will be destroyed after the analysis is complete.

What are the benefits of taking part?

It is not thought that you will directly benefit from the research visits, as we are not trialling a new treatment or therapy. However, you will be helping us to better understand osteoarthritis pain which could in turn benefit you, and other osteoarthritis patients, in the future through the development of more effective treatment methods. The MRI scans are not, however, used for diagnostic purposes in individual cases, and are not reviewed for this purpose.

What are the possible disadvantages and risks of taking part?

In the event that a recent knee x-ray has not been carried out as part of routine clinical investigation we may need you to undergo a knee x-ray for which you will be exposed to a small amount of ionising radiation. This level of risk is deemed 'trivial' by The Health Protection Agency (HPA), and in radiation terms, is equivalent to approximately 34 days natural background radiation or a single flight to New York.

Part of the QST procedure uses a small device (Peltier Thermode) applied to the skin which will become warm, and cool in temperature, and part of the procedure uses another small device (Pressure Algometer) to press against your knee.

As described above, during one of the scans, you will feel a little pressure on your knee. This may be a little uncomfortable for you, and you can request that we stop at any time. Taking part will also mean taking time out of your normal activities, which may be for a few hours. This may inconvenience you, though we will be as flexible as we can with arranging a suitable time and day, and we will reimburse travel costs (30p per mile if you have driven or had a lift and full reimbursement of public transport travel upon production of the appropriate receipts).

It is possible that if the MRI scan is undertaken by a pregnant woman it will harm the unborn child. Pregnant women, or women who plan to become pregnant during the study period, must not therefore take part in this study. Women who are at risk of pregnancy may be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. Women who could become pregnant must use an effective contraceptive during the course of this study. Any woman who finds that she has

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become pregnant while taking part in the study should *immediately* tell the research doctor.

As the MRI scan uses a magnetic field you should not take part in this study if you have any metallic foreign bodies in your body (Eg. Pacemaker, aneurysm clips, shrapnel, other metal fragments). Body piercings are allowed providing they can be removed.

In the unlikely event that we should discover any significant unexpected findings on your MRI brain scans, MRI knee scans or knee x-ray, we will ask you to nominate whether you wish us to disclose this information to your GP, who will then discuss it with you. In some cases you will need to disclose a significantly abnormal finding to your employer, and it may affect your insurance status.

What if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)

We will seek permission to inform your GP should any abnormal findings be detected on your MRI brain scan, MRI knee scan, or knee x-ray, who will then inform you of the findings, rather than the research clinician.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact Professor Dorothee Auer in the first instance, telephone 0115 823 1178. If you remain unhappy and wish to complain formally, you can do this through NHS complaints. Details can be obtained from the Patient Advice and Liaison Service (PALS) at QMC by calling 0800 1830204

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept on a password protected database and is strictly confidential. Any information about you which leaves the research unit will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

The results will be published in medical journals and will be submitted as part of a PhD thesis. You will not be identified in any way in any report or publication. If you ask, we can send you a summary of our findings when the project finishes.

Who is organising and funding the research?

This work is supported by the University of Nottingham and Arthritis Research UK.

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Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Nottingham Research Ethics Committee.

Expenses & Payments

Your travel expenses will be reimbursed upon production of a receipt/ticket. Alternatively, if you have travelled to your appointment using your own vehicle, your travel expenses will be reimbursed at 30p per mile.

Contact for Further Information

If you have any questions please feel free to contact:

Maggie Wheeler
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HEALTHY VOLUNTEER'S INFORMATION SHEET

"Imaging to Understand Pain in Osteoarthritis"

Name of Investigators: ***Prof. Dorothee Auer, Prof. David Walsh, Prof. Brigitte Scammell, Prof. Michael Doherty, Prof. Nadina Lincoln, Dr. Laura Condon, Dr. Jennifer Dixon, Mr. Hamza Alshuft, Ms Maggie Wheeler***

You have been invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish to. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you decide to take part you may keep this leaflet. Thank you for reading this.

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Patients with Osteoarthritis (OA) feel pain in their joints, particularly in the knee. This means that they may experience a persisting chronic pain which is processed in a specific way by the brain. By comparing the brains of patients with OA and the brains of healthy volunteers we hope to better understand the nature of knee pain in OA.

What does the study involve?

If you volunteer you will be asked to complete some health questionnaires by post and attend the Division of Academic Radiology at the Queen's Medical Centre, or the Sir Peter Mansfield Magnetic Resonance Centre at the University of Nottingham on up to three occasions. During these visits you may:

- Have an x-ray of your knee
- Undergo an MRI scan of your knee.
- Undergo an MRI scan of your brain at rest
- Undergo a quantitative sensory test (QST) to examine your threshold to different temperature and pressure sensations.
- Fill out some health questionnaires,
- Undergo an MRI scan of your brain as you feel manual pressure applied to your knee.
- Undergo an MRI scan of your brain after you have walked up and down for a little while.

The MRI scans can take place in up to three separate visits. This will be discussed with you by the investigator upon your first visit. Also, we may ask you to take a sample of your saliva in a container (which we will provide for you) and bring it along to your appointment.

Why have you been chosen?

You have been asked to take part because we need to compare patients with OA to healthy people of a similar age.

Do you have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. If you decide to take part in the study it may be that you are not called upon because we need to age-match the healthy control group to the OA patient group, however, we would like to seek your permission to contact you again in the future regarding other research studies taking place at The University of Nottingham.

What will happen to any samples I give?

The samples will be transferred to a commercial laboratory where they will be analysed for levels of the hormone, cortisol, which is associated with stress. They will not become part of a human tissue bank and will be destroyed after the analysis is complete.

What are the possible benefits of taking part?

It is not thought that you will directly benefit from the research visits. However, you will be helping us to better understand osteoarthritis pain which could in turn benefit osteoarthritis patients in the future through the development of more effective treatment methods.

The MRI scans are not used for diagnostic purposes in individual cases, and are not reviewed for this purpose.

What are the possible disadvantages and risks of taking part?

We will need you to undergo an x-ray of your knee to confirm the health of your joint, which will mean that you will be exposed to a small amount of ionising radiation. This level of risk is deemed 'trivial' by The Health Protection Agency (HPA), and in radiation terms, is equivalent to approximately 34 days natural background radiation or a single flight to New York.

Part of the QST procedure uses a small device (Peltier Thermode) applied to the skin which will become warm, and cool in temperature, and part of the procedure uses another small device (Pressure Algometer) to press against your knee.

As described above, during one of the scans, you will feel a little pressure on your knee. This may be a little uncomfortable for you, and you can request that we stop at any time. Taking part will also mean taking time out of your normal activities, which may be for a few hours. This may inconvenience you, though we will be as flexible as we can with arranging a suitable time and day, and we will reimburse travel costs (30p per mile if you have driven or had a lift and full reimbursement of public transport travel upon production of the appropriate receipts).

It is possible that if the MRI scan is undertaken by a pregnant women it will harm the unborn child. Pregnant women must not therefore take part in this study, neither should women who plan to become pregnant during the study. Women who are at risk of pregnancy may be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. Women who could become pregnant must use an effective

contraceptive during the course of this study. Any woman who finds that she has become pregnant while taking part in the study should *immediately* tell her research doctor.

As the MRI scan uses a magnetic field you should not take part in this study if you have any metallic foreign bodies in your body (Eg. Pacemaker, aneurysm clips, shrapnel, other metal fragments). Body piercings are allowed providing they can be removed.

In the unlikely event that we should discover any significant unexpected findings on your MRI brain scans, MRI knee scans or knee x-ray, we will ask you to nominate whether you wish us to disclose this information to your GP, who will then discuss it with you. In some cases you may need to disclose a significantly abnormal finding to your employer, and it may affect your insurance status.

What if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw from the study at any time, without giving a reason, and without your legal rights being affected. If you withdraw from the study then the information collected so far will not be erased and this information will be carried forward to be used in the project analysis.

Involvement of the General Practitioner/Family Doctor (GP)

We will seek permission to inform your GP should any significant unexpected findings be detected on your MRI brain scan, MRI knee scan, or knee x-ray, who will then inform you of these findings, rather than the research clinician.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact Professor Dorothee Auer in the first instance, telephone 0115 823 1178. If you remain unhappy and wish to complain formally, you can do this through NHS complaints. Details can be obtained from the Patient Advice and Liaison Service (PALS) at QMC by calling 0800 1830204

In the unlikely event that you suffer injury to yourself or damage to your property as a result in taking part in this research, the University does have an insurance policy to cover harm arising as a result of the defect in the design of the study. In addition, all medical practitioners taking part in the research have personal medical negligence cover.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept on a password protected database and is strictly confidential. Any information about you which leaves the research unit will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

The results will be published in medical journals and will be submitted as part of a PhD thesis. You will not be identified in any way in any report or publication. If you ask, we can send you a summary of our findings when the project finishes.

Who is organising and funding the research?

This work is supported by the University of Nottingham and Arthritis Research UK.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Nottingham Research Ethics Committee.

Expenses & Payments

Your travel expenses will be reimbursed upon production of a receipt/ticket. Alternatively, if you have travelled to your appointment using your own vehicle, your travel expenses will be reimbursed at 30p per mile.

