Individual Differences in the Vicarious Perception of Pain

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I hereby declare that this thesis has not been and will not be submitted in whole or in part to another University for the award of any other degree.

Signature……

Thomas Grice-Jackson

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These last few years have been exciting, challenging and hugely rewarding and I can only think to describe them with what I am aware is a terrible metaphor that has been in my mind since the middle of my second year of studies. I have felt like I am a human cannon ball who has been fired out, arms spread eagle, clutching at a million and one skills, life experiences, opportunities and friendships. I can't imagine another environment which would have allowed to learn and grow as person as much as my years at Sussex have and it was only possible because of the array of wonderful people who joined me through the experience.

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SUMMARY

Vicarious pain refers to the processes and experiences that arise from observations of other people in pain. Due to the interpersonal and multi-modal nature of these processes, research into the field is highly relevant for a number of key concepts in social cognitive neuroscience, such as empathy, multi-sensory processing and social cognition. The dominant approach in the field has been to focus on normative samples with little focus being given to inter-individual differences. The discovery of a subsample of the population who report conscious experiences of pain when observing it, so called 'mirror-pain responders', presents a significant opportunity for developing our understanding of the neural processes and characteristics associated with vicarious pain. The present thesis aims to extend understanding of this group who appear to lie on an extreme end of a spectrum of vicarious pain perception. Although past research has highlighted this group and made some attempts to identify their prevalence, few formal attempts have been made to stringently discover the prevalence and identify the characteristics of their qualitative experience. As such, **ARTICLE I** developed a questionnaire, named the Vicarious Pain Questionnaire (VPQ), which characterises mirror-pain responders based on their subjective experiences of pain. The results showed a surprisingly high prevalence rate for the condition, ~30%. In addition through the use of a cluster analysis, the VPQ identified subgroups within mirror-pain responders, which included a group who experienced sensory and localised mirror-pain, and a group that experienced affective and generalised mirror-pain. **ARTICLE I** and **ARTICLE II** both aimed at assessing the neural basis for the experiences and successfully highlighted the role of hyperactivity in vicarious somatosensory processing, through the use of electrophysiological (EEG) neuro-markers for somatosensory processing (mu rhythm) and functional magnetic resonance imaging (fMRI) activation in the somatosensory cortex during pain observation. Additionally, these articles highlighted the role of self-other processing regions through

the use of voxel-based morphometry (VBM) which revealed reduced grey-matter volume in the right temporo-parietal junction (rTPJ), and psycho-physiological interactions (PPI) of fMRI processing which revealed connectivity networks between pain matrix regions and self-other processing regions (rTPJ and dorsomedial prefrontal cortex (DMPFC)).

Characteristics of the mirror-pain were further assessed in **ARTICLE III** which in a battery of behavioural and physiological tests were administered to mirror-pain responders and controls. This study showed abnormal autonomic nervous system processing for Affective/General mirror-pain responders and confirmed the link between the condition and questionnaire measures of empathy. Finally, **ARTICLE IV** failed to provide a causal link between self-other processing regions (rTPJ) and somatosensory activation in response to pain observations through the use of theta-burst transcranial magnetic stimulation (TMS) in non-responders. This calls into question the direct causality of neural mechanisms associated with self-other theories of mirror-pain. This thesis demonstrates the importance of studying inter-individual differences in vicarious pain by reporting a set questionnaire and neuroimaging results which contribute to debates in the field and raises questions for future research. This work, its implications, and contributions to the wider literature are reviewed in the **DISCUSSION** chapter.

Author Contributions

The thesis conforms to an 'article format' in which the empirical chapters consist of discrete articles written in a style that is appropriate for publication in peer-reviewed journals in the field. The first and final chapters present an introduction to and discussion of the field and the research undertaken. I am the principle author on the manuscripts that form this thesis and take responsibility for the design, implementations, analysis, and write-up of the research. Prof Jamie Ward is listed as a senior author on **ARTICLES I & II** to reflect the contributions of his expertise and advice throughout all stages of the research processes relative to these papers. Prof Hugo Critchley and Dr Michael Banissy are co-authors on **ARTICLES 1 & II.** Prof Critchley contributed by providing his technical expertise during the design and analysis of **ARTICLE II** and supervised during the write up of **ARTICLES I & II.** Dr Banissy is credited for his contributions to data experimental design and data interpretation of **ARTICLES I & II**.

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Contents

List of Figures and Tables

Introduction

Throughout life, a person is likely to encounter other people in pain on a fairly regular basis. Whether it be witnessing a friend stub their toe on a piece of furniture, seeing a family member during an illness, or viewing a sports person break a bone, we all recognise the unpleasantness associated with these adverse experiences and find them deeply unpleasant to view them. During these experiences, affective and physiological responses are elicited to help us, as observers, to identify the implied threat and the causes of the pain, therefore motivating an appropriate response and allowing us to learn how we can avoid pain in ourselves. This interpersonal process is known as vicarious pain and comes about as a result of a number of processes such as empathy, multisensory integration and social cognition. For most people these processes result in a range of normative emotional and behavioural response; however, for some, observing pain results in a conscious experience of pain on the observer's own body (Giummarra & Bradshaw, 2008). This thesis seeks to study the neural and cognitive processes underpinning the experiences of these individuals in order to explore what they can teach us about empathy and vicarious processing.

This chapter will begin with a review of empathy theories relating to vicarious pain, before discussing neural networks associated with actual experiences of pain. This will be followed by a discussion of the role of relevant multi-sensory processes, and a review of the literature associated with the vicarious processing of touch and pain in normative populations. It will then discuss findings associated with populations who abnormally experience vicarious touch and/or pain on their own bodies before describing the objectives of this research programme and the methodological approaches used in previous empirical projects that support this thesis.

1. Models of Empathy

Empathy refers to is a series of cognitive, affective, and sensory processes which allow us to understand the emotions, actions, and states of other others by 'feeling with', or, 'as if' them (Gallese,

2003; Eisenberg, 1990; Hoffman, 1991). It is generally thought of as a high-level, multifaceted construct in which a person spontaneously experiences similarity between their own affect and that of other people, whilst maintain knowledge of to whom that affect belongs (Decety & Jackson, 2004; de Vignemont & Singer, 2006). Its functions and origins are considered to be inherently social and are manifest in the promotion of interpersonal experiences. Evolutionary theorists have suggested that empathy arose, and then contributed to, the increased complexity of social and cognitive abilities of early humans (Dunbar, 1998; Barrett, Henzi & Dunbar, 2003). Its origins might lie in behaviours such as emotional contagion (e.g. crying when others cry), which is often regarded as a 'proto' form of empathy both in terms phylogenetic and ontogenetic development. Empathy is also thought to be a chief driver of altruistic behaviours (behaviours which are directed at benefiting others rather than the self), which positively contributes to survival in social groups (Batson, 1991). It may have developed with and contributed to language abilities, as highlighted by a functional overlap between neural regions associated with communication and empathy (Iacoboni, 2005). Perhaps the greatest example of the necessity for empathy is that it is not something that we seem to learn; rather it is something intrinsic that is vital for our ability to function in a social world (Ickes, 2003).

Early definitions of empathy have focused on dissociating it from other interpersonal experiences and emotions such as sympathy, personal distress and projection (Eisenberg, 1990). Sympathy can be thought of as 'feeling for' another's emotions, particularly distress, and heightened attention to one's own feelings associated with those thoughts (Wispé, 1986; Katz, 1963). Personal distress focuses on the unpleasant emotions experienced by a person when seeing another is distress and thus is egocentric (Batson & Coke, 1981); and projection refers to the cognitive act of imposing one's own attitudes and perceptions onto another person, (Feshbach, 1978). Whilst all of these experiences may be closely associated with empathy, they differ because empathy is characterised by the spontaneous sharing of affect and experiences from the other to the self.

Later, researchers in the field largely focused on the affective and cognitive aspects of empathy as a construct. Affective aspects concern the spontaneous vicarious sharing of affect and cognitive aspects

focus on the cognitive capacities that allow for a person to put themselves in the shoes of another, or 'think as' another (Hoffman *et al.* 2001). The affective components are often thought of as the basic building blocks of empathy which provide the emotional contagion abilities necessary to feel for another, whilst cognitive empathy is thought of as a form of appraisal which allows one to make inferences from affective contagion about the mental states and perspectives of others (Preston and de Waal, 2002). Cognitive empathy includes 'mentalizing' or theory-of-mind mechanisms that involve attributing mental states (e.g. beliefs, desires, feelings) to the self and others, that do not necessarily reflect ongoing reality (de Waal, 2007). As such, classic measures of empathy such as the empathy quotient (EQ) (Baron-Cohen & Wheelwright, 2004; Lawrence, Shaw, Baker, Baron-Cohen, David, 2004) and the interpersonal reactivity index (IRI) (Davis, 1980; Davis, 1983) both contain clear and distinct components for these two subtypes of empathy.

The common view is that empathy development begins with an automatic affective resonance before developing into more complex cognitive and perspective-taking abilities (Eisenberg, 1986; Feshbach, 1975; Hoffman, 1978). This development involves the incorporation of task-specific processes into a network for cognitive empathy, rather than the development of a single system for processing both cognitive and affective empathy. Whilst the two constructs are highly related, research into clinical populations with empathy-related conditions (autism, Asperger's and schizophrenia) have shown dissociations between cognitive and affective empathy which indicates that the two systems are functionally distinct. Individuals with Asperger's were shown to display normal levels of affective empathy but underperformed on measures of cognitive empathy (Dziobek, Rogers, Fleck, Bahnemann, Heekeren, Wolf & Convit, 2008), whilst the opposite has been observed in individuals with schizophrenia (Lee, Farrow, Spence, & Woodruff, 2004). Neuroimaging studies on patients with lesions in regions associated with cognitive empathy (the ventromedial prefrontal cortex) and affective empathy (the inferior frontal gyrus) displayed a double dissociation between the two constructs of empathy (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). Whilst evidence for this functional dissociation is strong, it is generally considered that the two regions function in tandem

with one another, with both systems contributing to social cognition. The dissociation observed in these lesion studies represents unusual but functioning independence (Heberlein & Saxe, 2005).

The following two sections of this chapter will assess theories and models of affective and cognitive empathy constructs before moving towards an explanation of their relationship to multi-sensory integration, mirror-sensory synaesthesia and mirror-pain.

1.1 Affective models of empathy

Affective empathy refers to the spontaneous sharing of other people's emotional representations to the self (including external expressions and internal bodily states). It can be seen in young infants who attend to the emotional states of their mothers (Plutchik, 1987) and in the animal world where macaque monkeys respond to the distress of their kin with protective or comforting behaviour (de Waal, 1996). That feeling of intense unpleasantness experienced when you see someone suffering or the happiness experienced when you see a friend smiling are examples of this process in daily life. Affective empathy is often considered to be an in-built low-level component of empathy which operates through a process of emotional contagion in a variety of experiences, mental states, sensations and emotions (de Waal, 2007). It is considered to be so fundamental as to be called the lowest common denominator of all empathic processes (de Waal, 2008).

One of the key theories describing the low-level contagion-based account of affective empathy is Preston & de Waal's (2002) 'Perception-Action Model' (PAM). This model, based on both animal and human studies, states that the perception of a behaviour in another individual automatically activates a representation of the behaviour in the observer. PAM also states that representations of other people and execution of one's own behaviours are inextricably linked, meaning that observations of a behaviour activate the same physiological and behavioural responses that would occur from the execution of that behaviour by the self. This allows for an egocentric experience of other people's behaviour. Preston & de Waal take the view that this ability represents a 'proximate'

aspect of empathy that, without components of cognitive empathy (which they call the 'ultimate' aspect of empathy), does not fully explain human empathy as it lacks the appraisal and top-down functions which help us to explain and understand others. They do however consider this affective aspect of empathy as a necessary precursor for 'true empathy.'

PAM is closely related 'simulation' accounts of empathy (Gallese, 2007; Adolphs, 1999; Gallese & Golman 1998). This theory is based on the same basic principles as PAM; that is, that state-matching occurs in which the observation of other people's states generate representations that would be generated when an individual experiences that state themselves. These theories offer a neurological basis for this processing based on the discovery of so called 'mirror-neuron systems' (MNS) in the brains of macaque monkeys (Rizzolatti, Fadiga, Gallese, & Fogassi, 1996; Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995). In these studies, single-cell recordings were taken from the premotor regions of monkeys when they are shown grasping actions by the experimenter, and were then prompted to perform a similar grasping action themselves. For both action and observation, the monkey's premotor regions displayed similar patterns of activity thus leading to the hypothesis that this region must be involved in both the observation and execution of grasping actions. Later fMRI meta-analysis studies have concluded that humans possess the same characteristics of MNS in the premotor cortex (Molenberghs, Cunnington, & Mattingley, 2012).

Simulation theorists describe mirrored activation as an automatic translation of observed actions into neural activity for the execution of such actions, which allows for, or at least contributes to, the individual's understanding of the actions observed. Whilst this model was based on research into motor simulation, more recent research has highlighted similar systems related to a wider variety of states which are more traditionally associated with empathy, such as recognition of emotional face expressions (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003, Wicker, Keysers, Plailly, Royet, Gallese, Rizzolatti. 2003*;* Jabbi, Swart, & Keysers, 2007). A number of these studies have focused primarily the inferior frontal gyrus and ventral premotor area as areas of interest for MNS (Molenberghs *et al.* 2012). This automatic representation matching system is thought to offer an

explanation to the 'correspondence problem', a long-held issue in social cognition (Brass & Heyes 2005). The problem refers to the ease with which humans perform imitative behaviours. Imitation is a highly complex behaviour if one takes the view that the brain must decode and find meaning in the actions of others. Simulation theory explains the correspondence problem with overlapping activation between observation and execution of actions/bodily states that result in a far more automatic vicarious processing.

Simulation theories are influential within social-cognitive sciences. However, they are subject to some criticism, and to an extent, their weaknesses are recognised by their key promoters. One of the key criticisms is that of the assumption that mirror-processing leads directly to understanding as there is no simple one-to-one mapping between observation and meaning. The observation of an event is affected by the state, context and past experiences of the observer, therefore indicating a much greater influence of top-down processes (Jacob, 2008). Others argue that the information offered by simple simulation of an action state is insufficient for generating higher-level inferences such as intentions (Borg, 2007). Indeed, most simulation theorists recognise the importance of higher-level cognitive empathy processes and generally do suggest that this is required for fully developed empathy abilities. The following section will discuss the influence of cognitive processes in empathy.

1.2 Cognitive models of empathy

Cognitive empathy refers to the higher-level interpersonal processes which arise out of executive functions and mental representations of the self and others. This construct is made up of a series of interconnected processes whose primary function is to enable a person to form and attribute mental states to another and is a necessary for high-level social cognition (Smith, 2006; Davis, 1996). Key processes within this construct include perspective taking, self-other control/discrimination, mentalizing, theory of mind and self-awareness, amongst others.

Perspective taking refers to the cognitive capacity to see the world through another person's viewpoint, which allows an individual to anticipate the behaviour and reactions of others (Davis, 1983). It is a top-down process in which one imaginatively transposes themselves to another person (Batson, Fultz, & Schoenrade, 1987) and can refer to the ability to imagine themselves in the visual perspective (Aichhorn, Perner, Kronbichler, Staffen, & Ladurner, 2005), bodily location (Blanke, Mohr, Michel, Pascual-Leone, Brugger, Seeck *et al.* 2005), or mental perspective of another (e.g. someone else's beliefs) (Frith & Frith, 2006). Abilities such as knowing where a person is looking and what they can see, given their vantage point, enables us to identify the causes and reasons for their behavioural or emotional responses. These capacities allow a person to participate in role-taking by means of understanding the perspective that another in a role would assume (Iannotti, 1978). Perspective taking is known to have a modulatory role in emotional empathy and neural responses during social emotions (Ruby & Decety, 2004). When asked to take a first person perspective, participants produce neural activity which is indicative of responding to social emotions in themselves; however this activity is not present when participants are asked to take a third person perspective. Therefore, intentionally taking the perspective of another can be seen to influence the way one responds other people's bodily and emotional states.

A crucial process required for successful perspective taking is the capability for self-other control/discrimination which includes not only the ability to distinguish representations of the self and others but also to switch between these representations (Sowden & Shah, 2014; Brass, Derrfuss, & von Cramon, 2005). When taking the perspective of another, it is important that we inhibit representations of the self and promote other representations, and when we want to prevent imitative behaviours of the other we must inhibit the other representation in order to focus on the self-perspective. De Vignemont (2013) argues that in order for empathy to operate effectively we must possess a 'whose system' process for determining who (the self or the other) is undergoing an experience based on incoming perceptual information. Common behavioural test for this process, such as the 'Control of Imitation' task, rely on a switching of bodily representations (Brass, Bekkering, & Prinz, 2001) and are able to display individual differences in self-other control abilities.

Mentalizing and Theory of Mind (ToM) refer to the processes by which we make inferences about mental states (Goldman, 2012; Frith & Frith, 2005). ToM is seen as an intuitive understanding about others (many people with high functioning autism pass ToM tasks but do so through long-form reasoning rather than intuition; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) whilst perspective taking is seen as a flexible orienting towards representations of the other. Perspective taking depends upon at least two kinds of representations other people: a representation of another person per se (that is, as another being with the capacity for mental states), and a representation of that other person's mental states (Scholl & Leslie, 1999).

ToM also refers to a milestone of cognitive development in which we are able to remove ourselves from the egocentric perspective and to think like another person. This milestone is thought to be responsible for children of 5-6 years old being able to pass the 'false-belief' task (Apperly, Samson, Chiavarino, & Humphreys, 2004). In this classic development task children observe a person placing an object in an obscured location before leaving the room. At this point a second person comes into the room and moves the object to a separate obscured location. The child is then asked where the first person would look for the object. Before ToM develops the child will point to where the second person has placed the object, however they should have answered with the first person's location. Passing this task requires an understanding of the first person's mental state, and therefore ToM, to realise that this person does not know the object has been moved.

The neural basis of cognitive empathy has been extensively studied and a number of key regions have been highlighted. The right temporo-parietal junction (rTPJ) is a region commonly associated with neural processes for social interactions, particularly with processes linked to cognitive empathy (Hetu, Taschereau-Douchel & Jackson, 2011). It is considered to be key for ToM as it displays activation when reading passages in which one is asked to imagine the mental states of others, and it can be dissociated from regions which process the mere presence of other people in one's surroundings (Saxe & Kanwischer, 2003). Additionally, repetitive transcranial magnetic stimulation (rTMS) studies have

shown that inhibiting this region results in worsened performance on both perspective taking and ToM task (Costa, Torriero, Oliveri, & Caltagirone, 2008). It is considered to be particularly relevant for controlling self-other representations, with excitatory stimulation of the region resulting in increased performance on the Control of Imitation task (Santiesteban, Banissy, Catmur & Bird, 2013). A study examining lesions to the TPJ found imitative control and perspective-taking performance to be relatively impaired in a manner that was significantly correlated (Spengler, von Cramon, & Brass, 2010). There is evidence which suggests that this region is important for perspective taking and self-other control because it plays a role in the maintenance of bodily representations and because it is involved in switching between self and other representations (Sowden & Catmur, 2013). The region is also linked with cognitive attentional switching and orientation, which may operate via a similar mechanism to self-other control (Krall, Volz, Oberwell, Grefkes, Fink & Konrad, 2016). An fMRI meta-analysis showed that anterior portions of the region are specifically attuned to social interaction, however posterior portions are involved in perspective taking, theory of mind and attentional shifting. This was considered to be indicative of a shared mechanism for perspective taking, self-other control, and attentional shifting (Krall, Rottschy, Oberwelland, Bzdok, Fox, Eickhoff, Fink & Konrad, 2014).

In addition to the rTPJ, Frith & Frith's (2003) review has highlighted a three component system involved in cognitive empathy and mentalizing processes, which involves the medial prefrontal cortex (MPFC), the temporal poles, and the posterior superior temporal sulcus (STS). The latter is generally taken to encompass part of the rTPJ region, already discussed. The MPFC is thought to be the basis of distinguishing mental states from the observed physical behaviours of another; the STS region has a role in detecting and assigning agency (the mechanism for processing ownership of observed or perceived actions and experiences), and the temporal poles are thought to be involved in accessing social memories which may act as scripts for ToM. Cumulatively, the abilities of these regions contribute to mentalizing and theory of mind abilities. Frontal regions such as the dorsolateral prefrontal cortex have also been highlighted in cognitive empathy processes, with inhibitory stimulation to the region resulting in decreased false belief task performance (Costa *et al.* 2008). Decety & Jackson (2004) also suggest that a network of frontal regions made up of the dorsolateral

prefrontal cortex (DLPFC), the ventromedial prefrontal cortex (VMPFC), the medial frontal cortex (MFC) and the frontopolar cortex (FPC), are responsible for the cognitive processes which mediate empathy. These regions are involved in a number of functions that influence our empathic experience such as emotional regulation, self-awareness and executive functioning.

This is by no means an exhaustive account of cognitive empathy processes but the key abilities described above provide an account of cognitive empathy as a set of processes involved in the development, maintenance and attention orientation of other people's representations, both mental and bodily. Such processes are key to the complex empathic responses of humans and are key in the development of social cognitive abilities. They are particularly important for the top-down control of empathy and are considered be distinct from affective empathy, however their processes are highly complementary in social cognition and empathy (Smith, 2006).

1.3 Interactions between affective and cognitive aspects of empathy

So far in this chapter I have described empathic processes in terms of divided, though complementary, systems of cognitive and affective constructs of empathy. However, a number theories described herein have been developed out of research into perception action models and simulation theories, and cognitive empathy. A key theory among these is described by Decety and Jackson (2006), in which they offer a social cognitive perspective on empathy (see also: Jackson, Melztoff & Decety, 2005; Decety and Sommerville 2003; Jackson and Decety 2004). Their models propose that empathy is an interaction between three key components: [1] *simulation based affective sharing* based on perception action coupling; [2] *self-other awareness and control,* which prevents confusion between self and other perspectives; and [3] cognitive processes which allow for the *mental flexibility* required to adopt the subjective perspectives of others (e.g. ToM). This model of empathy integrates various constructs of empathy and dictates that overall empathy abilities rely on dissociable information processing mechanisms. It predicts that dysfunctions within individual components, or in the interaction between

components, is related to empathy-related conditions such as autism spectrum disorder (ASD) and schizophrenia.

A number of studies have highlighted the importance of self-other distinction and awareness on empathic processes. For example when participants are trained to increase self-other control processes via a behavioural task, they display increased subjective responses and corticospinal responses associated with empathy (de Guzman, Bird, Banissy & Catmur, 2015). When participants are asked to adopt a self-perspective (as opposed to another's perspective) during observations of pain or suffering, neural and subjective empathic responses are increased (Greezes & Decety, 2006, Lamm, Batson & Decety 2006). Conscious modulation of self-other discriminations is therefore shown to influence empathic simulation responses. Additionally, a review of rTMS stimulation to self-other control neural regions has shown a link between these processes and empathic responses (Hetu *et al.* 2012).

Combined psychophysiology and neuroimaging evidence suggest that these cognitive empathy processes provide a mediating or facilitatory role in a person's empathic experience (Preston, Bechara Damasio, Grabowski, Stansfield, Mehta, & Damasio, 2007). When asked to imagine themselves in the shoes of a person with whom they could relate, participants showed greater simulation, or affective empathy. Activation in neural regions associated with cognitive empathy only showed overlap with simulation regions when they could relate to the person in the scenario, and as a result these simulation processes were generally reduced. Other cognitive processes such as cognitive appraisal have also been shown to affect simulation processes for empathy (Lamm *et al.* 2006). Here participants viewed another person suffering and were told that they were receiving treatment which was to be either successful or unsuccessful. Emotional empathy was increased when participants knew the treatment was going unsuccessful and was decreased when they knew it would be successful. This difference in response based on cognitive appraisal was displayed in both subjective reports and neural simulation for the suffering. These studies show that cognitive empathy processes,

whether they be subliminal or conscious, can have a significant impact on emotional empathy processing.

The social cognitive account of empathy model has received particular attention in the field of vicarious pain processing (Jackson & Decety 2006; Cheng, Yang, Lin, Lee, & Decety, 2008; Bufalari, Aprile, Avenanti, Di Russo, & Aglioti, 2007, Avenanti, Minio-Paluello, Bufalari, &Aglioti, 2009, *See* Lamm Decety & Singer 2011 *for review*) and visual-tactile empathy (*see* Keysers 2010 *for review*) with a number of studies using it as the theoretical basis for their research. As such, this theory of empathy will form the basis of the predictions I make during the empirical studies described in the present thesis.

2. The Neural Processing of Pain

This thesis will focus on the application of the above described affective simulation and cognitive appraisal empathy theory to observations of pain. Consequently, it is important to describe the neural underpinnings of pain experiences in humans. The International Association for the Study of Pain defines it as follows: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in such terms of damage" (Mersky & Bogduk, 1994). Pain is often used to describe a variety of unpleasant experiences ranging from tissue damage to suffering and can be acute or chronic. In this thesis I will focus largely on the physical pain related to tissue damage, also known as nociception, however other aspects of pain, e.g. emotional and social pain, will be covered in certain studies (**Articles II** and **III**). Nociception refers to the detection of tissue damage by specialised receptor cells throughout the surface of the body (A delta and C fibres) that cause a variety of central neural responses which cover sensory, emotional and cognitive dimensions (Loeser & Melzack, 1999).

In a review of PET and fMRI articles, Peyron, Laurent & Carcia-Larrea (2000) highlighted a series of neural regions that formed a network which showed specificity to the encoding of pain stimuli. The

critical components of these regions included the primary and secondary somatosensory cortex (SI and SII) and the insula, which all process the sensory aspects of pain (such as the intensity and location of stimuli); and the anterior cingulate cortex (ACC), which processes the affective and attentional components of pain. These findings showed support for one key component of neurocognitive theories of pain, the 'neuro-matrix', also known as the 'pain-matrix (Melzack, 1999, see **Figure 1**). This theory states that a network of regions exists that show specificity for the processing of pain. This network has three key nodes: the sensory-discriminative node, made up of the somatosensory cortices and insula, and the affective-motivational node, which is primarily made up of the anterior cingulate cortex, and cognitive evaluative, made up of frontal regions. Whilst this system acts as the primary processing regions for pain, a number of input systems are required, including: (1) sensory inputs; (2) visual and other sensory inputs that influence the cognitive interpretation of the situation; (3) cognitive and emotional inputs; (4) the neural inhibitory modulation inherent in all brain function; (5) the activity of the body's stress-regulation systems. This interconnected system reflects the complex and multi-faceted nature of pain processing.

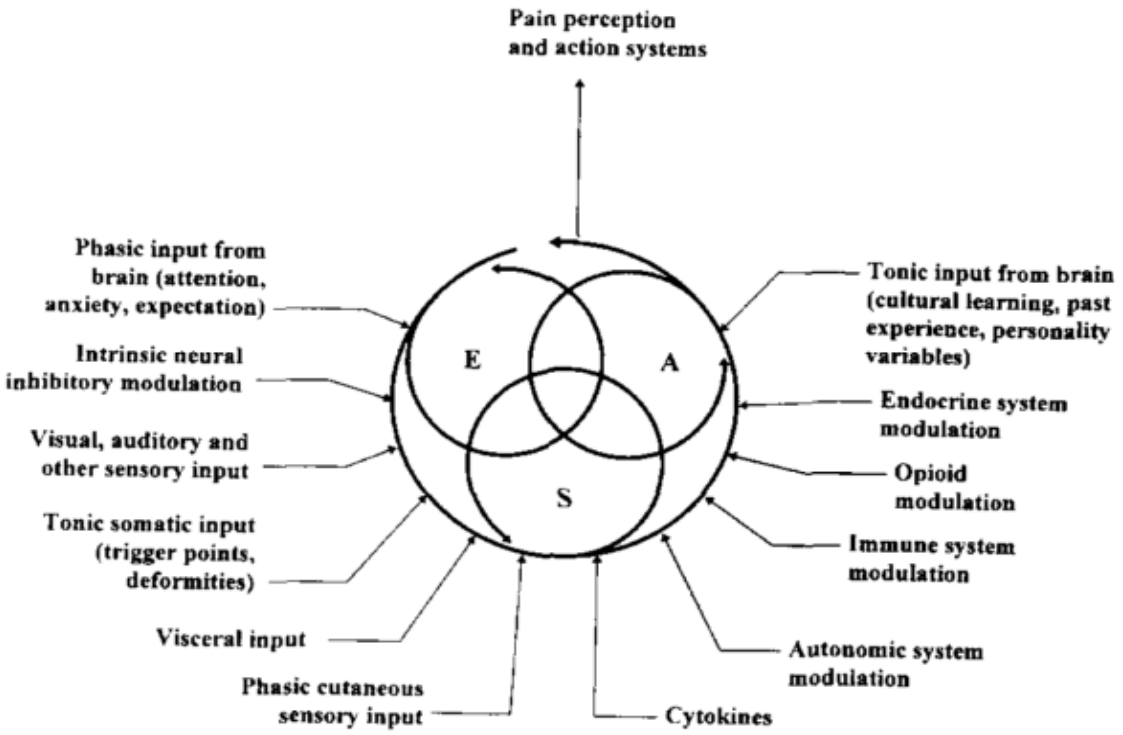


Figure 1.1: From Melzack (1999): The 'body-pain neuro-matrix' model describing three distinct nodes which contribute to pain processing, and the bodily and cortical inputs associated with each. These include: (A) Affective-motivational, (S) Sensory-discriminative, (E) Evaluative cognitive dimensions. The position of each ingoing arrow refers to the degree to which each process draws on each node.

More recent accounts of the network have challenged the assumption that the pain matrix is specific for the processing of pain (Iannetti & Mouraux, 2010). In a review of electroencephalography (EEG), magnetoencephalography (MEG), functional Magnetic resonance imaging (fMRI) and positron-emission tomography (PET) neuroimaging studies the researchers showed that this network responded similarly to non-painful sensory stimuli. Rather than a pain specific network it was suggested that the pain matrix is primarily involved in processing the salience of stimuli in the environment. Mouraux, Diukova, Lee, Wise, & Iannetti (2011) suggest that processing in the matrix can be largely triggered by: [1] multimodal neural activities (regardless of sensory modality) and [2] somatosensory-specific but not pain-specific neural activities (i.e., activities elicited by both nociceptive and non-nociceptive somatosensory stimuli). Critically, the degree of processing in the region showed a positive correlation with the perceived salience of the stimuli. These more recent accounts of the system propose an alternative view, which reflects a system involved in detecting, orienting attention towards, and reacting to the occurrence of salient sensory events (Legrain, Iannetti, Plaghki & Mouraux (2011).

As a result of these theories researchers have suggested using the term 'pain matrix' with some caution, as by a neuroimaging study which showed that observations of individuals who are congenitally unable to experience pain (through a mutation affecting sensory neural channels which are required for nociceptive pain inputs) showed normal functioning in pain matrix regions when compared to typical controls (Salomans, Iannetti, Liang & Wood, 2016). The research in this thesis will acknowledge this non-specificity for pain and the caution required when using the term pain matrix. However, when studying pain stimuli the pain matrix is still seen as a good guide for

understanding the mechanisms associated with the experience, and activation in the regions during the presentation of pain stimuli is still considered to be a marker of pain processing (Eisenberger, 2015).

3. Visual-Somatosensory Multisensory Processing and Vicarious Touch and Pain

One's body can be perceived through multiple sensory channels however in order to successfully navigate, perceive, experience our world we rely on the integration of information from multiple channels (Alias, Newall & Mamassian, 2010). A classic example of this is the degree to which taste and smell sensory modalities interact to result in the experience of flavour (Auvray & Spence, 2007). Whilst each of these modalities are distinct the experience of eating food is significantly diminished when either one is not functioning. Multi-sensory processing is considered to be so widespread in cognition that it is a common view that the neocortex is 'essentially multisensory' (Ghazanfar & Schroeder, 2006).

When perceiving our bodies as a whole, vision and somatosensation (a collective term for the sensations of touch, temperature, body position, and pain) are the most notable sensory modalities. The interactions between these modalities are crucial for our abilities to move through and interact with the world. When we walk through a crowded space our visual and somatosensory must constantly monitor the position of our bodies in relation to nearby objects in order to seamlessly pilot us through our environment (Popper & Eccles, 1977). This automatic interaction between the senses leads to the development of a 'body schema' which could be thought of a multimodal sense itself. This touch and vision interaction also extends outside of our bodies into a region known as peripersonal space (PPS) (Rizzolatti, Fadiga, Fogassi & Gallese, 1997). It is defined as the region of space or immediate vicinity in which objects can be grasped, manipulated and interacted with. A number of key studies have identified collections of neurons which seem to be exclusively associated with visual tactile multisensory processing and PPS. Neurons in ventral premotor cortex (PMv) which respond to objects within the PPS are shown to be active even when the object can no longer be seen

(i.e. when the lights are turned off) but which are inactive when the participant sees that the object has been moved out of PPI (Graziano, Hu, & Gross, 1997).

The plasticity of this integration can be demonstrated when mirrors are used within our PPS. When observing a mirrored image of one's left hand using a mirror placed parallel to the hand, it appears to be the right hand. However, one still knows how to manipulate objects in this perspective in the appropriate way (Maravita, Spence, Clarke, Husain, & Driver 2000). Additionally, visual modulation of the appeared size of our hands can significantly alter the way we perceive tactile differences in PPS. When the hand is magnified or shrunk using a magnifying glass, participants perceive the tactile distance between objects and their hands as smaller or larger, respectively. This is an example of the brain using cross-modal information to attune to the tactile experience to that observed in vision (Taylor-Clarke, Jacobsen, & Haggard 2004).