Contact for Further Information

If you have any questions please feel free to contact:

Maggie Wheeler
Division of Academic Rheumatology, University of Nottingham, CSB Building, City Hospital Campus, Nottingham, NG5 1PB
Tel: 0115 823 1676, Email: maggie.wheeler@nottingham.ac.uk

Or, the Chief Investigator:

Professor Dorothee Auer, Division of Academic Radiology, University of Nottingham, QMC Campus, Derby Road, Nottingham, NG7 2UH
Tel: 0115 8231178, E-mail: dorothee.auer@nottingham.ac.uk

Nottingham University Hospitals NHS
NHS Trust

The University of Nottingham

CONSENT FORM
(Version 1.6 date 27/07/2012)

Title of Study: **Imaging to Understand Pain in Osteoarthritis**

REC ref: **10/H0408/115**

Name of Researchers: Prof. Dorothee Auer, Prof. David Walsh, Prof. Brigitte Scammell, Prof. Michael Doherty, Prof. Nadina Lincoln, Dr. Laura Condon, Dr Jennifer Dixon, Mr. Hamza Alshuft, Ms Anita French, Dr Naranjargal Dashdorj, Ms Maggie Wheeler

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 1.6 dated 27/07/12 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I agree to my GP being informed of my participation in this study. ☐

5. Should there be any abnormal findings on either the MRI scans, or x-rays taken as part of this study, I agree to my GP being contacted.

GP name/address.....

6. I agree to having a saliva sample taken ☐

7. I agree to take part in the above study. ☐

8. **Only for those people who participated in the recent questionnaire study on knee pain in osteoarthritis (REC reference: 10/H0403/70):**
   - I give permission for access to my results from questionnaire study (REC reference: 10/H0403/70) (Optional) ☐

9. I give permission for the data from this study to be accessed by researchers from the ARUK Pain Centre ☐

10. I agree to being contacted regarding future research studies (optional) ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Nottingham University Hospitals NHS
NHS Trust

The University of Nottingham

CONSENT FORM
(Version 1.5 date 27/07/12)

Title of Study: Imaging to Understand Pain in Osteoarthritis
REC ref: 10/H0408/115
Name of Researchers: Prof. Dorothee Auer, Prof. David Walsh, Prof. Brigitte Scammell, Prof. Michael Doherty, Prof. Nadina Lincoln, Dr. Laura Condon, Dr Jennifer Dixon, Mr. Hamza Alshuft, Ms Anita French, Dr Naranjargal Dashdorj, Ms Maggie Wheeler

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 1.5 dated 27/07/12 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4a I agree to having a saliva sample taken. ☐

4b I agree to having an x-ray of my knee. ☐

5. Should there be any significant unexpected findings on either the MRI scans, or x-rays taken as part of this study, I agree to my GP being contacted ☐

Name/Address of GP.....

.....

6. I give permission for the data from this study to be accessed by researchers from the ARUK Pain Centre ☐

7. I agree to take part in the above study. ☐

8. I agree to being contacted regarding future research studies. (optional) ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

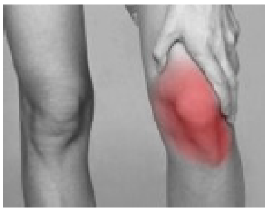
The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Radiological and Imaging Sciences
School of Clinical Sciences
Faculty of Medicine and Health

HEALTHY VOLUNTEERS REQUIRED, 45+

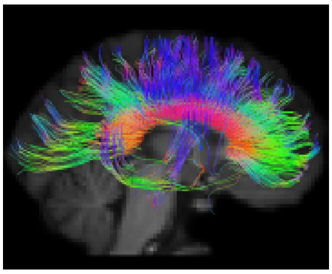
Imaging to understand pain in osteoarthritis

We are looking for healthy volunteers with no knee problems to take part in a brain imaging study aimed at better understanding the pain experienced by patients with Osteoarthritis.

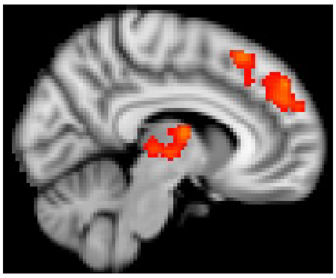


You will be required to attend the Queens Medical Centre, on up to three occasions during which you will be asked to complete a pain questionnaire and undergo an MRI brain scan, and an MRI scan of your knee.

YOU MUST BE:



- Over 45 years old;
- Not Pregnant;
- Have no significant medical conditions;
- Have no metal in your body (Eg. pacemaker, aneurism clips).



Final version 2.1 31.07.2012

FOR MORE INFORMATION, PLEASE CONTACT:

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The University of Nottingham

HILF/Medical School MRI scanners

MR Volunteer Safety Screening Questionnaire:

NAME	Date of Scan	Date of Birth
ADDRESS	Volunteer Number	
	Ethics Code	
Phone number	Weight	Height if applicable

MR scanning uses strong magnetic fields. For your own safety and the safety of others it is **very important** that you do not go into the magnet halls with any metal in or on your body or clothing. Please answer the following questions carefully and ask if anything is not clear. All information is held in the strictest confidence.

1. Do you have any implants in your body? e.g. replacement joints, drug pumps Y/N
2. Do you have aneurysm clips (clips put around blood vessels during surgery)? Y/N
3. Do you have a pacemaker or artificial heart valve? *(These stop working near MR Scanners)* Y/N
4. Have you ever had any surgery? Please give brief details over. Y/N
   (We do not need to know about uncomplicated caesarean delivery, vasectomy or termination of pregnancy)
5. Do you have any foreign bodies in your body (e.g. shrapnel)? Y/N
6. Have you ever worked in a machine tool shop without eye protection? Y/N
7. Do you wear a hearing aid or cochlear implant? Y/N
8. Could you be pregnant? (Pregnancy tests are available in the female toilets) Y/N
9. Have you ever suffered from tinnitus? Y/N
10. Do you wear dentures, a dental plate or a brace? Y/N
11. Are you susceptible to claustrophobia? Y/N
12. Do you suffer from blackouts, epilepsy or fits? Y/N
13. Do you have any tattoos? (If yes, you may be asked to read and sign another form) Y/N
14. Do you have any body piercing jewellery that cannot be removed? Y/N
15. Do you have any skin patches (trans-dermal patches)? Y/N
16. Do you have a coil in place (IUD) for contraception? Do you know what type? Y/N
17. Do you have any condition that may affect your ability to control your temperature ?
    (e.g. Do you have a fever, cardiovascular disease, hypertension, diabetes or cerebrovascular disease?) Y/N
18. Will you remove all metal including coins, body-piercing jewellery, false-teeth, hearing aids etc. before entering the magnet hall? *(lockers available by the changing rooms)* Y/N
19. Is there anything else you think we should know? Y/N

I have read and understood all the questions **Signature:**	**Date:**
Verified by: **Scanner Operator Only:**	**Date:**

HILF/MIU

11.2.2 Questionnaires used for the ImPOA study

The following questionnaires were used within the study and will be presented in this order:

Edinburgh handedness inventory

Educational level

Beck's Depression Inventory

McGill Pain Questionnaire

State Trait Anxiety Inventory

Pain Catastrophizing Scale

PainDETECT

Edinburgh handedness inventory

Please indicate your preferences in the use of hands in the following activities **by putting a tick in the appropriate column.** Where the preference is so strong that you would never try to use the other hand, unless absolutely forced to, **put 2 ticks**. If in any case you are really indifferent, **put a tick in both columns.**

Some of the activities listed below require the use of both hands. In these cases, the part of the task, or object, for which hand preference is wanted is indicated in parentheses.

Please try and answer all of the questions, and only leave a blank if you have no experience at all with the object or task.

	Left	Right
1. Writing	☐ ☐	☐ ☐
2. Drawing	☐ ☐	☐ ☐
3. Throwing	☐ ☐	☐ ☐
4. Scissors	☐ ☐	☐ ☐
5. Toothbrush	☐ ☐	☐ ☐
6. Knife (without fork)	☐ ☐	☐ ☐
7. Spoon	☐ ☐	☐ ☐
8. Broom (upper hand)	☐ ☐	☐ ☐
9. Striking Match (match)	☐ ☐	☐ ☐
10. Opening box (lid)	☐ ☐	☐ ☐

Educational level

Educational level

Date: / /

Study ID: .....

Please tick the appropriate box that best describes your educational attainment

(Information will be kept private and confidential)

	Level 1	Higher degree and professional qualifications, Postgraduate degree/qualifications
	Level 2	Undergraduate degree
	Level 3	Diploma, certificate (tertiary qualification below degree level)
	Level 4	Other sub-degree (technical and business qualifications above A-level but below degree level)
	Level 5	A and AS level GCE
	Level 6	Below AS level (O-level GCE/ GCSE, CSE, vocational qualifications below sub-degree level)
	Level 7	Apprenticeship
	Level 8	None

Reference: modified from Muriel Egerton and Killian Hulihan (2006)

Pain duration=.....

Body weight=..... **Kg**

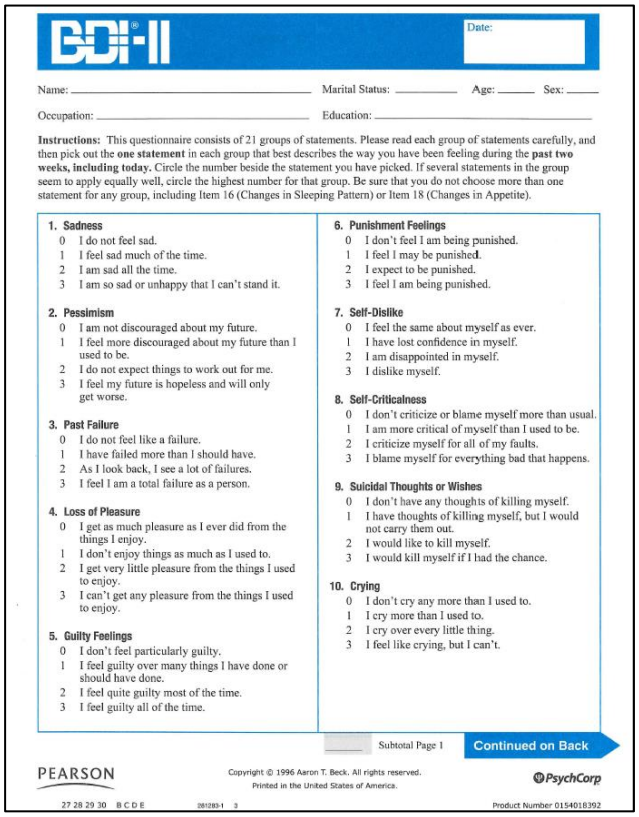
Body height=..... **cm**

BMI=

Notes: .....