The conscious experience of this visual-tactile integration is a crucial process within 'bodily self-consciousness'; the experience of where an individual is in space and experience of the world from where an individual is located in space (first person perspective) (Blanke, 2012). Connectivity fMRIs have revealed a network of regions associated with the multi-sensory processing involved in bodily self-consciousness which includes the right temporo-parietal junction, premotor area, supplementary motor area and insula (Ionta, Martuzzi, Saloman & Blanke 2014). One of the clearest demonstrations of visual tactile multi-sensory processing and bodily self-consciousness is the rubber hand illusion (RHI) (Tsakaris & Haggard, 2005). In this paradigm participants place one of their hands under a cover so they cannot see them whilst a rubber hand is placed on a table on the side of the occluded hand. The experimenter then strokes both the hand and the rubber hand synchronously with a brush. Participants in this experiment regularly report feelings of ownership of the rubber as if it were their own. Furthermore, when asked to guess the distance between their own hand and the rubber hand participants experience a proprioceptive drift in which they report feeling as if their hand is closer to the rubber hand after the illusion Here the interaction of visual and tactile information leads to the incorporation of the rubber hand into their own bodily self-consciousness. This paradigm has also

been applied to a whole-body level using virtual reality goggles to give the illusion of the ownership of another person standing in front of them (Leggenhager, Tadi, Metzinger & Blanke 2007).

So far I have discussed visual tactile integration in relation to self-awareness and consciousness (as the RHI shows); however there is also strong evidence for its involvement when encountering other people's bodies. Bimodal visual tactile neurons in the ventral premotor region in macaque monkeys have shown activation when visually observing tactile and visual stimuli being placed on another person's body and when those same stimuli are placed on the monkey's own body (Ishida, Nakajima, Inase, & Murata, 2009). Morrison, Lloyd, Pellegrino & Roberts (2004) claim that multisensory processing is vital for empathy and simulation theories suggesting that mirrored-representations are achieved through a process of multi-sensory integration. It is also notable that the rTPJ is considered an important region in networks for both visual tactile integration and self-other discriminations within empathy theories (Jackson & Decety, 2006). In the next two sections I will discusses how concepts of multisensory processing and empathy apply to the processing of observations of other people's touch and pain.

3.1 The vicarious processing of touch

Understanding observations of touch is an important part of our social world and provides an excellent example of visual-tactile empathic processes. When we see two people's hands touch or an individual touch a soft fabric we are able to vividly imagine how that feels and to generate useful social information from it. fMRI studies have shown that the secondary somatosensory cortex (SII), but not the primary somatosensory cortex (SI), shows a significant degree of overlap between observations and experiences of touch (Keysers, Wicker, Gazzola, Anton, Fogassi & Gallese, 2004). In this study participants were shown videos of people's legs being touched and objects being touched, whilst they received touch to their own leg; here, overlapping SII activity was observed across the two conditions. In a later review Keyser s*et al.* (2010) suggest that activation in SI (particularly area BA3) may demarcate self-experienced touch relative to vicarious touch. EEG

studies have also displayed modulation of somatosensory-evoked potentials, known to emanate from SI and SII, when individuals view touch (Martinez-Jauand, González-Roldán, Muñoz, Sitges, Cifre, & Montoya, 2012; Bufalari *et al.* 2007). In these studies participants are touched on the hand, which causes a reaction in the somatosensory cortex. Simultaneously they view videos of touch, which then modulates the somatosensory responses initiated by the experienced touch. This modulation is taken as evidence for the activation of the somatosensory cortex by the observed touch through simulation processes.

Keysers' *et al* (2004) study also showed that similar SII vicarious activation occurred when participants viewed objects being touched, thereby calling into question the notion that these processes are inherently social. However, in a later study a similar methodology was used which also varied the degree of intentionality in the touch administered to an object (i.e. intentionally poking a person/object or accidently brushing against a person/object). The researchers showed that SII activation showed overlap in all conditions, but critically, they showed that vicarious activation area BA2 of the SI correlated positively with the degree of intentionality in the touch (Ebisch, Perrucci, Ferretti, Del Gratta, Romani, & Gallese 2008). This raises the possibility that both the SII and some portions of the SI are involved in vicarious touch and that the regions may process the meaning behind touch. Similar findings supporting this idea have been found in the SI which have shown that this region is sensitive to differentiating between pleasant touch (e.g. caressing) and unpleasant touch (e.g. forceful touch; Walker, Trotter, Woods & McGlone, 2017). Additionally, neural reactions to touch observations in the SI have been shown to correlate positively with inter-individual trait levels of empathy, thereby demonstrating the close link between vicarious processing and empathy (Schaefer, Heinze, & Rotte, 2012).

3.2 The vicarious processing of pain

Vicarious pain processing refers to the neural activity exhibited when individuals observe someone else experiencing pain. The prominent social cognitive models of empathy largely based their theories

upon these empathic processes for pain (Decety & Jackson, 2004, Jackson, Meltzoff & Decety, 2006). Here the assumption is that multisensory processing occurs between visual inputs of others in pain and the observers' own systems for processing privately-experienced pain (the pain matrix) through a process of simulation.

The earliest example of neuroimaging research into vicarious pain highlighted the role of simulation however unlike research into touch, only regions which processed the affective components of privately-experienced pain (the affective pain matrix: ACC, AI) showed simulation (Singer, Seymour, O'Doherty, Kaube, Dolan, & Frith 2004). In this study participants were shown videos of loved ones experiencing pain which primarily activated the anterior insula (AI) and rostral anterior cingulate cortex (rACC). This finding has been established across a number of fMRI studies, which show simulation responses in the affective pain matrix, particularly the ACC, but not in sensorimotor systems (Jackson, Brunet, Meltzoff & Decety, 2006; Morrison *et al.* 2004). It is thought that this type of affective motivational response prepares a person for the appropriate behavioural responses to adverse events. It has also been suggested that the vicarious processing of pain may relate to responses, memory and encoding rather than sensory discriminative processing (Godinho, Magnin, Frot, Perchet, & Garcia-Larrea 2006). Interestingly, simulation of pain is not limited to physical pain. Observing others experiencing social exclusion and social pain also activates the same affective motivational regions associated with physical pain (Eisenberger, 2015; Eisenberger, Leiberman, & Williams 2003). In this case these regions may be involved in regulating the affective response and adaptive behaviours of this kind of pain.

In addition to emotional empathy components, cognitive empathy processes such as perspective taking are known to have a modulatory role in simulation responses to observing others in pain (Lamm, *et al.* 2007). When asked to take the perspective of another experiencing pain, participants produce neural activity which is indicative of responding to self-experienced pain, whereas when participants were asked to take the 'other' perspective they produced activity which is associated with

altruistic behaviours. As such, intentionally taking the perspective of another can be seen to affect the way one responds affectively to observed pain.

Whilst the majority of fMRI studies have only explored the affective-motivational pain matrix, non-fMRI studies have displayed results which are indicative of sensory-discriminative simulation. In MEG and EEG studies participants have been shown to display suppression of mu rhythm (Rolanic) oscillations (Cheng, *et al.* 2008; Yang, Decety, Lee, Chen, & Cheng, 2009). These oscillations are known to be representative of sensorimotor activation, and suppression is linked with increased activity across the regions. EEG has also been used to show the effect of observing pain on pain-related potentials known as laser-evoked potentials (LEP). Here participants are stimulated with mild pain which causes a known LEP response that is known to originate from sensory-discriminative pain regions. Observing pain modulates these potentials, which is taken as evidence of the somatosensory cortices' involvement in vicarious pain (Valeriani, Betti, Le Pera, De Armas, Miliucci, Restuccia, Avenanti, & Aglioti 2008). Finally, transcranial magnetic stimulation (TMS) has also been used to assess corticospinal inhibition when observing pain. Whilst participants view needles injecting hands, TMS was used to generate a motor-evoked potential (MEP) over the same topographic region as the observed pain (the hand). The sight of pain inhibited this potential relative to no-pain which was taken as evidence of the involvement of sensorimotor regions in observing pain (Avenanti, Minio Paluello, Bufalari & Aglioti, 2006; Minio Pauello, Avenanti & Aglioti, 2006; Avenanti, Bueti, Galati & Aglioti, 2005). The degree of corticospinal inhibition has also been shown to correlate with participant's judgements of pain unpleasantness and inter-individual differences in trait empathy (Avenanti, *et al.* 2009). Furthermore, it has also been shown that this effect is sensitive to racial bias in the participants, with caucasian participants who showed more implicit bias displaying reduced inhibition when viewing black people in pain, compared with white (Avenanti, Sirigu, & Aglioti, 2010).

In a review of fMRI papers assessing vicarious pain, a core network of the anterior insula and anterior cingulate cortex was displayed (Lamm *et al.* 2011, see **Figure 1.2**). This network is thought to represent global states and feelings and is responsible for generating adaptive states for both other-representations and self-experienced pain. This study also showed that certain image-based paradigms did activate the sensory-discriminative regions of the pain matrix. These paradigms involved vivid displays of pain to particular parts of the body, known as 'flesh and bone' pain. Overall this study suggests that whilst sensory-discriminative regions are sometimes activated during pain observations they do so on a less consistent basis than affective-motivational regions. Whilst simulation may occur in affective-motivation regions, connectivity patterns for self- and other-experienced pain are shown to be different; self-experienced pain shows connectivity with midbrain structures, such as the periaqueductal grey matter, whilst other-experienced pain shows connectivity with frontal and parietal cortical regions, such as the dorsolateral-prefrontal cortex and the TPJ (Zaki, Oshsner, Hanelin, Wager & Mackay, 2014). This indicates that whilst vicarious pain does involve simulation of pain matrix regions, the networks responsible may be related to cognitive empathy processes rather than just visual-tactile integration.

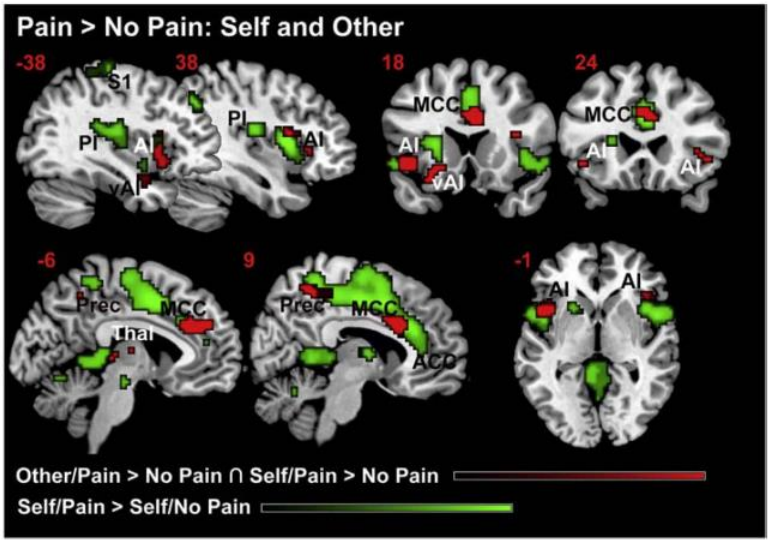


Figure 1.2: From Lamm's *et al.* (2011) meta-analysis of empathy for pain fMRI studies. Common and distinct neural regions which show activations during experiences of pain in the self (green) and overlapping activation during observations of others in pain (red). Areas of common activation

include affective motivation pain regions (AI, ACC/MCC, Thalamus and Precuneus) and distinct activation of self-experiences includes sensori-discriminative pain regions (SI/SII, PI).

Observing pain is known to be linked with our own perception of pain as well as empathy. For example, increasing levels of empathy by exposing individuals to observations of pain affects an individual's own perception of pain by increasing sensitivity to it (Loggia, Mogil, & Bushnall, 2008). In addition, when one has been administered painkillers such as paracetamol, which reduce our capability to experience pain, empathic judgements of other people's pain is reduced (Mischkowski Crocker & Way, 2016) Individuals with Alexythemia (characterised by low emotional responses) display low vicarious responses to observed pain in the ACC and lower empathic responses and judgements to observed pain (Moriguchi, Decety, Oshnishi, Maeda, Mori, Nemoto *et al.* 2007). These processes are also influenced by the way we view other people; if the person in pain is thought to be similar to the observer, empathic perceptions of pain are increased (Serino, Giovagnoli & Ládavas, 2009) and observations of outgroup individuals (based on race) is known to affect the degree of our empathic neural responses to pain (Avenanti *et al.* 2009). These studies show that functioning systems for self-perceived pain and interpersonal factors are crucial for simulation processes to occur and to elicit empathic responses.

4. Mirror-Touch, Mirror-Pain and Mirror-Sensory Synaesthesia

The vicarious processing of both pain and touch is known to activate regions associated with the private experience of those sensations; however, for the majority of people these processes are implicit and do not elicit conscious sensations of the observed experience. However for some people observations of touch and pain do elicit conscious sensation on their own bodies, which is known as 'mirror-sensory synaesthesia' (Fitzgibbon, Enticott, Rich, Giummarra, Georgiou-Karistianis & Bradshaw 2012).

Synaesthesia is a crossmodal sensory experience in which stimulation to one sensory modality (the inducer) causes an unusual experience in another or within the same modality (the concurrent) (Grossenbacher & Lovelace, 2001). A common example is grapheme colour synaesthesia, in which a letter or phoneme induces a colour perception. This condition is marked by significant inter-individual differences and variations making it difficult to categorise (Simner 2012). It is thought to occur of the basis of abnormality in existing crossmodal networks perhaps through a process of hyperactivity or disinhibited feedback (Kadosh, Hendik, & Rubinstein, 2008; Grossenbacher & Lovelace, 2001), or on the basis of the atypical connections between sensory modalities formed during early neural development (Baron-Cohen, Harrison, Goldstein & Wyke 1993).

Mirror-sensory synaesthesia is distinct from other kinds of synaesthesia in that it is thought to be based on the simulation-systems which are typically used for empathic processes which have inherently social functions (Blakemore, Bristow, Bird, Frith & Ward, 2005). Rothen & Meier (2014) claim that mirror-sensory experiences cannot be fully characterised as a synaesthesia based on the following factors: [1] the inducer (observing touch/pain) always induces a predictable response (that is, one matching the observed sensation); [2] that it lacks the idiosyncrasy of other types of synaesthesia (the concurrent sensation is not usually categorised by the observer); and [3] it has an inherently social component as it is based on empathic simulation-systems. Whether or not the sensation can be classified as a synaesthesia it remains an important condition with the potential to gain understanding of how the empathic processes for touch and pain operate. Mirror-sensory synaesthesia represents an extreme of empathic touch and pain processes, and by understanding the underlying processes involved in this extreme we can better understand the factors that contribute to empathy for pain and touch. The following section will discuss mirror-touch synaesthesia and then mirror-pain, which will be of particular interest for the current thesis.

4.1 Mirror-touch synaesthesia

Mirror-touch synaesthesia is a condition characterised by perceptions of touch on one's own body when they observe touch on another's body. It was initially highlighted in an fMRI study of a single individual and the results showed that regions that are normally associated with vicarious touch, i.e. the sensorimotor system, were activated in the synaesthete to a greater extent than controls (Blakemore *et al.* 2005).

Later attempts to study the prevalence of the condition estimated that 1.6% of the population displayed these experiences, making prevalence comparable to that of the other most common types of synaesthesia, e.g. grapheme-colour synaesthesia (Banissy, Kadosh, Maus, Walsh & Ward 2009). This study used a visual-tactile congruency task in which participants viewed someone's face being touched on the left and right side whilst they were touched on the left and right side of their own face. Mirror-touch synaesthetes were characterised by making a significant number of errors on the task, i.e. stating that congruent and incongruent felt and observed touch were on the same hemisphere of the face. The condition was also found to have two subtypes (Banissy & Ward 2007): 'specular', where observed touch is felt on the body as if one were looking in a mirror (i.e. if the left side of the other face was touched the observer would experience touch on the right side of their face), and, less commonly, 'anatomical' in which individuals feel the touch in the same anatomical location of the observed touch (i.e. observation of touch to the left side of the other's face would elicit perceptions in the left side of the observer's face). Usually it is considered to be a development condition; however a study of amputees displayed that it can be acquired, in this case after a traumatic injury (Goller, Richards, Novak & Ward, 2013). In this study the prevalence was significantly higher than in the general population (~30%) and the mirrored sensations were more likely to be experienced in their amputated limb.

Mirror-touch synaesthetes have been shown to display a number of characteristics relevant for empathy processes. When tested on self-other control and inhibition, mirror-touch participants performed significantly worse than controls, however they showed normal levels of performance on

measures of visual perspective taking and theory of mind (Santiesteban, Bird, Tew, & Cristina, 2015). This atypical processing of self-other representations also impacts the way these synesthetes process their self-representations; after observations and mirrored experiences of touch, mirror-touch individuals perform poorly on tasks of self-recognition, which was not the case prior to observing this touch (Malster, Banissy & Tsakiris, 2013). Similarly, mirror-touch participants have been shown to experience disturbances in their sense of agency and bodily ownership to a greater degree than typical participants (Cioffi, Banissy & Moore, 2016). These studies indicate that mirror-touch individuals have a greater degree of malleability in the formation of self and other representations. Where neurotypical individuals are able to distinguish between representations of the self and other, mirror-touch individuals experience a blurring which has significant impacts in the way they perceive their own bodies and the bodies of others (Cioffi, Moore & Banissy, 2014).

Additionally mirror-touch synesthetes have been shown to display both functional, when viewing touch, and structural fMRI differences, when compared with controls (Holle Banissy & Ward, 2013). When viewing pain MTS participants activated both the primary and secondary somatosensory cortices more so than controls, and MTS groups showed significantly greater grey matter volume in the secondary somatosensory cortex when compared with controls. This indicates that synaesthetes show atypical processing in their simulation of touch in both somatosensory cortices; however the structural effects indicate that the secondary somatosensory cortex is of particular significance in the condition. Interestingly, it has been shown that when non-synaesthetic controls are exposed to cortical excitability of the somatosensory cortex via transcranial direct current stimulant (tDCS), they report experiencing effects similar to those experienced by mirror-touch synaesthetes thus indicating the role of heightened somatosensory cortex activation in MTS (Bolognini, Minlussi, Gallo & Vallar, 2013).

Based on these findings two prevalent theories have been developed to explain the neural underpinning of MTS (Ward & Banissy, 2015). The first, Threshold Theory, states that mirror-touch experiences are rooted in a hyperactive mirror-system for touch. This system, which when functioning normally processes non–conscious vicarious processes, displays hyperactivity in MTS which results

in vicarious processing reaching a threshold for conscious experiences. The second, Self-other theory, states that mirror-touch synaesthesia is contributed to by disturbances in the self-other processing which leads to a blurring of self-other representations and an over-extension of the self to others. These two theories are thought to work in conjunction with one another with Threshold theory explaining the over-activity in the somatosensory cortices in these groups, and Self-other theory explaining the misattribution of other people's experiences to the self and the wider social cognitive effects observed in mirror-touch synaesthesia, i.e. self-other control, agency and sense of bodily ownership. More recently commentaries on these theories have suggested a third process which may run in parallel to Threshold theory and Self-other theory, that is, predictive coding (Ward & Banissy, 2017). This concept states that internal models about our surrounding world are developed which are adapted based on incoming sensory information. It is suggested that mirror-touch synesthetes participants may rely too heavily on their internal models of observed pain which leads to perceptions of pain.

Banissy *et al.* (2009) also suggest a neurocognitive model to explain the condition with three factors: 'what', 'who, and 'where'. The 'what' factor processes the nature of the touch being observed, i.e. object vs. human; the 'who' system processes to whom the touch sensation belongs, i.e. self vs. other; and the 'where' system focuses on whether the touch observed is the result of our own sensations or from a source outside of our bodies, i.e. embodied or disembodied. In mirror-touch synaesthesia the model assumes that abnormal interaction between these factors contribute to mirror-touch experiences.

4.2 Mirror-pain synaesthesia/responders

Mirror-pain operates in a similar way to mirror-touch in that observations of others in pain lead to conscious experiences of pain in the observer. It stands apart from mirror-touch synaethesia due to the extended network of neural regions involved in processing pain, including affective-motivational regions, and because of the high salience of pain sensations. Mirror-pain is generally not referred as a

form of synaesthesia, as is the case with mirror-touch synaesthesia. This is due the seemingly high prevalence, its somewhat contextual nature and because it is often describe as an acquired condition, all of which will be described herein. These factors mean that mirror-pain does not meet the criteria of synaesthesia described by Rothen & Meier (2014). Instead, this thesis will refer to this group as 'mirror-pain responders' as has been used in prevalent articles in the field (Osborn & Derbyshire 2010).

Whilst mirror-touch synaesthesia is generally considered to be a developmental condition, the majority of early research into mirror-pain focused on acquired synaesthesia following traumatic and painful events. One of the earliest presentations of mirror-pain was in a woman who acquired the experience after having a particularly traumatic pregnancy (Giummarra & Bradshaw, 2008). In another case a man with hyperalgesia, a condition characterised by heightened pain responses, experienced pain sensations when viewing his wife experiencing pain. Whilst hyperalegisia is a developmental disorder, his mirror-pain sensations were said to have developed through the course of his lifetime (Bradshaw & Mattingley, 2001). One of the most frequently researched groups in the field are amputees, particularly those who also report feeling phantom limb pains (Giummarra, Fitzgibbon, Chou, Georgia-Karistianis & Bradshaw 2008; Giummarra & Bradshaw 2008). In a sample of amputees with phantom limb pains 16.7% of participants reported that observing pain triggered their phantom pains, leading researchers to suggest that their past experiences of traumatic pain may be linked to their vicarious experience (Fitzgibbon, Enticott, Rich, Giummarra, Georgiou-Karistianis, Tsao, Weeks, & Bradshaw, 2010). TMS studies of these populations showed that these individuals displayed significantly higher corticospinal responses to observations of pain when compared with controls (Fitzgibbon, Enticott, Bradshaw, Giummarra, Chou, Georgiou-Karistianis, & Fitzgerald, 2012). Contrary to expectations, amputees who display mirror-pain experiences have been shown not to differ from controls on measures of empathy (Giummarra, Fitzgibbon, Georgiou-Karistianis, Micholls, Gibson & Bradshaw, 2010). As a result the researchers suggested that vicarious pain in phantom limbs is likely to develop because of past experiences and hypervigilance to pain, and a lack

of tactile feedback from their amputated limbs when their SI and SII simulate observations of pain, rather than because of increased levels of empathy in the group.

Mirror-pain has been researched in populations who have not experienced traumatic pain. An fMRI neuroimaging study of student populations showed that participants activated both the affective-motivation pain matrix and, critically, the somatosensory cortices (Osborn & Derbyshire 2010, ***See* Figure 1.3**). Control participants in this study failed to activate somatosensory regions, as have participants in the majority of fMRI studies on the topic. This study recruited MPS participants from a large student population by asking them to view a series of pain videos and images; if participants said that they experienced mirror-pain during one of these stimuli they were classified as mirror-pain responders. This fairly liberal and casual identification method displayed a prevalence rate of approximately 30%. More recent attempts to identify and characterise mirror-pain responders have resulted in the development of a psychometric measure for mirror-pain known as the Empathy for Pain Scale (EPS) (Giummarra, Fitzgibbon, Georgiou-Karistianis, Beukelman Verdejo-Garcia, Blumberg *et al* 2015). This study used principle component analysis to highlight three factors that contribute to mirror-pain experiences: affective distress, vicarious pain, and empathic concern. The researchers also correlated scores on these measure with Interpersonal-Reactivity Index scores and showed that only the 'personal distress' subcategory correlated with EPS; a scale which is related to affective empathy. This correlation with an empathy measure highlights a difference between traumatic MPS individuals, who do not show empathy correlations (Fitzgibbon *et al.* 2010), and mirror-pain responders. Critically this study placed the prevalence rate of mirror-pain experiences at 34% which is consistent with Osborn and Derbyshire's study. Behavioural studies have also been used to investigate mirror-pain responders (Vandenbrouke, Crombez, Van Ryckeghem, Brass, Van Damme, and Goubert, 2013). This study adopted a similar congruency-based paradigm to Banissy *et al.* (2009) in which participants viewed videos of people being pricked on the left and right hands whilst they received a mildly painful electronic pricking to their own left or right hand. The number of errors of congruency between the hemisphere of the observed and experienced pain was again used as a measure of mirror-pain experiences. Using this methodology the prevalence rate of mirror-pain

responding was significantly lower than previous estimates, 6.6%. However when the researchers asked participants to rate how often they experienced vicarious pain in their daily life the prevalence of mirror pain was approximately 22%. This difference in prevalence rate highlights the challenges of identifying mirror-pain responders and indicates that mirror-pain may be reliant on the context of empathic pain.

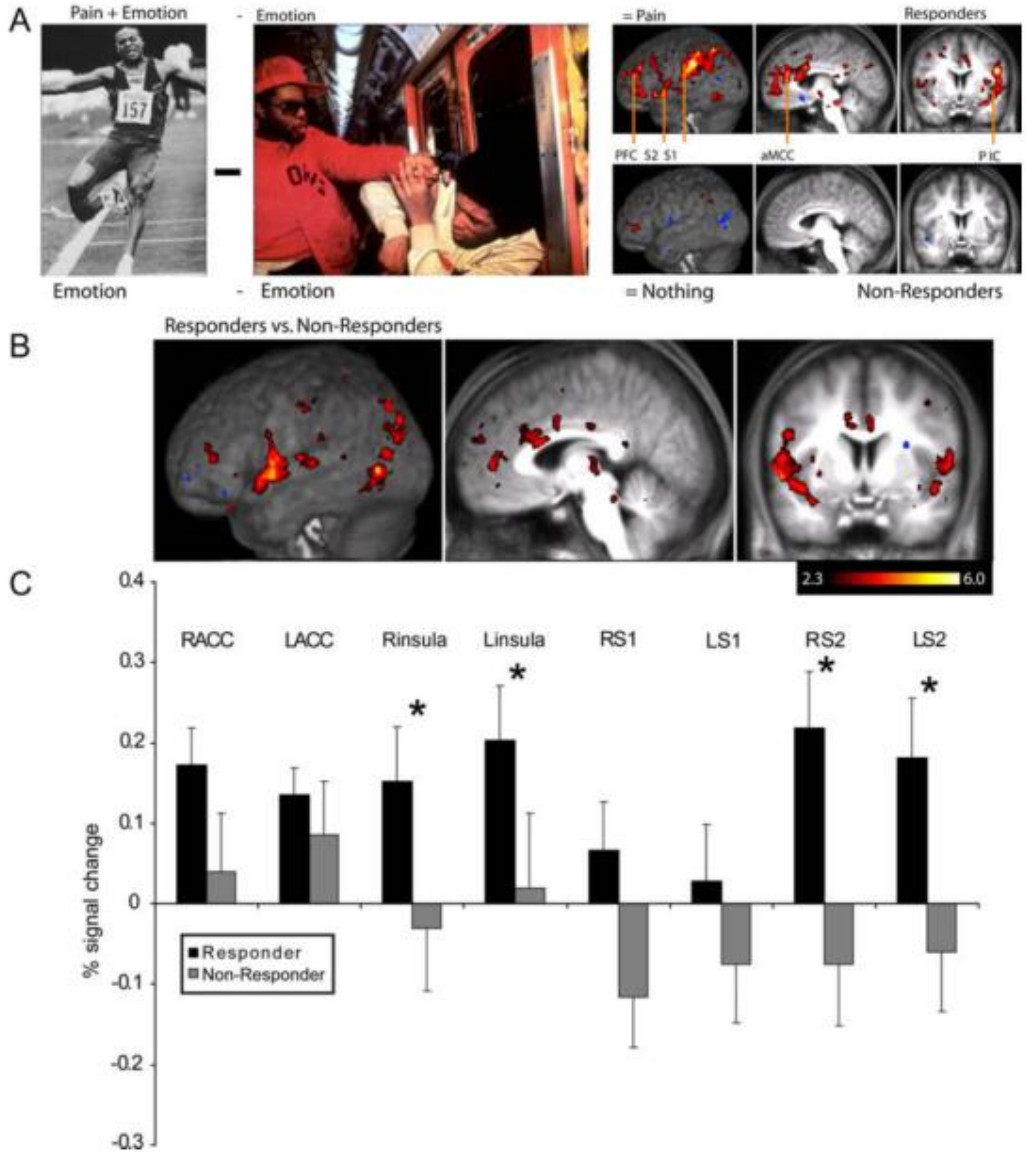


Figure 1.3: From Osborn & Derbyshire (2010). fMRI results showing secondary somatosensory activation in mirror-pain responders during the observation of physical and emotional pain (A). Controls in this study did not show any vicarious activation of these sensory-discriminative regions.

Responders showed increased activation in SII, ACC and frontal regions compared with controls (B). ROI analysis displays the distinct SII vicarious processing observed in mirror-pain responders (C).

These previous attempts to highlight mirror-pain responders have been useful in identifying the condition and providing a broad estimate of their prevalence. However, the screening measures described have either used fairly casual screenings methods, such as asking participants whether they felt mirror-pain in response to one video (Osborn & Derbyshire, 2010), relied on questionnaire measures without presenting pain stimuli (Giummarra *et al.* 2015), or have used opportunity sampling from unique populations (Fitzgibbon *et al.* 2010). Furthermore they have not attempt to characterise and categories individuals based on their subjective reports of mirror-pain experiences, instead they have assumed some degree of homogeneity of individuals who experience. These methods mean that it is difficult to establish however mirror-pain responders are represented in the population and how their experience of mirror-pain differs between one another. Neuroimaging investigations are also fairly limited with only Osborn and Derbyshire's (2010) study displaying evidence for a neural underpinning of mirror-pain in the general population and Fitzgiboon *et al.*(2010) showing neurophysiology effects in amputees. Currently the field is lacking evidence from a variety of MRI techniques which can provide information about the structural connectivity patterns and findings from other neuroimaging techniques such as EEG and TMS which will allow for the assessment of temporally specifically and causally linked effects.

Mirror-pain responders have been shown to display differences across a number of behavioural measures compared with controls (Derbyshire, Osborn, & Brown, 2013). This includes increased performance on a visual perspective-taking task which indicated that responders were less able to control for the visual perspectives of another. They also showed insula effects in the rubber illusion. In this experiment participants viewed an inanimate (rubber) hand whilst theirs was obscured. The rubber was stroked whilst the participant's hand was also stroked, which provokes an illusion of ownership in the rubber. Responders also showed an illusion of ownership when the stroke to the

rubber hand was asynchronous with the stroking to their own hand, a findings which is not displayed in controls. This indicates that mirror-pain responders are more likely to feel agency and ownership for other bodies. Finally, the study also showed that past experiences with pain can influence the likelihood of an individual feeling mirror-pain. Individuals who reported having sensitive teeth reported sensations of pain when observing another experiencing pain whilst eating an ice popsicle, many of these participants did not report mirror-pain in other contexts. This indicates that mirror-pain is malleable based on the context of the observed pain and that it is influenced by past experiences with pain, as suggested by findings with trauma patients and amputees. Currently, this is the only study which has attempted to assess the wider characteristics and traits associated with mirror-pain responders. Further profiling of this group is required in order to test expected links with interpersonal and empathic processes which have been hypothesised in the literature which contributed to mirror-pain and empathy for pain.

One of the key theories developed to explain mirror-pain follows broadly the same approach of Ward & Banissy's (2015) explanation of MTS. Fitzgibbon *et al.*'s (2012) model of empathy states that the experience of mirror-pain responders is based on three factors: [1] Hyperactivity of the mirror system; [2] Enhanced empathic capacity; and [3] Learned associations. Like MTS models this model assumes that mirror-pain responders display hyperactivity in the mirror/simulation processes than are normally present in participants. This hyperactivity is thought to be based on two potential mechanisms: [1] atypical structural connectivity in simulation systems which leads to increased neural connections between observation and experience; and/or [2] abnormalities in disinhibition between visual and somatosensory processing regions which results in a lack of suppression for the simulation that results from pain observations. The increased empathic capacity described in this model refers to a combination of cognitive affective empathy processes which are enhanced or abnormal in mirror-pain responders. This includes increased visual perspective and self-other control as well as an increased capacity for affective contagion. Finally, learned experiences refer to the influence of past pain or trauma experiences, which may lead to a hypervigilance for all types of pain or specific examples of it. This hypervigilance may activate neural responses for pain that cause perceptions of that pain.

Examples of this can be seen in amputees or hyperalgesic populations, or in individuals who have sensitivity to a particular type of pain. Both Osborn & Derbyshire's (2010) study and Fitzgibbon's *et al.* (2012) neurophysiological assessment of amputees suggest that the mirror-pain responders display evidence for the hyperactivity account of mirror-pain. However, no mirror-pain studies have specifically tested Ward & Banissy's (2015) Self-other theory and Fitzgibbon's *et al.* (2012) empathic capacity theory. In both theories these modulation of these empathic processes is thought to drive the hyperactivity observed in mirror-touch synesthetes and mirror-pain responders but the link is difficult to establish without specifically designed experiments and neuroimaging tasks.