.....

Beck's Depression Inventory



BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today.** Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism
0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure
0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure
0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

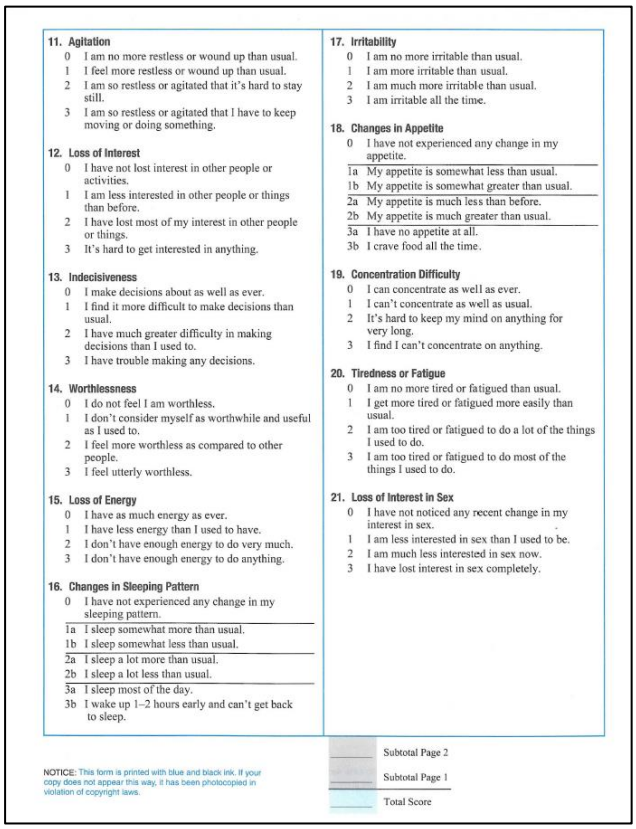
7. Self-Dislike
0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness
0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying
0 I don't cry any more than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

_____ Subtotal Page 1 **Continued on Back**



11. Agitation
0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest
0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness
0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness
0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy
0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern
0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability
0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite
0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

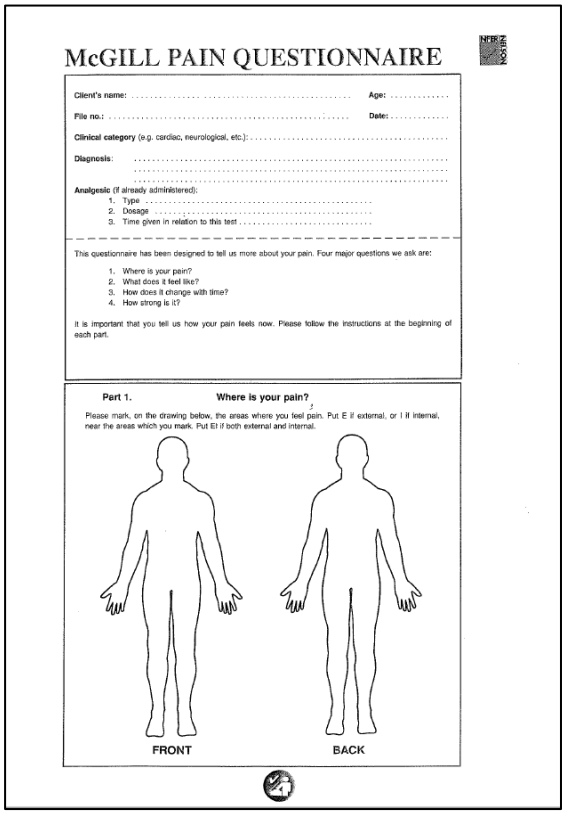
19. Concentration Difficulty
0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue
0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex
0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

_____ Subtotal Page 2
_____ Subtotal Page 1
_____ Total Score

McGill Pain Questionnaire



McGILL PAIN QUESTIONNAIRE

Client's name: ..... **Age:** .....

File no.: ..... **Date:** .....

Clinical category (e.g. cardiac, neurological, etc.): .....

Diagnosis: .....

Analgesic (if already administered):
1. Type .....
2. Dosage .....
3. Time given in relation to this test .....

This questionnaire has been designed to tell us more about your pain. Four major questions we ask are:

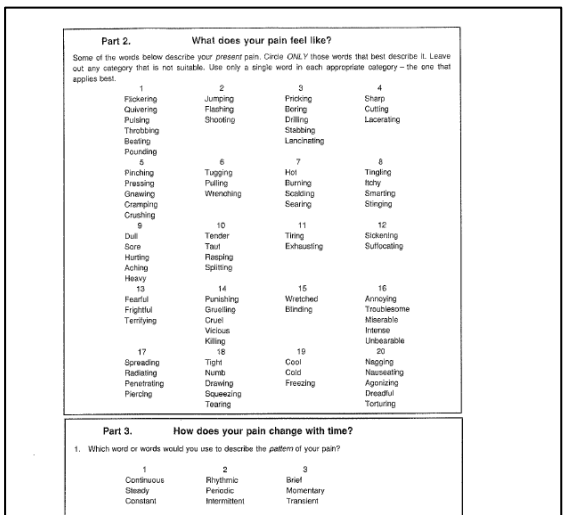
1. Where is your pain?
2. What does it feel like?
3. How does it change with time?
4. How strong is it?

It is important that you tell us how your pain feels now. Please follow the instructions at the beginning of each part.

Part 1. Where is your pain?

Please mark, on the drawing below, the areas where you feel pain. Put E if external, or I if internal, near the areas which you mark. Put EI if both external and internal.

FRONT BACK



Part 2. What does your pain feel like?

Some of the words below describe your *present* pain. Circle ONLY those words that best describe it. Leave out any category that is not suitable. Use only a single word in each appropriate category – the one that applies best.

1	2	3	4
Flickering	Jumping	Pricking	Sharp
Quivering	Flashing	Boring	Cutting
Pulsing	Shooting	Drilling	Lacerating
Throbbing		Stabbing	
Beating		Lancinating	
Pounding			
5	6	7	8
Pinching	Tugging	Hot	Tingling
Pressing	Pulling	Burning	Itchy
Gnawing	Wrenching	Scalding	Smarting
Cramping		Searing	Stinging
Crushing			
9	10	11	12
Dull	Tender	Tiring	Sickening
Sore	Taut	Exhausting	Suffocating
Hurting	Rasping		
Aching	Splitting		
Heavy			
13	14	15	16
Fearful	Punishing	Wretched	Annoying
Frightful	Gruelling	Blinding	Troublesome
Terrifying	Cruel		Miserable
	Vicious		Intense
	Killing		Unbearable
17	18	19	20
Spreading	Tight	Cool	Nagging
Radiating	Numb	Cold	Nauseating
Penetrating	Drawing	Freezing	Agonizing
Piercing	Squeezing		Dreadful
	Tearing		Torturing

Part 3. How does your pain change with time?

1. Which word or words would you use to describe the *pattern* of your pain?

1	2	3
Continuous	Rhythmic	Brief
Steady	Periodic	Momentary
Constant	Intermittent	Transient

2. What kind of things *relieve* your pain?

3. What kind of things *increase* your pain?

Part 4. How strong is your pain?

People agree that the following 5 words represent pain of increasing intensity. They are:

1	2	3	4	5
Mild	Discomforting	Distressing	Horrible	Excruciating

To answer each question below, write the number of the most appropriate word in the space beside the question.

1. Which word describes your pain right now? .....
2. Which word describes it at its worst? .....
3. Which word describes it when it is at its least? .....
4. Which word describes the worst toothache you ever had? .....
5. Which word describes the worst headache you ever had? .....
6. Which word describes the worst stomach-ache you ever had? .....

State anxiety

DIRECTIONS:

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

Trait anxiety

DIRECTIONS

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you *generally* feel.

	ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am "calm, cool, and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that really doesn't matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self-confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

Pain Catastrophizing Scale

PCS

Client No.: _____ Age: _____ Sex: M(__) F(__) Date: _____

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

When I'm in pain …

1. ☐ I worry all the time about whether the pain will end.
2. ☐ I feel I can't go on.
3. ☐ It's terrible and I think it's never going to get any better.
4. ☐ It's awful and I feel that it overwhelms me.
5. ☐ I feel I can't stand it anymore.
6. ☐ I become afraid that the pain will get worse.
7. ☐ I keep thinking of other painful events.
8. ☐ I anxiously want the pain to go away.
9. ☐ I can't seem to keep it out of my mind.
10. ☐ I keep thinking about how much it hurts.
11. ☐ I keep thinking about how badly I want the pain to stop.
12. ☐ There's nothing I can do to reduce the intensity of the pain.
13. ☐ I wonder whether something serious may happen.