5. Aims and Objectives

At this point, research into mirror-pain responding is at a relatively early stage. Whilst the population has been highlighted and theories have been developed to explain responders' experiences, little is known about the characteristics associated with the condition and evidence for its neural underpinning has not yet developed findings to fully support the neural models. It is also a condition that has the potential to teach us a great deal about how empathic pain, and empathy more generally, operates. These individuals represent an extreme on a spectrum of empathic pain, and a thorough investigation of their experiences and neural responses could provide insight into the mechanisms responsible for empathy for pain. Through a combination of neuroimaging, behavioural and questionnaire studies, this thesis will attempt to develop scientific understanding of mirror-pain responding and, as a result, empathic pain more generally. Broadly, this thesis has three primary goals:

1. *To identify and characterise a population of mirror-pain responders (**Articles I, II & III**).*
2. *To assess the neural regions and networks underpinnings the experiences of mirror-pain responders (**Articles I** & **II**).*
3. *To test neurocognitive models of mirror-pain and empathy for pain using neuroimaging and behavioural techniques (**Articles I, II, III** & **IV**).*

Article I: Common and distinct neural mechanisms associated with the conscious experience of vicarious pain

Abstract

Vicarious pain perception has been an influential paradigm for investigating the social neuroscience of empathy. This research has highlighted the importance of both shared representations (i.e. involved in both experiencing first-hand physical pain and observing pain) and mechanisms that discriminate between self and other. The majority of this research has been conducted in healthy younger adults using a group-average approach. There are, however, known inter-individual differences that can contribute to vicarious experience. One factor relates to the degree to which individuals experience reportable pain-like sensations/feelings in response to seeing others in pain. Here we conduct the first systematic investigation of the neural basis of conscious vicarious pain in a large sample of participants. Using cluster analysis, we firstly demonstrate that consciously experiencing the pain of others is surprisingly prevalent and, exists in two forms: one group experiences sensory and localised pain whilst the other group report affective and non-localised experiences. Building on this, we used electroencephalography (EEG) and structural brain imaging to examine the neural correlates of vicarious pain in the three different groups. We find that the dominant electrophysiological marker used to index vicarious pain in previous studies (mu and beta suppression) was only found to be significant in the sensory and localised pain responder group (with a sensitive null result in the 'neurotypical' group). Finally, using voxel-based morphometry we identify a common differences in the two pain responder groups relative to typical adults; namely increased grey-matter in insula and somatosensory cortex and reduced grey matter in the right temporal-parietal junction (rTPJ). We suggest that the latter reflects a reduced ability to distinguish bodily self and other, and may be a common factor distinguishing conscious from unconscious vicarious experience.

Introduction

Our capacity to share the experiences of others is a critical aspect of human social behaviour. One characteristic considered to be important to this process is the ability to match observed states of other people onto representations of our own body. This process has been referred to under several names in the literature including empathy, simulation, contagion, and vicarious perception / experience. There is now good evidence of a near universal tendency for humans to vicariously perceive the actions, emotions, and sensations displayed by others. This evidence has most commonly been provided by human brain imaging experiments that have shown that passively observing experiences (e.g. touch, pain, disgust, actions) recruits similar brain regions to those that become active when we experience the states ourselves (Molenbergh *et al.* 2012). While most of us do not feel pain when observing pain to others, , some individuals do experience overt sensations of pain when observing it in others (Osborn & Derbyshire, 2010; Fitzgibbon *et al.* 2012; Vandenbrouke *et al.* 2013; Giummarra *et al.* 2012),. The source of such inter-individual difference in vicarious experience remains unknown. To explore this question, the current set of studies contrasts people who report experiencing the pain of others against the more typical scenario of those who do not. Whilst the latter participants could be construed as having an implicit simulation of pain, this notion is controversial as it relies on an assumption of reverse inference (i.e. inferring mental operations from brain activity). Crucially, our approach does not hinge on this assumption as we ask participants to report their state rather than infer it in this way.

Prior findings indicate that observing pain results in brain activity in neural regions that partial overlap with those involved in experiencing first-hand pain. Moreover, the central processing of first-hand experience of pain takes place in a widely distributed and nonexclusive network of regions known as the 'pain matrix' (Rütgen, Seidel, Riecansky & Lamm 2015; Melzack 1999; *for critical response see* Iannetti & Mouraux 2010). The primary and secondary somatosensory cortices and the posterior insula have been associated with the processing of the sensory qualities of pain and regions such as the cingulate cortices and the anterior insula have been associated with its affective

processing. Functional magnetic resonance imaging (fMRI) findings have shown that the perception of pain (or empathy for pain) also involves activity within this network (Lamm *et al.* 2011). This is most commonly linked to brain activity within the anterior insula and mid-cingulate, but the somatosensory cortices are also recruited when body parts are observed in pain, as opposed to simply knowing about the presence of pain. Further evidence for the involvement of sensory processes in vicarious pain has been provided by electrophysiological (EEG) and non-invasive brain stimulation findings showing the suppression of neural activity, known to emanate from sensorimotor cortex, during the observation of pain (Avenanti *et al.* 2006; Bufalari *et al.* 2007; Martinez-Jauand *et al.* 2012; Cheng *et al.* 2008; Yang *et al.* 2009).

While of clear importance, these influential studies have not considered whether individuals are consciously experiencing the pain of others or not, despite other research showing that consciously experienced vicarious pain may be as common as 15-30% (Osborn and Derbyshire, 2010; Fitzgibbon *et al.* 2012; Vandenbrouke *et al.* 2013; Giummarra *et al.* 2012), and are linked to different profiles of brain activity when observing pain in other people (Osborn and Derbyshire, 2010). The studies, however, have been limited in a number of important ways. The cut-off score on the screening procedures are arbitrary and, hence, the prevalence rates themselves are not independently derived. Finally, qualitative differences in the nature of conscious vicarious pain perception (e.g. 'stinging', v. 'wincing') have not been used to discriminate people. The novel approach taken here addresses these issues by using a data-driven approach (a k-means cluster analysis, Zhang *et al.* 1996) such that the diagnostic cut-off (hence, prevalence) and the groupings reflect the individual differences inherent in the data rather than being set by the experimenter.

Why is it that some people might report conscious vicarious pain experiences and for others do not? There are several possibilities. One is that the same neural mechanisms are used for both groups of individuals but that, in the case of conscious vicarious perception, the level of activity exceeds a threshold for perceptual awareness (so-called Threshold Theory, *see* Ward & Banissy 2015). Another possibility is that different regions within the pain matrix discriminate between these different modes

of vicarious perception (de Vignemont 2012). For instance, the sensory regions of the pain matrix may be crucial for conscious vicarious pain (Osborn & Derbyshire, 2010). A final possibility is that it is regions outside of the pain matrix (i.e. that do not normally respond to physical pain) that underpin this difference. In addition to shared representations, recent accounts of empathy highlight the importance of mechanisms for discriminating self and other (to avoid self-other confusion), which determines whether feeling states are attributed externally or internally (Decety & Jackson's, 2004; Bird & Viding, 2014). This has frequently been linked to the right temporo-parietal junction (rTPJ). This region may provide flexibility in terms of the degree of vicarious perception that takes place (e.g. resulting in a greater vicarious pain response to racial in-groups, Avenanti *et al.* 2010) and a disruption of this cognitive flexibility may result in an over-reliance on shared representations and a tendency to consciously experience the pain of others (so-called Self-Other Theory, Ward & Banissy 2015). The rTPJ has a particularly important role to play in embodiment: tDCS stimulation of this region can lead to a reduced tendency to imitate (Santiesteban *et al.* 2012), and disturbed body ownership (Tsakiris, Costantini & Haggard 2008), including out-of-body experiences (Blanke *et al.* 2005).

The current studies aim to identify, characterise and profile conscious vicarious pain and to assess the neurological basis of this experience using a multi-method approach. Study 1 presents evidence for three qualitatively different forms of vicarious pain perception using a new measure, the VPQ (Vicarious Pain Questionnaire) along with a two-step cluster analysis to produce data driven groups based on VPQ responses. Study 2 examines vicarious pain in the sensorimotor cortices observed via suppression of EEG oscillations in vicarious pain groups identified by the VPQ. The ~10Hz rolandic alpha (mu) and ~20Hz rolandic beta (beta) oscillations have been associated sensorimotor activity (Pfurtschuller & Lopes, 1999; Ritter, Moosmann, Villringer 2009) and are a commonly used marker for studies on the neural correlates of vicarious pain perception (Cheng *et al.* 2008; Yang *et al.* 2009). The novel question here is whether prior findings linking cortical oscillations with vicarious pain perception (found in non-differentiated samples; e.g. Cheng *et al.* 2008; Yang *et al.* 2009) are limited to one or more groups, rather than reflective of a population-level characteristic. This question will be

further addressed by modelling the results of these previous studies data in light of our own EEG findings. Finally, Study 3 assesses structural differences in the brains of our three groups using voxel-based morphometry (VBM) on grey matter volume (Ashburner & Friston 2000). Our hypothesis is that conscious vicarious pain perception will be linked reductions in grey-matter volume in the rTPJ, alongside differences in regions of the pain matrix that code the affective (e.g. dorsal anterior cingulate cortex, anterior insula) and sensory (e.g. somatosensory cortex) properties that characterise each sub-type.

Study 1: The vicarious pain questionnaire and two-step cluster analysis

Methods

Participants: Vicariaux pain questionnaire (VPQ)

The sample was comprised of 573 individuals who had who had not previously been assessed for vicarious pain experiences (Age: 18-60yrs, M=20.37, SE= 0.181, SD= 4.32; Gender: 134 male, 438 female). Participants from this initial pool agreed to be contacted again for future research (Studies 2 and 3). Consent for the study was provided in accordance with the approved ethical review of the project carried out by the University of Sussex (C-REC).

Materials & procedure: VPQ

The VPQ was run using Bristol Online Survey© and was adapted from the technique used by Osborn & Derbyshire (2010).

The main body of the questionnaire had participants view 16 videos of people experiencing pain. They were edited to be 10 seconds in duration, these videos using the following link: https://www.youtube.com/channel/UCT8goTgWGRsu14NjVaPCSGw/videos

After each video participants were asked questions about their experience of watching the video. Participants were initially asked whether they experienced a sensation of pain in their own body when viewing the video (yes/no). If participants answered 'yes' they were asked three further questions: (1) how intense their pain experience was (1-10 likert, 1= very mild, 10= intense pain); (2) to indicate the localization of their experience (either 'localised to the same point as the observed pain' , 'localised but not to the same point, and 'a general/ non-localisable pain experience'); and (3) to select pain adjectives from a list which best described their experience (descriptors selected from the McGill Pain Questionnaire (Melzack, 1975): 10 sensory, 10 affective & 3 cognitive, *see supplementary methods for examples*). All participants (regardless Q1 answer) were asked to rate how unpleasant they found the experience of viewing the video (1-10 likert, 1= neutral, 10= extremely unpleasant). The end of the questionnaire also included dispositional items (e.g. empathy) and items relating to daily experiences of vicarious pain (*see supplementary methods*).

VPQ: Two-step cluster analysis design

A two-step cluster analysis was performed (Zhang, Ramakrishnan & Livny 1996). This analysis clusters participants into groups based on their responses to number of input variables from the VPQ. Once completed the analysis produces cluster centroids and categorises participants into the cluster in which they fit best.

The cluster analysis initially involved a hierarchical cluster analysis using Ward's method (Ward, 1963) followed by a non-hierarchical k-means analysis with 50 iterations. The cluster centroids and number of clusters for the k-means analysis were guided by the hierarchical analysis. The two-step approach is considered more suitable for large datasets as it produces relatively inconsistent results whilst avoiding arbitrary selection of initial centroids in an independently run k-means analysis.

Three variables of interest were selected as input variables for the cluster analysis:

1) *Total pain response (TPR): The total number of conscious vicarious experiences across all video observations (0-16).*

2) *Localised-general: The total number of localised experiences minus the total number of non-localisable experiences.*
3) *Sensory-affective: the total number of sensory descriptors used minus the total number of affective descriptors used.*

The level of multi-collinearity between these variables was low.

Results and summary

A two-step cluster analysis was used to produce the VPQ clusters (Zhang *et al.* 1996). At step 1, observation of the dendrogram indicated a three cluster solution using a Euclidean distance measure of d=10 and generated initial cluster centroids that were carried forwards to Step 2. Step 2 (k-means) provided final cluster centroids for the three groups and completed the final group classification of participates.

The clusters included a non-responder group (n=393), who reported few, if any, conscious experiences of pain. The remaining two groups reported high levels of consciously experienced pain (the two groups did not differ on TPR) but formed a dissociation on localised-general and sensory-affective dimensions. The first of these were 'affective/general group', (n=68; 11.9% of participants tested), who displayed an increased use of affective pain descriptors and less tendency to localise. The second group were 'sensory/localiser group, (n=111; 19.4% of participants tested), who displayed a tendency for sensory descriptor use and to localise their experiences to a point on their bodies (*see* **Figure 2.1** for the bootstrapped cluster means).

There was no difference in age across the groups but there was a disproportionate amount of females in the vicarious pain groups (χ^2 (391) =11.510, p=0.003, *See supplementary table 1* VPQ demographics). When corrected for 50/50 gender distribution our prevalence estimates are as follows; 16.8% for sensory-localiser vicarious pain responders 10.4% for affective-general vicarious pain responders, and 72.9% for the group reporting no conscious vicarious pain. This represents the first

bias-free estimate of prevalence for conscious vicarious pain perception, and the first evidence for two qualitatively different sub-types. In addition the two pain responder groups reported being more empathic, reported experiencing vicarious pain in daily life, and reported being more sensitive to physical pain (but the two groups did not differ on these measures; See appendix 1 Figure 2).

These three groupings was assessed in terms of whether they predict neural functioning (Study 2) and brain structure (Study 3) even when these subsequent studies were conducted many months later (range 2-18 months).

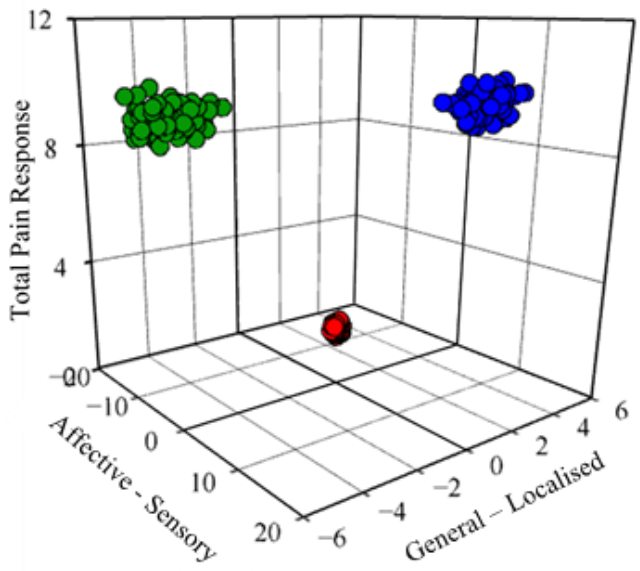


Figure 2.1: Bootstrapped resampled means for Sensory/Localiser responders (blue), Affective/General responders (green) and controls (red). High values on 'total pain response' indicates a high number of vicarious experiences during the questionnaire. Positive values on 'affective-sensory' indicates increased use of sensory descriptors and positive values on 'general-localised' indicates increased localised experiences. The method randomly selections 100 participants, with replacement, and then performs a cluster analysis and computes the cluster means. The procedure is repeated 100 times per condition. Based of Sui & He (2012).

Study 2: Somatosensory oscillations during pain and no-pain observations

Methods

Participants

Forty participants (Age: mean=23.27, SD=6.04; 18 males, 22 females) were recruited via the online questionnaire. The sample included: 20 non-responders, 10 affective/general responders and 10 sensory/localizer responders (identified from Study 1). The study was reviewed and approved by the University of Sussex's (C-REC) Ethics Committee.

Experimental Stimuli

Stimuli for the EEG experiment were a series of 128 color images (600x450p) depicting hands and feet in painful (6 4images) and non-painful situations (64 images). The images have been used in previous research (*i*ncluding Cheng *et al.* 2008, Yang *et al.* 2009, Jackson, Meltzoff & Decety 2005) and each was displayed twice in the current experiment (256 images).

Apparatus

Two Dell OptiPlex 745 PCs with Windows Vista OS were used for data collection and data recording; stimuli was presented on a 19" Dell LCD monitor (75Hz refresh rate). A Nebraskan synamp^2 system, amplifier and a Neuroscan cap (standard 10-10 placement system) was used for data collection. Neuroscan 4.3 software was used for recording and Eprime version 2.0 was used for stimuli presentation. All EEG processing and analysis were computed on Matlab 2014b using the EEGlab plugin (http://sccn.ucsd.edu/eeglab/).

EEG Procedure

Once the EEG cap was applied, there were two sections to the experiment. The first was the baseline recording session in which resting and movement EEG oscillations were observed. Resting mu rhythms were recorded by asking participants to remain still with their palms facing up on their laps and movement recording was produced by self-regulated clenching movements (Pineda, 2005).

The second stage of the experiment involved passive observation of the pain and no pain images. The 256 trials were blocked in eight sets of 32 images, lasting approximately 2.5mins. The trial blocks either contained 32 pain images or 32 no pain images and the order of the blocks were randomized. Presentation of each trial began with a 1s fixation cross [+], followed a 2s stimuli presentation display and finished with a 1s hashtag presentation, (see **Figure 2.2** for stimuli examples).

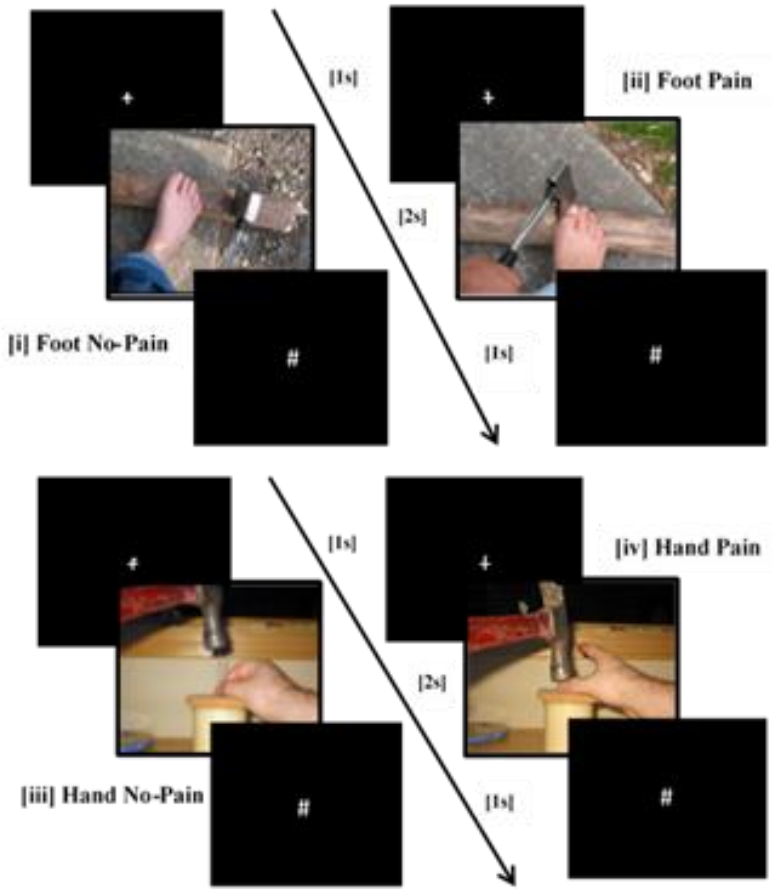


Figure 2.2 Examples of four stimuli conditions:[I] observations of foot in no-pain , [II] observation of foot in pain (with matched environment), [III] observation of hand in no-pain, [IV] observation of hand in pain (with matched environment). Stimuli were supplied by Philip Jackson of Universiti Laval, Quebec. Stimuli have previously been used in: Jackson *et al.* (2005), Jackson *et al.* (2006), Cheng *et al.* (2008), and Yang *et al.* (2009).

EEG Data Acquisition and processing

Twenty-one channels were recorded over the somatosensory and motor cortices (FCz,FC1,FC3,FC5,FC2,FC4,FC6,CZ,C1,C3,C5,C2,C4,C6,CPZ,CP1,CP3,CP5,CP2,CP4,CP6) as well as two bipolar ocular electrodes either side of the eyes, vertically above and below the right eye and two mastoid electrodes. The impedance was set at 5kΩ.

Offline, the sampling rate was adjusted to 500 Hz, a bandpass filter of 0.1-30Hz was applied, and epochs were extracted -200-2000ms after onset of the stimuli. Channels were then re-refenced to mastoid electrodes, eye blinks were removed via visual inspection and a threshold of +/- 50mv was used to eliminate artefacts and abnormal data.

Fast Fourier transform (3 0.5 wavelet cycles, -200-0 baseline corrected) was computed in an 4-75Hz frequency range to epoched data over a 0-2000ms post stimuli time window to event related spectral permutation data. Suppression values were produced by computing ratios for the power of each experimental condition relative to pre-stimulus baseline.

Analysis of somatosensory mu rhythm and beta oscillations was undertaken from electrodes C3, CZ and C4, which area known to be reliable locations for sensorimotor oscillations (Pineda, 2005). The three electrodes were interpolated to produce averaged time-frequency event related spectral permutations, relative to a 200ms pre-stimuli baseline, for pain and no pain observations.

Results and summary

Our hypothesis is that the conscious vicarious pain groups will demonstrate greater mu/beta suppression than controls, and that this will be particularly true of the sensory/localiser groups because we assume that their experiences derive from sensori-motor brain regions linked to mu/beta suppression. The final analysis included 18 Controls (Gender: 11 Females, 7 Males; Age: 23.722, S.E: 1.15), 8 Sensory/Localiser Responders (Gender: 4 Females, 4 males; Age: 25.571, S.E: 1.571) 7 Affective/General Responders (Gender: 4 Females, 3 Males; Age: 23.500, S.E: 1.822).Three

participants were excluded for technical errors (triggers not recorded), three for a high rate of trials with artefacts (>50%), and one for having very noisy data (from visual inspection).

Two 2 (condition: pain vs. no-pain) x 3(group: VPQ groups) mixed ANOVAs were carried out for both frequency ranges. Participant's age and gender were added as covariates of no-interest. We are interested in whether there is a general trend for suppression (as assumed by others) or whether this is limited to one or more groups (as would be revealed by an image * group interaction).

The ~10Hz mu-alpha oscillations ANOVA revealed a borderline significant main effect of image type, $F(1,30)=2.589$, $p=.119$, $r=.343$, and a borderline significant main effect of group, $F(2,31)=2.820$, $p=.077$. $r=.509$. However the analysis did reveal a significant interaction of image type* group $F(2,30)=4.387$, $p=.022$, $r=.710$. (Note that the presence/absence of a main effect of group is not directly relevant to the conclusions as we are interested in how the groups differ when contrasting pain v. no-pain, rather than group differences per se).

A similar pattern of effects was shown for the ~20Hz beta oscillation ANOVA with no significant main effects being shown for image type, $F(1,31)=2.608$, $p=.118$, $r=0.345$, or group, $F(1,31)= 1.269$, $p=.297$, $r=.253$. However a significant interaction of image*group was displayed, $F(2,30)=6.115$, $p=.004$, $r=.882$. In both cases the interaction was driven specifically by suppression of synchronisation to the stimuli depicting pain for the sensory-localiser group (see **Figure 2.3** for summary). Within group between planned comparisons showed that the sensory/localiser group were the only group to show differences in pain vs. no pain conditions and between group comparisons showed this group displayed higher suppression than the other two (*see supplementary results for details*). Bayesian statistics can be used to assess the sensitivity of statistical tests; for example, to determine whether a null result reflects a true null result versus insensitivity (e.g. due to being underpowered). A Bayes factor $p(H0|Data)>3$ implies rejection of the null hypothesis and a Bayes factor $p(H0|Data < 1/3$ implies acceptance of the null hypothesis. A value in between implies insensitivity (Dienes, 2014). The Bayes analysis was carried out using an online calculator (Dienes 2014) and priors were determined using a

previous EEG mu suppression study (Yang *et al.* 2009). There was evidence for the null hypothesis, when contrasting pain and no-pain for the non-responders (for both mu, *p(H0|Data)*= 0.33, and beta, *p(H0|Data)*= 0.29).This is an important piece of evidence because the dominant view in the social neuroscience literature is that suppression of these oscillations when observing pain is the neurotypical response. We cast doubt on this view because our non-responders (with the most 'neurotypical' profile) do not show this effect but, instead, it is found in the sensory-localised group. Additionally, the affective general group showed Bayes analysis showed was insensitivity for the mu/alpha band and a sensitive null for the beta band (for both mu, *p(H0|Data)* = 1.22, and beta, *p(H0|Data)* = 0.29). Critically, the sensory/localiser group show highly sensitive and significant using conventional and Bayesian statistical approaches (for both mu/alpha *p(H0|Data)* = 32.98, and beta, *p(H0|Data)* = 162.10). Additionally, despite the small sample size in this group, we see it at the level of individual participants (see Supplementary Results) that there are clear differences in the patterns of EEG responses relative to the other two groups.

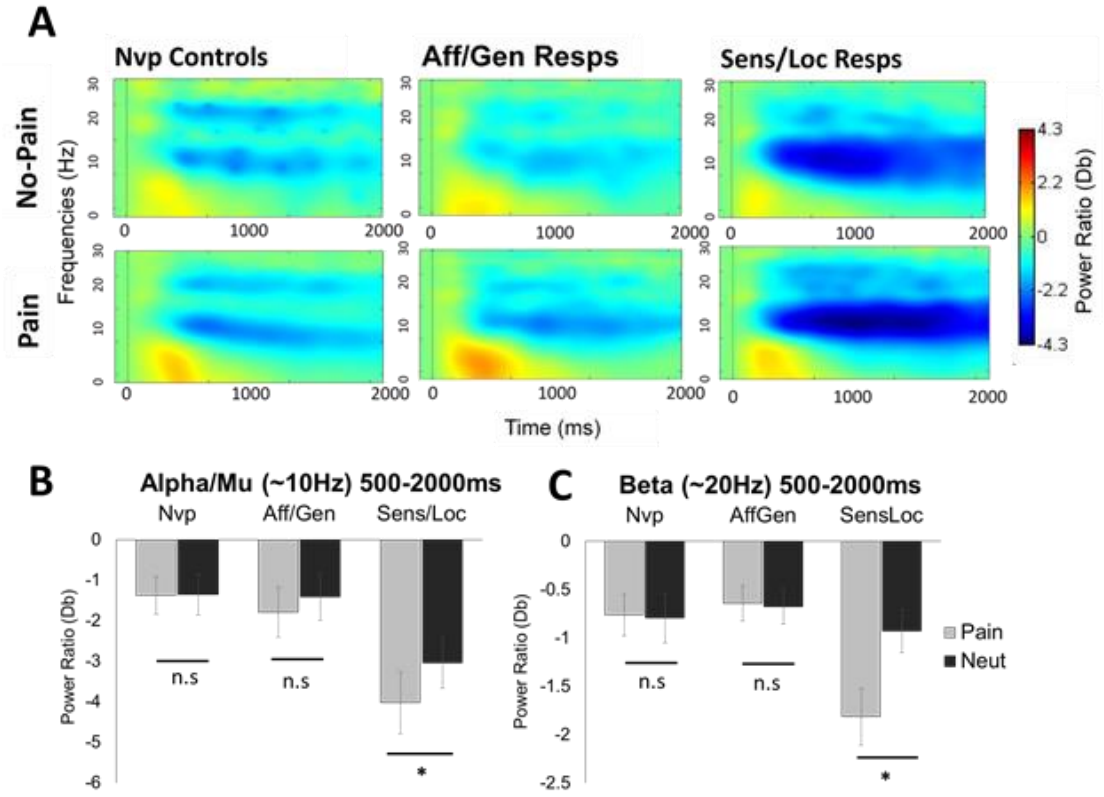


Figure 2.3: Analysis of somatosensory mu rhythm and beta oscillations was undertaken from electrodes C3, CZ, and C4, using 10-10 standard placement system, which are known to be reliable

locations for sensorimotor oscillations due to their placement above the post-central gyrus. The three electrodes were interpolated to produce averaged time-frequency event-related spectral permutations, relative to a 200ms pre-stimuli baseline, for pain and no-pain observations [A]. Pain and no-pain image observations were analysed as this period was likely to reflect voltage fluctuations related to ERP waveforms produced by stimuli onset (Martinez-Jauand, *et al.* 2012). Two frequency ranges were observed, each with an ANNOVA bar graph presented, [B} ~10Hz mu alpha range (8-13Hz) and [C] ~20Hz beta oscillation range (18-22Hz). SensLoc = Sensory/Localiser responders; AffGen = Affective/General responders.

To assess whether previous demonstrations of vicarious pain mu suppression in the general populations may have been influenced by the presence of sensory/localiser group (Cheng *et al.* 2008, Yang *et al.* 2009) we modelled the previous results of Cheng *et al* (2008) which had 16 participants shown pain and neutral images. The model varied the number of sensory/localiser participants included in the analyses and we show that the likelihood of $p<0.05$ is drastically increased by the inclusion of sensory/localiser participants. As few as 4/16 sensory/localiser participants gives a ~50% chance of obtaining a significant ($p<.05$) result. See **Figure 2.4**.

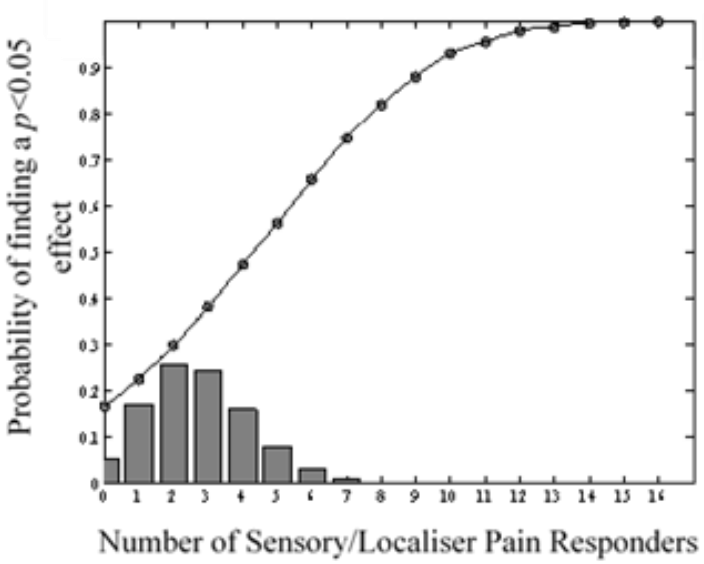


Figure 2.4: Line plot shows the estimated probability of a $p<0.05$ effect for mu suppression between observing pain vs. no-pain observations according to the number of sensory-localiser pain responders included in the sample (x-axis). For each value of *x* 10,000 iterations were carried out and the

probability of obtaining $p<0.05$ was computed by assessing the ratio of significant effects vs. non-significant effects. Bars show the estimated probability (based on VPQ prevalence rate) of obtaining this number of Sensory/Localiser responders in the modelled samples (mean of 2.68 out of 16). Additionally a logistic regression was carried out on the modelled data which showed that the number of responders included in the sample significantly predicted the increased likelihood of a $p<0.05$ finding, no. of responders $B=0.37$, $W(9998)$-24.64, $p<0.001$.

Group differences in alpha and beta suppression was also assessed during the hand movement task to investigate whether observed effects were due to underlying group differences in somatosensory oscillations (rather than vicarious perception in particular). All groups display suppression of alpha/mu oscillations (over the C3 scalp position) during hand movement and differences were observed between the groups ($F(2,29)= 3.745$,$p=0.036$, $r=.638$). However these effects did not mirror the group differences observed in the image observation analysis as post hoc (Bonferroni corrected) tests displayed that the Affective/General responders (M= -1.66, S.E.= 0.25) showed increased suppression relative to Sensory/Localiser responders (M=-0.56, S.E.=0.41; $p=0.041$) but not controls (M=-1.11, S.E.=0.166, $p=0.307$), no effects were observed between Sensory/Localiser responders and Controls ($p=0.441$). No groups effects were observed over the C3 Scalp position for beta oscillations ($F(2,29)= 0.638$, $p=0.535$, $r=.327$). That is, differences in mu and beta suppression for the sensory-localised group during vicarious pain perception do not reflect differences in these frequencies across all measures (such as physical movement). Moreover, the vicarious pain results are consistent with sensori-motor mu suppression rather than with visually-based alpha desynchronization because the effects were significantly greater over central electrodes than the adjacent frontal and posterior electrodes; a pattern that was also found for actual hand movements that can be directly linked to sensori-motor activity (see **Appendix 1** for details).

In summary, the results of Study 2 provide confirmatory evidence of the validity of the distinctions in vicarious pain perception identified in Study 1: i.e. differences in subjective report are reflected in differences in brain activity assessed at a later time point. They suggest a link between sensory-

localised vicarious pain and mu/beta suppression but raise doubts about whether mu/beta suppression are a good measure of 'mirroring' processes in the wider population. We establish this be showing a sensitive null result for the non-responder group (using a sample size comparable with previous research, N=18) and by showing a significant group X pain/no-pain interaction that is driven by a significant effect in the sensory-localised group.

Study 3: Structural differences based on subjective experiences of vicarious pain (voxel-based morphometry, VBM)

Methods

Participants

Ninety-three individuals were recruited for the VBM analysis however 9 participants were excluded because of outdated T1 scanning sequences, resulting in 84 participants in the analysis (Age: 18-39 yrs, M=24.17, SE= 0.54, SD= 9.17; Gender: 48 male, 36 female). The sample included 51 controls (Gender: 26 Females, 25 Males; Age: M=23.450, S.E= 0.54), 17 sensory/localiser responders (Gender: 8 Females, 9 Males; Age: M=24.882, S.E.=1.254) and 16 with affective/general responders (Gender: 9 Females, 7 Males; Age: M=25.687, S.E: 1.781). Recruitment was primarily driven by opportunistic sampling from participants who already had a T1 scan (resulting in more non-responder controls), but was augmented by purposive sampling to increase the N of the rarer groups. The project was approved by the Brighton and Sussex Medical School Research Ethics and Governance Committee.

MRI data acquisition: VBM

Participants were a placed in a supine position in a Siemens Avanto (Brighton, England) 1.5 T MR scanner. A T1-weighted MPRAGE interleaved sequence (TR = 2730ms, TE = 3.57ms, FOV = 240 x 256 x 192 mm, voxel size=1x1x1 mm) was used to acquire structural MR images.