… Total

PainDETECT

painDETECT

PAIN QUESTIONNAIRE

Date: _____ Patient: Last name: _____ First name: _____

How would you assess your pain **now**, at this moment?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the **strongest** pain during the past 4 weeks?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the pain during the past 4 weeks **on average**?

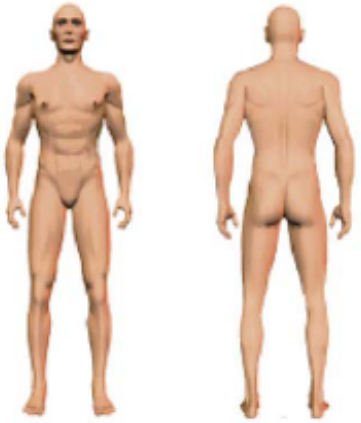
0 1 2 3 4 5 6 7 8 9 10

none max.

Mark the picture that best describes the course of your pain:

- **Persistent pain with slight fluctuations** ☐
- **Persistent pain with pain attacks** ☐
- **Pain attacks without pain between them** ☐
- **Pain attacks with pain between them** ☐

Please mark your main area of pain



Does your pain radiate to other regions of your body? yes ☐ no ☐

If yes, please draw the direction in which the pain radiates.

Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is light touching (clothing, a blanket) in this area painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have sudden pain attacks in the area of your pain, like electric shocks?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is cold or heat (bath water) in this area occasionally painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you suffer from a sensation of numbness in the areas that you marked?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Does slight pressure in this area, e.g., with a finger, trigger pain?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

(To be filled out by the physician)

never	hardly noticed	slightly	moderately	strongly	very strongly
☐ x 0 = 0	☐ x 1 = ☐	☐ x 2 = ☐☐	☐ x 3 = ☐☐	☐ x 4 = ☐☐	☐ x 5 = ☐☐

Total score ☐☐ out of 35

Development/Reference: R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle / Curr Med Res Opin, Vol.22, No. 10 (2006) ©2006 Pfizer Pharma GmbH

11.2.3 Supplementary material for chapter 6 (Coordinate based meta-analysis)

Table S1 - Papers included in the coordinate based meta-analysis. Adapted from (Tanasescu et al., 2016).

Patient abbreviations: PHN – Postherpetic neuralgia, CRPS – Complex Regional Pain Syndrome, FM – Fibromyalgia, SM – Syringomyelia, TNP – Trigeminal Neuralgia, CBP – Chronic Back Pain, BMD – Burning Mouth Disorder, NP – Neuropathic pain, OA – Osteoarthritis, MOH – Medication Overuse Headache, M – Migraine, DN – Diabetic Neuropathy, VVS – Vulvar Vestibulitis Syndrome.

Subject groups' abbreviations are listed in the Results section in the chapter 6. References are listed below the table.

Author	Subject group / modality	Healthy volunteer or patient	*N*	Field strength	Pain stimulus	Side	Contrast	Cued?	Standard space (MNI/Tal)	Table(s) used	Number of foci
(Albanese et al., 2007)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	8	1.5T	Heat	Right	Vs. innocuous	Cued	MNI	Table 2 and 3	12
(Albuquerque et al., 2006)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	8	1.5T	Heat	Right	Vs. innocuous	No cue	Tal	Table 7	10
	CP, $NEUR_{CP}$, CS_{CP}, NOX_{CP}, CP_HC_{MAC}	Patient - BMD	8	1.5T	Heat	Right	Vs. innocuous, Patient vs. Healthy volunteer	No cue	Tal	Table 5, 6	6, 4

(Apkarian et al., 2000)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	7	1.5T	Heat	Right	Vs. innocuous	No cue	Tal	Table 1	3
(Atlas et al., 2010)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	18	1.5T	Heat	Left	Vs. innocuous	Cue	MNI	Table S1.	7
(Baliki et al., 2006)	HC, $THER_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	11	3.0T	Heat	Central	Vs. innocuous	No cue	MNI	Table S4	16
	CP, MSK_{CP}, CS_{CP}, NOX_{CP}	Patient- CBP	11	3.0T	Heat	Central	Vs. innocuous	No cue	MNI	Table S4	10
(Baliki et al., 2008b)	CP, MSK_{CP}, CS_{CP}, NOX_{CP}, $MECH_{CP}$	Patient – OA	5	3.0T	Pressure	Mixed	Vs. rest	No cue	MNI	Table 4	13
(Baliki et al., 2010)	HC, $THER_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	16	3.0T	Heat	Central	Vs. innocuous	No cue	MNI	Table S4	17
	CP, MSK_{CP}, CS_{CP}, NOX_{CP}	Patient – CBP	16	3.0T	Heat	Central	Vs. innocuous	No cue	MNI	Table S4	17
(Becerra et al., 1999)	HC, $THER_{HC}$, $LEFT_{HC}$,	Healthy Volunteer	6	1.5T	Heat	Left	Vs. innocuous	No cue	Tal	Table 1	14

	$INNOC_{HC}$, $NCUED_{HC}$										
(Becerra et al., 2001)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	8	1.5T	Heat	Left	Vs. innocuous	No cue	Tal	Table 1 and 2	81
(Becerra et al., 2006)	CP, $NEUR_{CP}$, CS_{CP}, $ALDN_{CP}$, NOX_{CP}, $MECH_{CP}$, CP_HC_{MAC}	Patient – TNP	6	3.0T	Heat, Cold and Tactile	Right	Vs. innocuous, Patient vs. Healthy Volunteer, Hyperalgesia vs. normalgesia	No cue	MNI	Table 2, 3 and 4. Supplemental Table 1A, 2A and 3A	12, 14, 6, 20, 22 and 20.
(Berna et al., 2010)	LM_{HC}	Healthy Volunteer	20	3.0T	Heat	Left	Vs. rest	Cue	MNI	Table S3	15
(Bingel et al., 2002)	HC, $THER_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	14	1.5T	Heat	Mixed	Vs. rest	No cue	MNI	Table 1	12
(Bingel et al., 2003)	HC, $THER_{HC}$, $RIGHT_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	14	1.5T	Heat	Mixed	Vs. rest	No cue	MNI	Table 1	20
(Bingel et al., 2006)	HC, $THER_{HC}$, $RIGHT_{HC}$, $CUED_{HC}$	Healthy Volunteer	19	1.5T	Heat	Mixed	Vs. rest	Cue	MNI	Table 1	17

(Bingel et al., 2007a)	HC, $ELEC_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	16	3.0T	Electrical	Mixed	Vs. rest	No cue	MNI	Table 1	11
(Bingel et al., 2007b)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	20	3.0T	Heat	Left	Vs. innocuous	No cue	MNI	Table 1	21
(Bingel et al., 2011)	HC, $THER_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	22	3.0T	Heat	Right	Vs. rest	Cue	MNI	Table S1	20
(Bogdanov et al., 2015)	HC, THERHC, LEFTHC, NCUEDHC	Healthy Volunteer	24	3.0T	Heat	Left	-	No cue	MNI	Table 1	53
(Boly et al., 2007)	HC, $THER_{HC}$, $LEFT_{HC}$, $NCUED_{HC}$	Healthy Volunteer	24	3.0T	Heat	Left	-	No cue	MNI	Table 1 and 2	7 and 10
(Bornhovd et al., 2002)	HC, $THER_{HC}$, $LEFT_{HC}$, $NCUED_{HC}$	Healthy Volunteer	9	1.5T	Heat	Left	-	No cue	MNI	Table 1	18
(Botvinick et al., 2005)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	12	1.5T	Heat	Left	Vs. innocuous	Cue	MNI	Table 1	11

(Brinkmeyer et al., 2010)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	10	3.0T	Heat	Left	Vs. rest	No cue	MNI	Table 1	15
(Brooks et al., 2002)	HC, $THER_{HC}$, $RIGHT_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	18	1.5T	Heat	Mixed	Vs. innocuous	No cue	Tal	Table 1	23
(Brooks et al., 2003)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $HYPER_{HC}$	Healthy Volunteer	16	1.5T	Heat	Right	Vs. innocuous	-	Tal	Table 1	11
(Brooks et al., 2005)	HC, $THER_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	14	3.0T	Heat	Right	Vs. rest	No cue	MNI	Table 1	36
(Buchel et al., 2002)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	9	1.5T	Heat	Left	Vs. rest	No cue	MNI	Table 1	8
(Carlsson et al., 2006)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	9	1.5T	Electrical	Right	Vs. innocuous	Cue	Tal	Table 1	24

(Christmann et al., 2007)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	6	1.5T	Electrical	Right	Vs. rest	No cue	Tal	Table 2	29
(Coghill et al., 2003)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	17	1.5T	Heat	Right	Vs. innocuous	No cue	Tal	Table 1	7
(Cole et al., 2006)	HC, $MECH_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	15	1.5T	Pressure	Right	Vs. innocuous	No cue	MNI	Supplementary Table 1	21
(Cole et al., 2010)	HC, $MECH_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	30	1.5T	Pressure	Right	Vs. innocuous	No cue	MNI	Table 2	51
(Cook et al., 2004)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	9	1.5T	Heat	Left	Vs. innocuous	No cue	Tal	Table 2	6
	CP, FM_{CP}, RS_{CP}	Patient – FM	9	1.5T	Heat	Left	Vs. innocuous	No cue	Tal	Table 3	5