MRI data processing

Processing of T1-weighted images for voxel-based morphometry was undertaken using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) with the VBM8 toolbox (http://www.neuro.uni-jena.de/vbm/download/) on Matlab 2014b. Initially MR tissue segmentation was computed using the default parameters on SPM8's 'new segment' tool. VBM normalisation processes were carried out using the default options for the 'estimate and write' function on VBM8 toolbox, thereby creating grey and white matter templates using DARTEL algorithms, and then normalizing the participant images to MNI space using the previously created templates. This was followed by spatial smoothing, FWHM=8mm x 8mm x 8mm. The smoothing kernel size was used as we had no specific hypotheses about the variability, as a result the default SPM kernel size was used. Two participants were excluded from the analysis due to a lack of homogeneity of covariance (Ashburner and Friston 2000).

MRI data analysis

The VBM data was analysed using a General Linear Model with the pain groups variable acting as the variable of interest (Controls vs. Sensory/Localiser responders vs. Affective/General responders) and 3 variables of no interest including: Age, Gender and Intracranial volume (ICV). Particular attention was given to contrasts between Sensory/Localiser responders vs. Controls and Affective/General responders vs. Controls, and the conjunction analysis between these two contrasts. Initially a whole brain $p<0.05$ FWE corrected was used to threshold the data. An ROI analysis was also carried out using small volume correction (SVC) based on four ROIs which include [1] bilateral dorsal anterior cingulate cortex (dACC) (x=-2, y=23, z=40), [2] bilateral anterior insula (Left: x=-40, y=22, y=0; Right: x=39, y=23, z=-4), [3] bilateral primary and secondary somatosensory cortices (anatomical

maps from SPM anatomy tool box), [4] right temporo-parietal junction (x=57, y=-52, z=14). MNI locations for ROIs 1 and 2 were based on Lamm's *et al.*(2011) meta-analysis of vicarious pain and used a 10mm spherical mask , ROI 3 used full anatomical maps of SI+SII taken from SPM8's anatomy toolbox (Eickoff, Paud, Caspers, Grosbras, Evans, Zilles & Amuntes 2007) and ROI 4 was based on Krall's *et al.* (2015) meta-analysis of the rTPJ, again using a 10mm spherical mask. The ROI analysis was correction for multiple comparisons by using a $p<0.05$ FWE cluster threshold correction.

Results and summary

Initially, we compared grey matter volume differences between our three groups using a whole brain analysis. Although a number of regions displayed effects at $p<0.001$ (uncorrected) no regions showed significant effects at the $p<0.05$ (FWE corrected) threshold. Following this an ROI analysis (one-way ANOVA across groups followed by planned contrasts), using the 4 previously mentioned ROIs with small volume correction (SVC). Figure 5 shows the whole-brain results (left) and ROI results (right). Several significant differences were found between controls and the two responder groups, but direct comparisons between Affective/General and Sensory/Localiser groups revealed no significant effects across either whole brain $p<0.05$ (FWE corrected) or a SVC ROI $p<0.05$ (FWE corrected) threshold.

GM volume effects overlapping with the 'pain matrix'

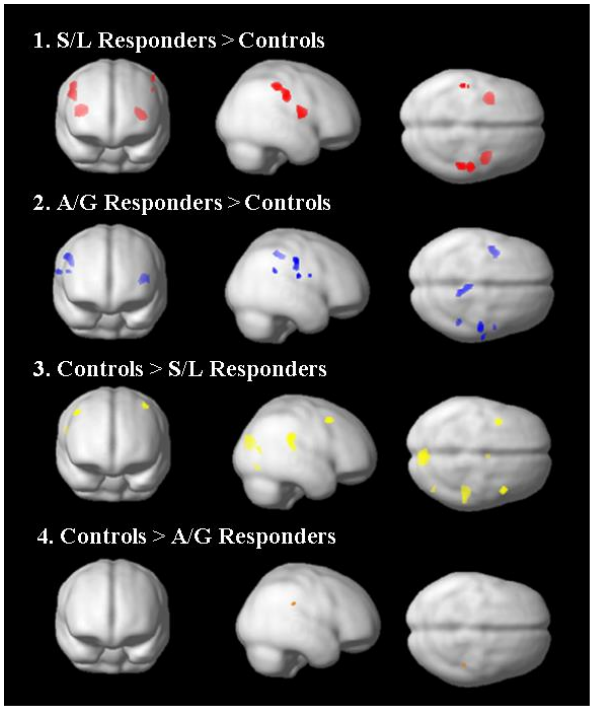
During the ROI analysis the sensory/localiser group displayed significantly increased grey matter volume relative to controls in the left anterior insula ($t(1,78)= 4.64$, $p=0.014$) and right anterior insula cortex ($t(1,78)=4.04$, $p=0.007$). Sensory/Localiser responders also showed increased grey matter volume relative to controls in the right, primary somatosensory cortex, in area 3b ($t(1,78)=4.47$, $p=0.02$).

The affective/general group displayed increased GM matter volume in the left anterior insula cortex ($t(1, 78)=3.95$, $p=0.026$) and a borderline significant effect over the right somatosensory cortex area 3b ($t(1,78)= 3.74$, $p=0.06$).

A conjunction analysis was computed on the Sensory/Localiser responders > Controls and Affective/General responder > Controls comparisons which showed significant conjunction at the $p<0.001$ (uncorrected) threshold over the left anterior insula and the right primary somatosensory cortex, area 3b.

GM volume effects in regions implicated in self/other processing

During the ROI analysis the Sensory/Localiser responders also displayed significantly reduced grey matter volume, relative to controls, in the right anterior temporo-parietal junction ($t(1,78)=3.76$, $p=0.001$) and the Affective/General responders showed significantly decreased GM volume, relative to controls, in a small portion of the right anterior temporo-parietal junction ($t(1,78)$ 3.37, $p=0.031$) . A conjunction analysis showed significant (surviving p=0.05 FWE correction) overlap between the Controls > Sensory/Localiser responders and Controls > Affective/General responders in the right anterior temporo-parietal junction ($t(2,78)=3.37$, $p=0.031$). See **Figure 2.5** for ROI effects in the rTPJ.



Anatomical region	Cluster size (mm^3)	*t*	x	y	z
S/Responders > Controls					
Left anterior insular cortex	470	4.71	-33	3	9
Right primary somatosensory cortex	457	4.47	48	-16	34
Right anterior insula cortex	502	4.04	42	-1	16
A/G Responders > Controls					
Left anterior insular cortex	448	3.95	-45	-4	13
Right primary somatosensory cortex	165	3.93	53	-16	40
Conjunction analysis: S/L > Controls + A/G > Controls					
Right primary somatosensory cortex	118	3.83	51	-16	39
Anterior insular cortex	76	3.62	-39	3	12
Controls > S/L Responders					
Right temporo-parietal junction	500	4.17	48	-33	30
Controls > A/G Responders					
Right temporo-parietal junction	18	3.37	44	-34	30
Conjunction analysis: Controls > S/L + Controls > A/G					
Right temporo-parietal junction	18	3.37	44	-34	30

Figure 2.5: T1 weighted structural MRI images were entered into a one-way ANCOVA model with the three cluser groups entered as the main variable of interest: age gender and inter-cranial volume (ICV) were added as covariates for the model. Planned t-contrasts between each of the two responder groups and controls were assessed for volumetric GM differences can be identified as follows: (Red) regions which displayed increased GM in Sensory/Localiser responders relative to controls, (Blue) areas in which Sensory/Localiser responders displayed decreased GM volume relative to controls, (Yellow) areas in which controls displayed increased GM volume compared with Sensory/Localiser responders, (Orange) areas which contrsols showed increased GM volume relative to Affective/General Responders. Rendered image shows whole comparisons using a $p<0.001$ whole brain analysis the table shows significant ROI effects at $p<0.05$ FEW corrected ($k=10$) using previously describedROIs. In addition the table also displays two conjunction analyses using a $p<0.05$ FEW corrected ($k=10$) showing overlap effects for [1] Sensory/Localiser responders > Controls + Affective/General responders > Controls, [2] Controls > Sensory/Localiser responders + Controls > Affective/General responders MNI coordinates, MRI images & GM volume bar charts are displayed for each effect which survived the threshold. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

Study 3 provides further confirmatory evidence for the distinction between qualitatively different forms of vicarious pain perception, identified in Study 1, notably between those who report conscious vicarious pain and those who do not. Although the two responder groups (sensory-localised v. affective-general) did not differ in our VBM analysis, we predict that such differences will be found on functional measures (see Study 2), behavioural measures, and/or using other forms of structural imaging (e.g. white-matter connectivity).

Discussion

Prior work has highlighted evidence for a shared system involved in perceiving and experiencing first-hand pain (or empathy for pain). This work has commonly been conducted on healthy young adult participants, and rarely addressed inter-individual variability in the extent to which people "feel" vicarious pain. Using a new measure, the VPQ, and cluster analysis we document, for the first time, that there are two distinct forms of conscious vicarious pain perception in addition to a more typical non-responder sub-type. One sub-type is characterised by sensory pain descriptors and a tendency to localise pain on the body (this is linked to suppression of sensorimotor EEG mu and beta oscillations when observing pain). A second sub-type is characterised by affective pain descriptors, and the vicarious pain is not-localised to a specific part of the body. Importantly, both types of conscious vicarious pain perception are linked to reduced grey matter in the right temporal-parietal junction (rTPJ). This region is not normally linked to pain perception, but is central to both social cognition and bodily self-consciousness (Blanke, Slater & Serino 2015). Both types are also linked to increased grey matter in regions involved in pain perception (anterior insula, primary somatosensory cortex) as well as other aspects of brain-body interaction more broadly. The non-responder subtype could be characterised as an absence of vicarious pain or an implicit/unconscious form of vicarious pain. Our results cannot distinguish between these possibilities, although the field as a whole tends to assume an implicit simulation of the pain of others (see Lamm's *et al.* 2011; and for a contrary view see Iannetti & Mouraux 2010).

Although previous research has reported conscious vicarious pain perception to be surprisingly common (Fitzgibbon *et al.* 2012; Vandenbrouke *et al.* 2013; Giummarra *et al.* 2012), there has been little consensus as to how to measure it and, hence, the current estimates of prevalence are unreliable. Our approach of using a data driven two-step k-means cluster analysis has enabled this question to be addressed without imposing arbitrary cut-offs. The results reveal a prevalence of conscious vicarious pain of 27%, further divisible into the two sub-groups. The results also indicate that females are over represented in these groups, by a factor of nearly 2:1. The reasons for this are unknown, but it is consistent with the finding that mu suppression when observing pain, tends to be greater in females (Yang *et al.* 2009). fMRI studies have not consistently revealed a greater activity in pain-related regions in females when watching others in pain (Lamm *et al.* 2011), but there is evidence that females modulate their vicarious pain less than men according to social context (Singer *et al.* 2006). These previous findings need to be revisited in light of our research to determine if they are driven by the presence of one or both types of conscious vicarious pain rather than reflecting a true difference between genders. More broadly, our results suggest that measures of mu/beta suppression in response to observing pain may not be a reliable neurotypical measure of 'mirroring' brain activity as noted also by others (Hobson and Bishop, in press). Our results show a sensitive null result in the non-responder group. Although our sample size is smaller, we show that the suppressions effects are present in the sensory-localised responder group (including at the individual level) and we mathematically model how this could give rise to significant results in a sample that does not take into account individual differences in vicarious pain.

Further, our research demonstrates that vicarious pain is not a unitary construct, as is commonly assumed in the literature, but exists in qualitatively different varieties in terms of both subjective experiences of pain and in terms of structural and functional differences in the brain. Based on our results we suggest two mechanisms that contribute to conscious vicarious pain perception: one relating to sensorimotor resonance and one relating to self-other discrimination. These are considered in turn.

Firstly, there is a greater involvement of sensorimotor processes in those people who report sensory/localiser vicarious pain, showing increased suppression of both mu-alpha and beta oscillations. The suppression of mu-alpha and beta frequency ranges are both known to be present when privately experienced physical somatosensory experiences occur, with suppression of mu-alpha oscillations is associated with somatosensory processes and nociception whilst suppression of beta is more associated with voluntary action and proprioception (Pfurtscheller, 1999; Ritter *et al.* 2009). Furthermore, similar occurrences of these alpha and beta suppression patterns which participants view touch and pain (Cheng *et al.* 2008; Yang *et al.* 2009). Additionally, the VBM results show that a number of regions involved in the private processing of pain display grey matter volume increases relative to controls. Most notable of these effects was increases in grey matter within primary somatosensory cortex, (with its somatotopic representation of the body) and in the anterior insula cortex, both central regions in the processing of affective and sensory qualities of personally experienced pain (Peyron *et al.*2000) and vicariously processed pain (Lamm *et al.* 2011; Osborn & Derbyshire 2010). We predicted that the affective/general group may have structural differences in affective regions of the pain matrix (e.g. insula), whereas the Sensory/Localiser group may have greater somatosensory cortical differences. This was not found and others have queried the validity of this affective-sensory division of pain networks (Iannetti *et al.* 2010). Instead the VBM data suggests that Sensory/Localiser responders and Affective/General responders display similar structural brain differences (albeit of a greater magnitude in the Sensory/Localiser group) which may account for their conscious experiences of vicarious pain. Further differences between the Sensory/Localiser and Affective/General subtypes may be found on functional measures (as in the previous EEG results) or using other structural measures (e.g. of white matter).

Secondly, both vicarious pain groups had less grey matter density in the TPJ region. This region is a key hub within the 'social brain' implicated in mental state attribution (Decety & Lamm, 2007), altruism (Morishima, Schunk, Bruhin, Ruff & Fehr 2012), and embodiment and attentional processes (Krall *et al.* 2014). Of particular interest in the current study is the rTPJ's role in self-other discrimination, specifically body-based representations (Decety & Sommerville, 2003; Brass *et al.*

2009; Banissy *et al.* 2009). In the case of conscious vicarious pain it may be that they are unable to properly monitor and control for representations of other people's bodily states resulting in a tendency for 'other' representations being incorporated in to self-processing thereby resulting in activation of shared representations for pain (Ward & Banissy, 2015; Sowden and Shah, 2014). In one study examining spontaneous perspective taking, it was found that vicarious pain groups were more likely to spontaneously adopt a third-person perspective as opposed to the typical egocentric bias (Derbyshire *et al.* 2013). We speculate that this may be a common behavioral profile of both sub-types of conscious vicarious pain that is linked to individual differences in the TPJ. Recent meta-analyses of the rTPJ have divided the region into anterior and posterior sections (Bzdok et al., 2013; Krall *et al.* 2014). Our VBM differences are centered on the anterior rTPJ and it is noteworthy that this region has strong functional connectivity with regions such as mid-cingulate and anterior insula implicated in bodily perception, including, but not limited to pain (Bzdok, Langner, Schilbach, Jakobs, Roski, Caspers *et al.*2013).

The findings from the sensory-localiser group resemble those reported for a rarer group of individuals (mirror-touch synesthetes, MTS) who report feeling tactile sensations on their own body when watching neutral (i.e. non-painful) touch on others (Avenanti *et al.* 2006; Fitzgibbon *et al.* 2012; Banissy *et al.* 2009). This is linked to activity in primary and secondary somatosensory cortex when watching touch (assessed through fMRI rather than EEG) and also reduced grey matter volume in the rTPJ (Holle *et al.*2013). Furthermore recent behavioural findings have shown that people with MTS are inhibited in controlling representations of other people, a process known to be associated with the rTPJ (Santiesteban *et al.* 2015). It would be interesting to know whether this Sensory/Localiser vicarious pain group are also more likely to report vicarious sensations when observing non-painful touch.

In conclusion, the vast majority of studies on empathy for pain have assumed that vicarious pain is not linked to reportable pain-like sensations/feelings. Those who have looked at conscious vicarious pain responses have not developed systematic ways of quantifying or characterising it. The present

research not only offers a new tool (the VPQ), it offers a new conceptualisation of vicarious pain into three groups characterised by differences in phenomenology and differences in brain structure and function. We show that differences in subjective accounts of vicarious pain perception differ across individuals that it is manifested in somatosensory mirroring (for sensory/localizer responders) and differences in self/other processing.

Article II: Consciously feeling the pain of others reflects atypical functional connectivity between the pain matrix and frontal-parietal regions

Abstract

A significant proportion of the population (~30%) report 'mirror pain' experiences in which bodily sensations of pain are elicited when viewing another person in pain. We have shown that this further fractionates into two distinct subsets (Sensory/localisers and Affective/Generals). The study of these 'mirror-pain responders' provides an important opportunity to investigate the neural underpinnings of individual differences in empathic responses. This study uses fMRI to determine how regions involved in the perception of pain and regions implicated in social cognition interact in these different groups. When viewing pain images the two mirror-pain responder groups displayed widespread activation not present in typical controls. Most crucially, they showed activation in the sensory/discriminative and affective/motivation pain matrix regions, whereas the control group only showed activation in the latter. Furthermore, the two mirror-pain responder groups displayed whole-brain increases in activity in the frontal regions associated with interpersonal empathy, and increased activity in a number of pain -matrix regions in a small volume corrected ROI analysis. A Psychophysiological Interaction (PPI) analysis showed increased connectivity from affective/motivation and sensory/discriminative pain- matrix regions to social cognition and cognitive empathy regulatory systems in the mirror-pain responder groups while viewing pain images. Notably, Sensory/Localised responders display a significant coupling between the right temporo-parietal junction (rTPJ) and bilateral anterior insula. We conclude that conscious experiences of vicarious pain are supported by specific patterns of functional connectivity between pain-related and regulatory regions, and not merely hyper-activity within the pain matrix itself. In a second experiment, we tested the degree to which vicarious social pain was modulated between the pain responder groups during a game in which participants could experience or observe social exclusion. The results showed

activation in a regions associated with metalizing and theory of mind when watching others being excluded but showed no effects during personal experiences of exclusion during the game.