(Corradi-Dell'Acqua et al., 2011)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	28	3.0T	Heat	Right	Vs. innocuous	Cue	MNI	Table 2	26
(Davis et al., 2002)	HC, $THER_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	7	1.5T	Cold	Right	Vs. rest	No cue	Tal	Table 1	19
(de la Fuente-Sandoval et al., 2010)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	13	3.0T	Heat	Left	Vs. innocuous	No cue	MNI	Table 2	8
(de la Fuente-Sandoval et al., 2012)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	13	3.0T	Heat	Left	Vs. innocuous	No cue	MNI	Table 2	8
(de Leeuw et al., 2006)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	9	1.5T	Heat	Left	Vs. innocuous	No cue	Tal	Table 1	16
(Derbyshire et al., 2004)	HC, $THER_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	8	3.0T	Heat	Right	Vs. rest	No cue	MNI	Table 1	14

(Derbyshire and Osborn, 2009)	HC, $THER_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	12	3.0T	Heat	Mixed	Vs. innocuous	No cue	MNI	Table 1	8
(Diers et al., 2012)	CP, FM_{CP}, RS_{CP}, NOX_{CP}, $MECH_{CP}$	Patient – FM	10	1.5T	Pressure	Left	Vs. rest	No cue	MNI	Table 2	5
(Downar et al., 2003)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	10	1.5T	Electrical	Right	Vs. rest	No cue	Tal	Table 1	19
(Dube et al., 2009)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	12	1.5T	Heat	Left	Vs. innocuous	No cue	MNI	Table 1 and 2	41
(Ducreux et al., 2006)	HC, $THER_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	6	1.5T	Cold	Right	Vs. rest	No cue	MNI	Table 4	25
	CP, $NEUR_{CP}$, CS_{CP}, $ALDN_{CP}$, $MECH_{CP}$	Patient – SM	6	1.5T	Cold and Pressure	Right	Vs. rest	No cue	MNI	Table 4 and 5	35
(Dunckley et al., 2005)	HC, $THER_{HC}$, $LEFT_{HC}$,	Healthy Volunteer	10	3.0T	Heat	Left	Vs. rest	No cue	MNI	Table 1	37

	$REST_{HC}$, $NCUED_{HC}$										
(Fairhurst et al., 2007)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	12	3.0T	Heat	Left	Vs. rest	Cue	MNI	Table 2	16
(Ferraro et al., 2012)	HC, $MECH_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	9	1.5T	Pressure	Left	Vs. rest	No cue	MNI	Table 2	8
	CP, CS_{CP}, NOX_{CP}, $MECH_{CP}$	Patient-MOH	9	1.5T	Pressure	Left	Vs. rest	No cue	MNI	Table 2	17
(Ferretti et al., 2003)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	8	1.5T	Electrical	Right	Vs. rest	No cue	Tal	Table 1	7
(Forkmann et al., 2013)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	24	3.0T	Heat	Left	Vs. innocuous	Cue	MNI	Table 1	14
(Frankenstein et al., 2001)	HC, $THER_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	10	1.5T	Cold	Right	Vs. rest	Cue	MNI	Table 1	10

(Freund et al., 2007)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	15	1.5T	Electrical	Mixed	Vs. rest	No cue	MNI	Table 2	11
(Freund et al., 2009)	HC, $THER_{HC}$, $RIGHT_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	15	1.5T	Heat	Mixed	Vs. rest	No cue	MNI	Table 2	10
(Freund et al., 2011)	CP, $NEUR_{CP}$, RS_{CP}, NOX_{CP}	Patient – CRPS	10	1.5T	Electrical	Mixed	Vs. rest	No cue	MNI	Table 2	18
(Gard et al., 2012)	HC, $ELEC_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	34	1.5T	Electrical	Left	Vs. rest	Cue	Tal	Table 1 and 2	27
(Geha et al., 2008)	CP, $NEUR_{CP}$, CS_{CP}, $ALDN_{CP}$, $MECH_{CP}$	Patient – PHN	11	3.0T	Pressure	Mixed	Vs. rest	No cue	MNI	Table 1	14
(Gelnar et al., 1999)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	9	1.5T	Heat	Right	Vs. innocuous	Cue	Tal	Table 3	9

(Geuze et al., 2007)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	12	1.5T	Heat	Right	Vs. innocuous	No cue	Tal	Table 2	15
(Giesecke et al., 2006)	CP_HC_{MAC}	Patient-CBP and healthy volunteers	22	1.5T	Pressure	Left	Patient vs. Healthy volunteer	No cue	Tal	Table 2	4
(Godinho et al., 2012)	HC, $ELEC_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	16	1.5T	Electrical	Mixed	Vs. innocuous	Cue	Tal	Table 1	16
(Gopinath et al., 2012)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	14	3.0T	Heat	Right	Vs. innocuous	No cue	Tal	Table 2	33
(Gracely et al., 2002)	CP_HC_{MAC}	Patient-FM, Healthy Volunteer	16, 16	1.5T	Pressure	Left	Vs. rest, Patient vs. Healthy Volunteer	No cue	Tal	Table 3	13
(Grant et al., 2011)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	13	3.0T	Heat	Left	Vs. innocuous	Cue	Tal	Table S1	10
(Gundel et al., 2008)	HC, $THER_{HC}$, $LEFT_{HC}$,	Healthy Volunteer	12	1.5T	Heat	Left	Vs. innocuous	No cue	MNI	Table 2	13

	$INNOC_{HC}$, $NCUED_{HC}$										
(Herde et al., 2007)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	8	1.5T	Heat	Right	Vs. innocuous	No cue	Tal	Table 2	28
(Hiramatsu et al., 2014a)	CP_HC_{MAC}	Patient-OA	12	3.0T	Electrical	Right	-	No cue	MNI	Table 2	7
(Hohmeister et al., 2010)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	9	1.5T	Heat	Left	Vs. rest	No cue	MNI	Table 3	13
(Iannilli et al., 2008)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	18	1.5T	Electrical	Right	Vs. rest	No cue	Tal	Table 2	24
(Ibinson and Vogt, 2013)	HC, ELECHC, RIGHTHC, NCUEDHC	Healthy Volunteer	15	3.0T	Electrical	Right	-	No cue	MNI	Tables 1 & 3	19
(Jantsch et al., 2005)	HC, $ELEC_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	8	1.5T	Electrical	Left	Vs. rest	No cue	Tal	Table 2	18

(Jensen et al., 2010)	CP, FM_{CP}, RS_{CP}, NOX_{CP}, $MECH_{CP}$	Patient-FM	83	1.5T	Pressure	Left	Vs. innocuous	No cue	MNI	Table 2	10
(Jensen et al., 2012)	CP, FM_{CP}, RS_{CP}, NOX_{CP}, $MECH_{CP}$	Patient-FM	40	1.5T	Pressure	Right	Vs. innocuous	No cue	MNI	Table 2	6
(Kamping et al., 2013)	HC, $THER_{HC}$, $LEFT_{HC}$, $NCUED_{HC}$	Healthy Volunteer	16	3.0T	Heat	Left	-	No cue	MNI	Table 2	15
	CP, FM_{CP}, RS_{CP}, NOX_{CP},	Patient-FM	16	3.0T	Heat	Left	-	No cue	MNI	Table 2	2
(Kakeda et al., 2010)	HC, $THER_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	12	3.0T	Cold	Mixed	Vs. rest	No cue	MNI	Table 2	11
(Kim et al., 2011)	HC, $MECH_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	22	3.0T	Pressure	Left	Vs. rest	No cue	MNI	Supplementary Table 1	18
	CP, FM_{CP}, RS_{CP},	Patient-FM	19	3.0T	Pressure	Left	Vs. rest	No cue	MNI	Supplementary Table 1	14

	NOX_{CP}, $MECH_{CP}$										
(Kim et al., 2013c)	HC, $MECH_{HC}$, $LEFT_{HC}$, $NCUED_{HC}$	Healthy Volunteer	11	3.0T	Pressure	Left	-	No cue	MNI	Table 1	9
	CP, FM_{CP}, RS_{CP}, NOX_{CP}, $MECH_{CP}$, CP_HC_{MAC}	Patient-FM	21	3.0T	Pressure	Left	-	No cue	MNI	Table 2 and 3	13, 8
(Kobayashi et al., 2009)	HC, $MECH_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	8	3.0T	Pressure	Central	Vs. rest	No cue	Tal	Table 3	4
	CP, MSK_{CP}, CS_{CP}, NOX_{CP}, $MECH_{CP}$	Patient-CBP	8	3.0T	Pressure	Central	Vs. rest	No cue	Tal	Table 3	8
(Kong et al., 2006)	HC, $THER_{HC}$, $RIGHT_{HC}$, $NCUED_{HC}$	Healthy Volunteer	16	3.0T	Heat	Right	High vs. low pain	No cue	MNI	Table 1	13
(Kong et al., 2010a)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	61	3.0T	Heat	Right	Vs. innocuous	Cue	MNI	Table 2	12

(Kong et al., 2013)	HC, $THER_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	46	3.0T	Heat	Right	Vs. rest	Cue	MNI	Table 1	15
(Koyama et al., 2005)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	10	1.5T	Heat	Right	Vs. innocuous	No cue	Tal	Supplementary Table 1	17
(Kucyi et al., 2013)	HC, $ELEC_{HC}$, $LEFT_{HC}$, $NCUED_{HC}$	Healthy Volunteer	51	3.0T	Electrical	Left	-	No cue	MNI	Supplementary Table 2	22
(Kurata et al., 2002)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	5	3.0T	Heat	Right	Vs. innocuous	No cue	Tal	Table 2	18
(Kurata et al., 2005)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	6	3.0T	Heat	Right	Vs. innocuous	No cue	Tal	Table 2	2
(La Cesa et al., 2014)	HC, $THER_{HC}$, $LEFT_{HC}$, $NCUED_{HC}$	Healthy Volunteer	12	3.0T	Cold	Left	-	No cue	MNI	Table 1	24
(Landgrebe et al., 2008)	HC, $THER_{HC}$, $LEFT_{HC}$,	Healthy Volunteer	15	3.0T	Heat	Left	Vs. rest	Cue	MNI	Table 2	10

	$REST_{HC}$, $CUED_{HC}$										
(Lebel et al., 2008)	CP, $NEUR_{CP}$, CS_{CP}, $ALDN_{CP}$, $MECH_{CP}$	Patient-CRPS	8	3.0T	Pressure	Mixed	Vs. innocuous	No cue	MNI	Table 5	13
(Lee et al., 2008)	$HYPER_{MAC}$	Healthy Volunteer	15	3.0T	Pressure	Right	Mechanical hyperalgesia vs. mechanical normalgesia	No cue	MNI	Supplemental Table 1	17
(Liljencrantz et al., 2013)	$HYPER_{MAC}$	Healthy Volunteer	18	3.0T	Pressure	Left	Mechanical hyperalgesia vs. mechanical normalgesia	Cue	MNI	Table 1	17
(Lloyd et al., 2008)	HC, $MECH_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	17	1.5T	Pressure	Central	Vs. rest	No cue	MNI	Table 1	9
	CP, MSK_{CP}, CS_{CP}, $ALDN_{CP}$, $MECH_{CP}$	Patient-CBP	28	1.5T	Pressure	Central	Vs. rest	No cue	MNI	Table 1	21
(Lloyd et al., 2014)	CP, MSK_{CP}, RS_{CP}, NOX_{CP},	Patient-CBP	24	1.5T	Heat	Right	Vs. Innocuous	No cue	MNI	Table 2	19

(Lopez-Sola et al., 2010b)	HC, $MECH_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	25	1.5T	Pressure	Right	Vs. rest	Cue	Tal	Table 1	19
(Lopez-Sola et al., 2010a)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	20	1.5T	Heat	Right	Vs. innocuous	Cue	MNI	Table 2	8
(Lui et al., 2008)	HC, $MECH_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	14	1.5T	Pressure	Right	Vs. rest	Cue	MNI	Table 1	20
(Lutz et al., 2013)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	14	3.0T	Heat	Left	Vs. innocuous	Cue	Tal	Supplementary Table 1	10
(Maeda et al., 2011)	HC, $MECH_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	12	1.5T	Pressure	Right	Vs. rest	No cue	Tal	Table 2	22
(Maihofner and	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$,	Healthy Volunteer	12	1.5T	Heat	Left	Vs. innocuous,	No cue	Tal	Table 1	11

Handwerker, 2005)	$NCUED_{HC}$, $HYPER_{HC}$										
	$HYPER_{MAC}$	Healthy Volunteer	12	1.5T	Heat and pressure	Left	Hyperalgesia vs. normalgesia	No cue	Tal	Table 2	27
(Maihofner et al., 2004)	$HYPER_{HC}$	Healthy Volunteer	11	1.5T	Pressure	Left	Vs. rest	No cue	Tal	Table 1	8
	$HYPER_{MAC}$	Healthy Volunteer	11	1.5T	Pressure	Left	Hyperalgesia vs. normalgesia	No cue	Tal	Table 1	7
(Maihofner et al., 2005)	CP, $NEUR_{CP}$, CS_{CP}, $ALDN_{CP}$, $MECH_{CP}$	Patient-CRPS	12	1.5T	Pressure	Right	Vs. rest	No cue	Tal	Table 2	19
(Maihofner et al., 2006b)	HC, $THER_{HC}$, $MECH_{HC}$ $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	14	1.5T	Heat and Pressure	Right	Vs. rest	No cue	Tal	Table 1	39
(Maihofner et al., 2006a)	CP, $NEUR_{CP}$, CS_{CP}, $ALDN_{CP}$, $MECH_{CP}$	Patients-CRPS	12	1.5T	Tactile	Left	Vs. rest	No cue	Tal	Supplementary Table 2	24
(Maihofner et al., 2011)	HC, $MECH_{HC}$, $LEFT_{HC}$,	Healthy Volunteer	12	1.5T	Pressure	Left	Vs. rest	No cue	Tal	Table 1	18

	$REST_{HC}$, $NCUED_{HC}$										
(Mantini et al., 2009)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	10	1.5T	Electrical	Right	Vs. rest	No cue	Tal	Supplementary Table 3	9
(Markl et al., 2013)	HC, $ELEC_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	15	1.5T	Electrical	Left	Vs. rest	No cue	MNI	Table 2	8
(Martin et al., 2013)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	23	3.0T	Heat	Left	Vs. innocuous	No cue	MNI	Table 2	6
(Misra and Coombes, 2014)	HC, $THER_{HC}$, $RIGHT_{HC}$, $NCUED_{HC}$	Healthy Volunteer	15	3.0T	Heat	Right	-	No cue	MNI	Table 2	25
(Mobascher et al., 2009a)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	20	3.0T	Heat	Left	Vs. rest	No cue	MNI	Table 1	17
(Mobascher et al., 2009b)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	12	3.0T	Heat	Left	Vs. rest	No cue	MNI	Table 1	17

(Mobascher et al., 2010b)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	32	3.0T	Heat	Left	Vs. rest	No cue	MNI	Table 1	17
(Mobascher et al., 2010a)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	57	3.0T	Heat	Left	Vs. rest	No cue	MNI	Table 1	17
(Mochizuki et al., 2007)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	14	3.0T	Cold	Left	Vs. innocuous	No cue	MNI	Table 2	7
(Mohr et al., 2008)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	15	1.5T	Cold	Right	Vs. innocuous	Cue	MNI	Supplementary Table 3	19
	$HYPER_{HC}$	Healthy Volunteer	15	1.5T	Cold	Right	Vs. innocuous	Cue	MNI	Supplementary Table 3	25
	$HYPER_{MAC}$	Healthy Volunteer	15	1.5T	Cold	Right	Hyperalgesia vs. normalgesia	Cue	MNI	Table 2	10
(Morrison et al., 2004)	HC, $MECH_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	14	1.5T	Pressure	Left	Vs. innocuous	Cue	Tal	Table 1	5

(Morrison and Downing, 2007)	HC, $MECH_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	11	1.5T	Pressure	Left	Vs. innocuous	No cue	Tal	Table 1	9
(Moulton et al., 2005)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	33	1.5T	Heat	Left	Vs. innocuous	No cue	Tal	Table 1	17
(Moulton et al., 2007)	$HYPER_{MAC}$	Healthy Volunteer	12	3.0T	Heat	Left	Vs. innocuous	No cue	MNI	Table 1	9
(Moulton et al., 2011)	HC, $THER_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	11	3.0T	Heat	Mixed	Vs. innocuous	No cue	MNI	Table 4	45
	CP, $NEUR_{CP}$, RS_{CP}, NOX_{CP}, CP_HC_{MAC}	Patient-M	11	3.0T	Heat	Mixed	Vs. innocuous, Patient vs. healthy volunteer	No cue	MNI	Table 3, Supplementary Table 3	34, 27
(Moulton et al., 2012)	HC, $THER_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	12	3.0T	Heat	Right	Vs. rest	No cue	MNI	Table 1	11
(Naglatzki et al., 2012)	HC, $ELEC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	13	1.5T	Electrical	-	-	No cue	MNI	Table 1	8

(Nickel et al., 2014)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $NCUED_{HC}$	Healthy Volunteer	48	3.0T	Electrical	Right	-	No cue	Tal	Supplementary Table 1	25
(Nicotra et al., 2006)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	7	1.5T	Electrical	Right	Vs. rest,	Cue	Tal	Table 2	5
(Obermann et al., 2009)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	11	1.5T	Electrical	Right	Vs. rest	No cue	MNI	Table 3	11
(Ochsner et al., 2006)	HC, $THER_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	13	3.0T	Heat	Right	Vs. rest	No cue	MNI	Table 1	19
(Oshiro et al., 2007)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	12	1.5T	Heat	Left	Vs. innocuous	Cue	MNI	Supplementary Table 1	15
(Oshiro et al., 2009)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	12	1.5T	Heat	Left	Vs. rest	Cue	MNI	Supplementary Table 1	20
(Parks et al., 2011)	HC, $MECH_{HC}$,	Healthy Volunteer	9	3.0T	Pressure	Mixed	Vs. rest	No cue	MNI	Supplementary Table 3	26

	$REST_{HC}$, $NCUED_{HC}$										
	CP, MSK_{CP}, CS_{CP}, NOX_{CP}	Patient-OA	14	3.0T	Pressure	Mixed	Vs. rest	No cue	MNI	Supplementary Table 3	22
(Peltz et al., 2011)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	11	3.0T	Heat and cold	Left	Vs. innocuous	No cue	Tal	Table 1	22, 18
(Perini et al., 2013)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	18	3.0T	Heat and Cold	Left	Vs. rest	Cue	Tal	Table 1	7
(Peyron et al., 2004)	CP, $NEUR_{CP}$, CS_{CP}, $ALDN_{CP}$, $MECH_{CP}$	Patient-NP	27	1.0T	Pressure	Left	Vs. rest	No cue	Tal	Supplementary Table 1	14
(Piche et al., 2010)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	11	3.0T	Electrical	Right	Vs. rest	No cue	MNI	Table 1, Supplementary Table 2	23, 21
(Ploner et al., 2010)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	16	3.0T	Heat	Right	Vs. innocuous	No cue	MNI	Table 1	17

(Pomares et al., 2013)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	21	3.0T	Heat	Left	Vs. rest	No cue	MNI	Table 1	34
(Pujol et al., 2009)	HC, $MECH_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	9	1.5T	Pressure	Right	Vs. rest	No cue	Tal	Table 1, 4	6, 12
	CP, FM_{CP}, RS_{CP}, NOX_{CP}, $MECH_{CP}$, CP_HC_{MAC}	Patient-FM	9	1.5T	Pressure	Right	Vs. rest, Patient vs. healthy volunteer	No cue	Tal	Table 1, 4	14, 12, 9
(Pukall et al., 2005)	CP, $NEUR_{CP}$, CS_{CP}, $ALDN_{CP}$, $MECH_{CP}$	Patient-VVS	14	1.5T	Pressure	Central	Vs. rest	No cue	Tal	Table 3	15
(Qiu et al., 2006)	HC, $THER_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	13	3.0T	Heat	Right	Vs. rest	No cue	MNI	Table 1, 2	10
(Raij et al., 2005)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	14	3.0T	Heat	Left	Vs. rest	No cue	Tal	Supplementary Table 3	11

(Remy et al., 2003)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	12	3.0T	Heat	Left	Vs. innocuous	No cue	MNI	Table 1	7
(Roberts et al., 2008)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	10	1.5T	Heat	Left	Vs. innocuous	No cue	Tal	Table 2	17
(Rolls et al., 2003)	HC, $MECH_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	9	3.0T	Pressure	Left	Vs. rest	No cue	MNI	In text	15
(Roy et al., 2009a)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	12	3.0T	Electrical	Right	Vs. rest	No cue	MNI	Supplementary Table 1	29
(Russo et al., 2012)	HC, $THER_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	16	3.0T	Heat	Mixed	Vs. rest	No cue	Tal	Table 3	14
	CP, $NEUR_{CP}$, RS_{CP}, NOX_{CP}, CP_{MAC}	Patient-M	16	3.0T	Heat	Mixed	Vs. rest, Patient vs. Healthy volunteer	No cue	Tal	Table 2	16, 1

(Schoedel et al., 2008)	HC, $MECH_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	11	1.5T	Pressure	Left	Vs. rest	No cue	Tal	Table 1	14
(Schweinhardt et al., 2006)	CP, $NEUR_{CP}$, CS_{CP}, $ALDN_{CP}$	Patient-NP	8	1.5T	Pressure	Mixed	Vs. rest	No cue	MNI	Table 3	18, 17
(Seifert and Maihofner, 2007)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$, $HYPER_{HC}$, $HYPER_{MAC}$	Healthy Volunteer	12	1.5T	Cold	Right	Vs. innocuous, Hyperalgesia vs. normalgesia	No cue	Tal	Table 1, 2	19, 21, 12
(Seifert et al., 2008)	HC, $THER_{HC}$, $MECH_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$, $HYPER_{HC}$, $HYPER_{MAC}$	Healthy Volunteer	14	1.5T	Heat and Pressure	Right	Vs. innocuous, Hyperalgesia vs. normalgesia	No cue	Tal	Table 1	6, 19, 21
(Seifert et al., 2009)	HC, $MECH_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$, $HYPER_{HC}$	Healthy Volunteer	12	1.5T	Pressure	Right	Vs. rest	No cue	Tal	Table 1	6, 19

(Seifert et al., 2013a)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	9	1.5T	Heat	Left	Vs. innocuous	No cue	Tal	Supplementary Table 1.1	28
(Seminowicz and Davis, 2006)	HC, $ELEC_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	22	1.5T	Electrical	Left	Vs. rest	No cue	Tal	Table 1	12
(Shelton et al., 2012)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	11	3.0T	Heat	Left	Vs. innocuous	No cue	MNI	Table 5	30
(Shenoy et al., 2011)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$, $HYPER_{HC}$,	Healthy Volunteer	12	1.5T	Heat	Left	Vs. rest	No cue	Tal	Table 1	14, 11
(Shukla et al., 2011)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$,	Healthy Volunteer	10	3.0T	Heat	Left	Vs. innocuous	No cue	Tal	Table 1	6
(Smith et al., 2002)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	8	3.0T	Heat	Left	Vs. innocuous	No cue	MNI	Table 2	13

(Sofina et al., 2014)	HC, $THER_{HC}$, $NCUED_{HC}$	Healthy Volunteer	4	3.0T	Heat	-	-	No cue	MNI	Table 1	16
(Sprenger et al., 2011)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	22	3.0T	Heat	Left	Vs. rest	No cue	MNI	Supplementary Table 2	35
(Stammler et al., 2008)	HC, $MECH_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$, $HYPER_{HC}$	Healthy Volunteer	12	1.5T	Pressure	Right	Vs. rest	No cue	Tal	Table 1	17, 28
(Starr et al., 2009)	HC, $THER_{HC}$, $LEFT_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	13	1.5T	Heat	Mixed	Vs. rest	No cue	MNI	Table 2	40
(Straube et al., 2009)	HC, $ELEC_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	24	1.5T	Electrical	Left	Vs. rest	No cue	Tal	Table 2	16
(Strigo et al., 2003)	HC, $THER_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	7	1.5T	Heat	Midline	Vs. innocuous	No cue	Tal	Table 2	25

(Symonds et al., 2006)	HC, $ELEC_{HC}$, $LEFT_{HC}$, $RIGHT_{HC}$, $REST_{HC}$	Healthy Volunteer	9	3.0T	Electrical	Mixed	Vs. rest	-	Tal	Table 1	15
(Takahashi et al., 2011)	HC, $ELEC_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	13	3.0T	Electrical	Left	Vs. rest	No cue	MNI	Table 3	16
(Ter Minassian et al., 2013a)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	20	1.5T	Electrical	Right	Vs. innocuous	Cue	MNI	Supplementary Table 3	73
(Theysohn et al., 2014)	HC, $ELEC_{HC}$, $LEFT_{HC}$, $NCUED_{HC}$	Healthy Volunteer	14	1.5T	Electrical	Left	-	No cue	MNI	Table 1	10
(Tracey et al., 2000)	HC, $THER_{HC}$, $LEFT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	6	1.5T	Heat, Cold	Left	Vs. innocuous	No cue	Tal	Table 1	25
(Tseng et al., 2010)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	12	3.0T	Heat	Right	Vs. innocuous	No cue	MNI	Table 2	31
(Tseng et al., 2013)	HC, $THER_{HC}$, $RIGHT_{HC}$,	Healthy Volunteer	11	3.0T	Heat	Right	Vs. innocuous	No cue	MNI	Supplementary Table 2	7

	$INNOC_{HC}$, $NCUED_{HC}$										
	CP, $NEUR_{CP}$, CS_{CP}, $ALDN_{CP}$	Patient-DN	11	3.0T	Heat	Right	Vs. innocuous	No cue	MNI	Supplementary Table 2	16
(Uematsu et al., 2011)	HC, $MECH_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	17	1.5T	Pressure	Right	Vs. rest	No cue	MNI	Table 2	31
(Vachon-Presseau et al., 2013)	HC, $THER_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	18	3.0T	Heat	-	Vs. innocuous	No cue	MNI	Supplementary Table 1	17
	CP, MSK_{CP}, RS_{CP}, NOX_{CP}	Patient-CBP	16	3.0T	Heat	-	Vs. innocuous	No cue	MNI	Supplementary Table 1	15
(Valet et al., 2004)	HC, $THER_{HC}$, $RIGHT_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	7	1.5T	Heat	Right	Vs. innocuous	No cue	MNI	Table 1	16
(Vanhaudenhuyse et al., 2009)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	13	3.0T	Heat	Left	Vs. rest	No cue	MNI	Table 2	10

(Vartiainen et al., 2009)	HC, $THER_{HC}$, $INNOC_{HC}$, $NCUED_{HC}$	Healthy Volunteer	9	3.0T	Heat	Mixed	Vs. innocuous	No cue	MNI	Table 2	15
	CP, $NEUR_{CP}$, RS_{CP}, NOX_{CP}	Patient-PHN	8	3.0T	Heat	Mixed	Vs. innocuous, Patient vs. healthy volunteer	No cue	MNI	Supplementary Table 2 and Table 3	3, 3
(Veldhuijzen et al., 2009)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $NCUED_{HC}$	Healthy Volunteer	10	3.0T	Heat	Left	Vs. rest	No cue	Tal	Table 2	20
(Villemure and Bushnell, 2009)	LM_{HC}	Healthy Volunteer	14	1.5T	Heat	Left	Vs. innocuous	No cue	MNI	Table 3	5
(Wager et al., 2004)	HC, $THER_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	23	3.0T	Heat	Left	Vs. rest	Cue	MNI	Supplementary Table 1	26
(Wagner et al., 2009)	LM_{HC}	Healthy Volunteer	40	1.5T	Heat	Mixed	-	No Cue	MNI		
(Wang et al., 2011)	HC, $MECH_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	8	3.0T	Pressure	Left	Vs. rest	Cue	Tal	Table 1	18

(Wiech et al., 2006)	HC, $ELEC_{HC}$, $LEFT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	12	3.0T	Electrical	Left	Vs. rest	Cue	MNI	Table 1	25
(Wiech et al., 2010)	HC, $ELEC_{HC}$, $RIGHT_{HC}$, $REST_{HC}$, $CUED_{HC}$	Healthy Volunteer	16	3.0T	Heat	Right	Vs. rest	Cue	MNI	Supplementary Table 3	25
(Wey et al., 2014)	HC, $MECH_{HC}$, $LEFT_{HC}$, $NCUED_{HC}$	Healthy Volunteer	11	3.0T	Pressure	Left	-	No cue	MNI	Table 1	9
(Zambreanu et al., 2005)	$HYPER_{MAC}$	Healthy Volunteer	12	3.0T	Pressure	Right	Vs. innocuous	No cue	MNI	Table 1	15
(Ziv et al., 2010)	HC, $THER_{HC}$, $INNOC_{HC}$, $CUED_{HC}$	Healthy Volunteer	10	3.0T	Heat	Mixed	Vs. innocuous	Cue	Tal	Table 1	15

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11.2.4 Supplementary material for chapter 8 (arterial spin labelling)

Rasch conversion of BDI-II scores

Rasch analysis of BDI-II reports from 180 subjects (age 39-90 years, 93 females) was carried out by Professor Nadina Lincoln and Dr Bryan Moreton on a separate study within the ARUK Pain Centre at the University Of Nottingham whom kindly made this data available.

Conversion was carried out by doing the following:

Rescore items 3 and 10 as follows: 0 = 0, 1 = 1, 2 = 1 and 3 = 2. Rescore items 9, 18 and 21 as follows: 0 = 0, 1 = 1, 2 = 1 and 3 = 1. Rescore item 16 as follows: 0 = 0, 1 = 1, 2 = 2 and 3 = 2. Discount scores from items 1, 5, 7 and 14. Sum the scores from the remaining items to produce a value from 0 to 42. Look up the score in the table below and match it to the corresponding 'Rasch' score:

Standard Score	*'Rasch' Score*
0	-7.76
1	-5.47
2	-4.27
3	-3.64
4	-3.18
5	-2.80
6	-2.48
7	-2.19
8	-1.92
9	-1.68
10	-1.44
11	-1.23
12	-1.02
13	-0.82
14	-0.64
15	-0.48
16	-0.32
17	-0.19
18	-0.06
19	0.06
20	0.16
21	0.27
22	0.37
23	0.47
24	0.57
25	0.67
26	0.77
27	0.88
28	0.98
29	1.09
30	1.21
31	1.33
32	1.46

33	1.60
34	1.75
35	1.92
36	2.12
37	2.37
38	2.67
39	3.09
40	3.74
41	5.16
42	8.32

Rasch conversion of PainDETECT scores

Discount scores from the picture selection item (about the 'course' of pain) and the yes/no item (asking does pain 'radiate'). Sum the scores from the remaining items to produce a value from 0 to 35. Look up the score in the table below and match it to the corresponding 'Rasch' score:

Standard Score	*'Rasch' Score*
0	-2.89
1	-2.22
2	-1.80
3	-1.53
4	-1.34
5	-1.18
6	-1.04
7	-0.92
8	-0.81
9	-0.71
10	-0.62
11	-0.53
12	-0.45
13	-0.38
14	-0.30
15	-0.23
16	-0.16
17	-0.09
18	-0.02
19	0.06
20	0.13
21	0.21
22	0.29
23	0.37
24	0.46
25	0.55
26	0.65
27	0.76
28	0.88
29	1.02
30	1.18
31	1.39
32	1.65

33	2.01
34	2.56
35	3.42

11.2.5 Supplementary material for chapter 9 (functional connectivity)

Supplementary Table S1.
Demographics of osteoarthritis patients

Participant	Age	Sex	Pain Duration	VAS	BDI	S-Anx	T-Anx	PCS	Mc-S	Mc-A	Mc-E
1	54	f	38	26	5	15	25	5	6	0	1
2	59	f	25	55	9	NA	NA	NA	NA	NA	NA
3	59	f	3	35	1	16	25	24	10	2	2
4	71	f	14	50	1	10	11	1	12	0	1
5	70	f	10	30	19	22	28	17	22	2	2
6	81	f	30	60	11	13	16	16	11	0	0
7	72	m	12	0	4	10	12	1	0	0	0
8	63	f	20	0	13	18	31	24	12	0	2
9	56	m	10	20	5	13	13	2	10	0	1
10	67	m	10	0	7	15	15	7	10	0	0
11	80	m	10	10	8	10	22	8	11	1	1
12	84	m	2	60	17	15	35	12	14	0	2
13	57	m	10	10	8	21	17	1	7	0	2
14	63	m	9	0	0	17	11	10	0	0	0
15	61	m	1	10	2	10	15	7	6	0	1
16	63	m	5	10	1	10	14	2	4	0	1
17	65	f	6	30	10	15	19	14	1	0	5
18	65	m	3	32	4	10	18	6	16	2	4
19	65	f	7.5	40	13	14	18	15	19	4	1
20	72	f	5	8	14	26	25	34	15	1	3
21	71	m	4	8	6	10	11	15	11	4	2
22	72	f	2	70	0	11	23	15	NA	NA	NA
23	77	m	20	70	10	12	21	38	16	0	2
24	56	f	1	0.0	0	11	13	16	15	0	1
25	65	f	2.5	60.0	19	20	26	28	0	2	0

Legend: Sex is keyed in as m=male and f=female, VAS – visual analogue score (0-100), BDI – Beck's depression index, S-Anx – State Anxiety, T-Anx – Trait anxiety, PCS – Pain catastrophizing scale, Mc-S – McGill pain questionnaire sensory subscore, Mc-A – McGill pain questionnaire affective subscore, Mc-E – McGill pain questionnaire evaluative subscore, NA – score not available.

Supplementary Table S2
Medicines of osteoarthritis patients

Participant	Medication
1	tranexamic acid
2	None taken
3	None taken
4	Paracetamol (2 x 500 mg) 3 hours prior to visit
5	Losartan (25 mg), bendroflumethiazide (2.5 mg), prochlorperazine
6	None taken
7	atropine eye drops, maxidex and cosopt eye drops, hypermellose eye drops, latanoprost drops
8	Paracetamol (1000 mg) 8 hours prior to visit
9	None taken
10	Glucosamine (100mg), bendroflumethiazide (2.5mg), simvastatin (20mg), contiflow (400 microg)
11	Amlodipine (5mg)
12	Aspirin (75mg-4 hours prior to visit), paracetamol (x8 last 24h, last taken 4 hours prior to visit), simvastatin (40mg)
13	None taken
14	Paracetamol (1000mg – taken 2.5 hours prior to visit), aspirin (75mg – taken 4.5 hours prior to visit), co-codamol (2 x 500/30mg – taken 15 hours prior to visit), lansoprazole (20mg), glucosamine (1000mg)
15	None taken
16	None taken
17	None taken
18	Bendroflumethiazide (2.5 mg), amlodipine (5 mg), ventolin, tiopsol eye drops, predsol eye drops, antibiotic eye drop
19	Paracetamol (2x500mg – taken 4 hours prior to visit), lansoprazole (30mg), losartan
20	Ramipril (10mg), Atorvastatin (10mg)
21	Felodipine (10mg), Ramipril (10mg), Atenolol (100mg), Furosemide (40mg), Warfarin (1.5mg), Candesartan (16mg), Gliclazide (80mg), Doxazosin (4mg), Spironolactone (4mg), Simvastatin
22	Oxybutynin (10mg)
23	Paracetamol (1000mg – taken 1 hour prior to study visit), co-codamol (2x30/500mg-taken 16 hours prior to study visit)
24	None taken
25	Amlodipine (5mg)

Supplementary Table S3

Demographics of healthy participants

Participant	Age	Sex	BDI	S-Anx	T-Anx	PCS
1	59	F	0	10	16	7
2	70	F	1	14	23	16
3	59	F	4	10	11	11
4	65	M	1	19	16	18
5	68	M	1	10	21	9
6	57	M	NA	10	11	0
7	51	F	0	10	16	22
8	66	F	1	11	12	5
9	58	F	1	NA	17	7
10	59	M	4	23	14	15
11	57	F	0	12	17	7
12	55	F	0	15	20	13
13	60	F	0	11	18	29
14	69	F	3	10	20	18
15	72	M	1	10	16	17
16	67	M	11	17	23	12
17	69	M	NA	NA	NA	24
18	70	M	3	13	13	8
19	80	F	12	16	21	23

Legend: Sex is keyed in as m=male and f=female, BDI – Beck's depression index, S-Anx – State Anxiety, T-Anx – Trait anxiety, PCS – Pain catastrophizing scale, NA – score not available.

Supplementary Table S4

Medications of healthy participants

Participant	Medications
1	None taken
2	None taken
3	None taken
4	Eye drops for Glaucoma
5	None taken
6	None taken
7	None taken
8	None taken
9	None taken
10	None taken
11	None taken
12	None taken
13[#]	Paracetamol (500 mg - 14.5 hours before visit), losartan (100mg, 4.5 hour prior to visit), bendroflumethiazide (2.5mg, 4.5 hours prior to visit), omeprazole (20mg, 4.5 hours prior to visit)
14	Fexfenadine (antihistamine, 3 hours prior to visit)
15	None taken
16	Simvastatin (40 mg, 18 hours prior to visit), valsartan (40 mg, 18 hours prior to visit), lacidipine (4 mg, 18 hours prior to visit)
17	ramipril (5 mg), bendroflumethiazide (5 mg), amlodipine (5mg)
18	Simavastatin (25mg, 15 hours prior to visit)
19	None taken

Legend: Sex is keyed in as m=male and f=female, BDI – Beck's depression index, S-Anx – State Anxiety, T-Anx – Trait anxiety, PCS – Pain catastrophizing scale, NA – score not available. [#]This subject reported having had a fall 9 weeks prior to scanning and suffered from a sore shoulder. The paracetamol had been taken prior to sleeping the night before the afternoon scan and so likely had been taken to aid sleeping and had little to no efficacy by time of scanning.