Introduction

For some people, seeing another person in pain, such as having an injection or falling off a bicycle, results in reportable pain-like experiences. These people have been referred to as mirror-sensory/mirror-pain synesthetes (Fitzgibbon et al., 2012) or as pain responders (Osborn & Derbyshire, 2010). Our recent study found a prevalence rate of mirror-pain of 27%, using a large scale screening questionnaire (n=600+) and a data-driven cluster analysis to classify participants (Grice-Jackson, Critchley, Banissy & Ward, 2017; **Article I**). Moreover, we found two sub-groups of mirror-pain responders who displayed qualitatively different pain experiences: Sensory/Localiser responders, who experienced localised and physical/sensory pain experiences, and Affective/General responders, who reported non-localisable mirror-pain experiences with more affective qualities. The validity of these groupings was established by showing that the groups dissociate on other measures. When observing pain, the Sensory/Localised responders, showed significant differences on a measure of neural synchrony (EEG suppression of mu and beta rhythms) that has previously been linked to somatosensory processing (e.g. Ritter, Moosmann, & Villringer, 2009). This pattern was not present in controls or the Affective-General responders (Grice-Jackson et al., 2017). In terms of brain structure, a VBM showed the pain responder groups to have increased grey matter volume of the somatosensory and insula cortices along with reduced grey matter volume of the rTPJ (Grice-Jackson *et al.* 2017).

This previous work established that the different phenomenological characteristics of mirror pain were reflected in systematic differences in brain structure and function. However, the technique of EEG is constrained by poor spatial resolution, so our knowledge of the underlying brain systems is limited. In this respect, functional magnetic resonance imaging (fMRI) may be more suited to study the neural underpinnings of individual differences in vicarious pain. The only previous fMRI study of

mirror pain classified participants according to whether they had one or more localised pain responses when observing a set of videos/images of pain (Osborn & Derbyshire, 2010). In this study, pain responders were reported to have greater activity when observing pain, relative to control participants, in regions including anterior insula and secondary somatosensory cortex. Here, we aim to extend this finding in a number of important ways. Firstly, we consider differences between our recently discovered subtypes of mirror pain. Secondly, we will further investigate the underlying connectivity associated with regions active during pain observations through the use of a psychophysiological interactions (PPI) analysis. Finally, a separate study will consider whether group differences are limited to observations of physical pain or also extend to so-called 'social pain' linked to ostracism (Eisenberger *et al.* 2003).

The neural processing of pain takes places in a series of interconnected neural regions known collectively as the pain matrix (Melzack, 1999). However, it should be noted that regions involved in the perception of pain typically process other kinds of related information too (see Iannetti & Mouraux, 2010). This 'neuromatrix' is commonly split into two subdivisions known as the affective/motivation subdivisions (processing the affective qualities of emotion preparedness of pain) and the sensory/discriminative subdivision (which processes the sensory aspects of pain). Correspondingly, we predict that our sensory/localised and affective/general responders will differentially activate these sub-systems and with the sensory/localised group eliciting a stronger somatotopic response (e.g. when viewing hands v. feet in pain). In normative populations (i.e. that do not separate out the presence/absence of mirror pain), there is consistent activation in the affective/motivation regions of the pain matrix (notably mid-cingulate cortex and anterior insula) when observing others in pain (Lamm *et al.* 2011). This occurs also when pain is implied, but not directly observed. It is argued that sensory/discriminative regions of the pain matrix may only be activated when the site of injury is observed, and not when pain is merely implied (e.g. via facial grimace or a symbolic cue) (Lamm *et al*. 2011). Brain stimulation studies also suggest the 'sensory simulation' of the pain of others when directly observing pain (Avenanti *et al.* 2005; Bufalari *et al.* 2007). However, these studies did not take into account the contribution of individual differences in

vicarious experience. Electroencephalography (EEG) has revealed a greater modulation of somatosensory evoked responses when viewing pain in mirror-pain responders compared to controls (Fitzgibbon *et al.* 2012). This observation suggest that for these individuals, vicarious pain affects neural processing at the level of cortical sensory processing, rather than just being an enhanced affective response.

Most models of empathy for pain assume that this involves not only shared representations of pain (whether affective and/or sensory), but also that regions outside of the pain matrix that are involved in self/other orientation, either in terms of bodily location (perspective taking) or in terms of orienting towards salient social and personal characteristics such as race (Bird & Viding, 2014; Decety & Ickes 2011; Decety & Jackson, 2006). For example, in controls, training the ability to regulate self-other representations has been linked with changes in the degree of sensory simulation of the pain of others when directly observing pain (de Guzmann *et al.,* 2016). These control mechanisms are needed to dynamically modulate the focus of attention towards other people (and suppress one's own feelings) or, conversely, to be able to focus on one's own feelings and suppress that of others (i.e. the down-regulation of empathy). One region that has been implicated as acting as a switch between self and other is the right temporo-parietal junction, TPJ (Bird & Viding, 2014; Lamm, Bukowski, & Silani, 2016). According to Ward & Banissy (2015) a disruption of this rTPJ mechanism in mirror pain (and mirror touch synaesthesia) underlies the tendency to experience the pain of others. In effect, for these individuals, pain is more likely to be shared rather than selectively attributed to self or other. Evidence for a role of this region in mirror pain comes from structural brain imaging studies where reduced rTPJ grey matter density is observed in people with both Sensory/Localised and General/Affective mirror pain (Grice-Jackson *et al.*, 2017), and in people with the related condition of mirror-touch synaesthesia (Holle, Banissy, & Ward, 2013). As such, we will consider in more detail the role of this region in our fMRI study of vicarious pain.

The current study will be split into two separate fMRI experiments. In Experiment 1 we will assess the neural underpinning of the mirror-pain experiences reported by our two responder groups relative

to controls. This will involve presenting participants with static images of others in pain as well as matched no-pain images so as to observe the regions activated during pain observations and the difference between the mirror-pain responder groups and controls. These pain and no-pain images will be further split into topographic (Hand vs. Feet) and laterality (left vs right) to allow for a study of the localisation of mirror-pain activation. We will also assess the connectivity patterns of regions activated during the observation of pain as these underlying networks of connectivity are crucial for holistically understanding the neurocognitive processes responsible for mirror-pain and will be the first analysis of its kind on this population. We propose a number of hypotheses for experiment 1 below:

1. *We expect the mirror-pain responder groups to display increased activity in both the affective/motivational and sensory discriminative regions of the pain matrix whilst controls will only show significant activity in the former.*
2. *We expect that a number of regions involved interpersonal processing (i.e. self/other representations) will show differing patterns of activity in the pain responder groups relative to controls.*
3. *We expect that the two pain responder groups will display differing patterns of activity with sensory/localisers showing greater sensory/discriminative simulations and affective generals showing greater affective/motivation simulation.*
4. *We expect that the pain responder groups will display differing patterns of activity depending on the body part and laterality of pain depicted images,*
5. *We expect to find wide spread patterns of connectivity with activated regions in the pain responder groups especially in areas thought to mediate mirror-pain (i.e. self/other regions).*

In experiment 2 we aim to assess how mirror-pain responder groups respond to observation of other kinds of non-nociceptive pain. Social pain, or social exclusion, has been well documented in functional neuroimaging studies using a ‘Cyberball’ ball tossing paradigm (Eisenberger *et al.*2003). In this experiment participants play a game in which they are asked to throw a virtual ball with two other

avatars. In inclusion rounds the avatars will free pass the ball between each other and the participant. During exclusion rounds the two avatars will not through the ball to the participant. Results show that social exclusion elicits activity in the affective/motivation regions of the pain matrix. Furthermore, when people observe others being excluded from the game they produce the same affective/motivation pain regions vicariously (Meyer *et al.* 2014). We will assess whether mirror-pain groups display differing fMRI response to vicarious social pain using an adapted version of the Cyberball study in a virtual reality version of the test in which they can both observe and experience social exclusion trials in the game (developed by Mavromihelaki, Eccles, Harrison, Grice-Jackson, Ward, Critchley & Mania 2014). The hypotheses for experiment two are below:

1. *We expect to find vicarious social exclusions for both observations of social exclusions and experiences of it in the Cyberball game.*
2. *We expect that there will be between group differences in the size of the social exclusion effects observed in the Cyberball study between pain responder groups and controls, however we make no specific predictions about the neural regions involved, or directions of these effects.*

Methods

Participants

Forty-four healthy participants (18 males, 26 females) aged between 18 and 42 years (mean=23.96, S.E.= 1.37) volunteered to take part in the study. All participants self-reported being right handed, had normal or corrected vision. Furthermore participants had previously completed the Vicarious Pain Questionnaire (VPQ), an online measure assessing reports and characteristics of conscious vicarious pain experiences (Grice-Jackson, *et al.* 2017). It involves watching 16 movies depicting injections (N=8) and sports injuries (N=8) and reporting whether it triggers pain on your own body (a score from 0 to 16), the intensity and unpleasantness (both on a 0-10 scale), a selection of pain descriptors

(Melzack, 1987), and to indicate whether the pain is localised or generalised. Participants were split between three groups that were classified within a larger dataset (n=573) in the original VPQ two-step cluster analysis. The sample consisted of 21 non-responder controls, 13 Sensory/Localiser responders and 10 Affective/General responders. The details of the participants, in relation to their performance on the VPQ, is summarised in **Table 3.1**. Participants provided written and informed consent in accordance with paid £15 for their participation in the study. The study's procedures were reviewed and approved by the Brighton and Sussex Medical School (BSMS) Research Ethics Committee.

Table 3.1: The characteristics of the three groups on the Vicarious Pain Questionnaire (VPQ) showing the mean (SD in parentheses) for the three dimensions used in the cluster analysis, together with mean intensity (0-10 scale). The three dimensions are: the number of movies in which pain is reported (/16); the number of sensory descriptors minus the number of affective descriptors; and the number of pain responses that are localised minus the number of pain responses that are generalised throughout the body.

	Total Pain Response	Localised-General responses	Sensory-Affective responses	Average intensity scores
Controls	0.05 (0.21)	0.05 (0.21)	0.09 (0.43)	0.003(0.01)
Sensory/Localiser	11.27 (3.06)	3.64 (6.71)	12.63 (6.43)	2.88 (1.77)
Affective/General	11.77 (2.04)	-4.67 (6.53)	-11.44 (10.17)	3.75 (1.46)

Apparatus

A Siemens Avanto 1.5 Tesla MRI scanner was used to collect all images throughout this experiment. A single row four-button button box was used for tasks 1 and 2 with only the two central buttons active so that participants could indicate movements to the left and right.

Scanning Protocol

Functional MRI data were collected using an interleaved scanning sequence 30° to AC-PC image line with coverage including the top of the somatosensory cortex and the temporal poles (TR = 2620ms, TE=43ms, FOV= 192mm x 192mm, voxel size 3x3x3mm, number of slices = 35). In addition to the EPI data, we collected a T1-weighted structural scan with a magnetization-prepared rapid gradient echo (MP-RAGE) pule sequence for use during non-linear spatial normalisation (TR = 2730ms, TE = 3.57ms, FOV = 240x256x192 mm, voxel size=1x1x1 mm). Each scanning session was split into three tasks, of which the main one is reported here. The whole session lasted for approximately 60 mins.

fMRI Pre-processing

Data was processed in MATLAB R2014a using the SPM8 toolbox (http://www.fil.ion.ucl.ac.uk/spm/). Initially, the EPI data were corrected for movement during the task by realigning all images to the first in the time series. These data were then co-registered to the T1-weighted structural scan which had been manually re-centred such that the origin located the anterior commissure. EPI data were then normalised to the standardised MNI (Montreal Neurological Institute) anatomical space using SPM's DARTEL non-linear spatial normalisation algorithms. Finally, a Gaussian smoothing kernel (8mm isotropic) was applied to the images to increase the signal to noise ratio.

Two controls participants and one Sensory/Localiser responder were removed because of excessive movement in the scanner (maximum translation > 3mm; maximum rotation > 5°). One further control participant was removed because of an error in recording the trial triggers on the stimuli display PC. As such, the sample reported here included 18 controls, 12 Sensory/localised and 10 Affective/generalised responders.

Experiment 1: Vicarious Pain Perception

Experimental Stimuli

This study included a series of 128 images depicting hands and feet being subjected to different types of pain stimuli that one might experience in the real world (i.e. fingers being caught in a car door). An additional 128 images served as contextually matched no-pain images (i.e. a hand closing a car door). The images were taken from a stimuli set that has been previously used in a series of fMRI and EEG studies to assess empathy for pain (Cheng et al., 2008; Jackson, Meltzoff, & Decety, 2005). This original stimuli set include 128 images all of which showed right hands and right feet. Equivalent images depicting left and right body parts were created by mirror reversal of the images. The images of hands and feet were displayed from a series of orientations with some of the images coming from a position which could be produced by the observer (i.e. the hand/feet coming from the base of the image) and some of which could not be produced by the observer (i.e. the hand of foot comes from the side or top of the image). The visual stimuli were presented on the projector via a stimuli PC running MATLAB R2014a and the Cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent.php).

Procedures and Design

The stimuli followed a 2 (image condition: pain vs no pain) x2 (topography: hand vs foot) event-related design. Each condition contained 8 trials/image presentations which were randomly drawn from the full image set for each condition. The full session lasted approximately 18 minutes (~410 volumes).

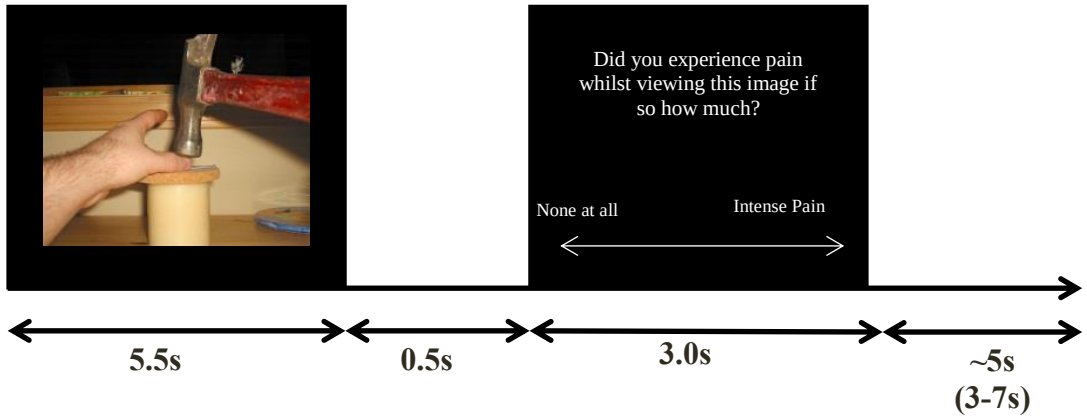


Figure 3.1: Stimulus example and trial timings for fMRI experiment 1.

Trials consisted of viewing an image followed by a judgement as to whether they experienced a pain sensation whilst viewing the image; Responses were made on a visual analogue scale which participants controlled using a button box (left extreme: no-pain, right extreme: intense pain). The image was displayed for 5.5s per trial, followed by a 0.5s blank screen, followed by a 3s pain judgement question (after 3s the response was not taken), followed by a jittered 3-7s inter trial interval (see **Figure 3.1** for trial setup).

fMRI Analyses

All fMRI analyses used the same cluster level threshold for significance; a false discovery rate (FDR) of $p < .05$. This was defined with a map-wide height threshold of $p < .001$ and, given the smoothens of statistical images, the mimulum cluster size required top reach significance was approximately 40 voxels. The statistical analysis of images was run in SPM8 using the 'MarsBar' (Brett, Anton, Valabregue & Poline, 2002) and 'Anatomy' (Eickhoff, Stephan, Mohlberg, Grefkes, Fink, Amunts & Zilles, 2005) toolboxes. Six rigid body motion parameters derived from the image realignment procedure (3 translations, 3 rotations) were included in each first level model as nuisance covariates.

Three sets of first and second level design matrices were created for the fMRI analysis. The first focused primarily on the observations of pain and no pain for the three pain groups. The first level

design matrices computed parameter estimates for all pain and no pain observations (32 trials per condition) using two event related regressors. At the second level, a full factorial design was used to model first level parameter estimates in a 2 factor design: Pain group (3 Levels: Controls, Sensory/Localisers, Affective generals) and Image observations (2 Levels: Pain Vs No Pain).

The second set of design matrices, like the fist, had regressors for pain vs no-pain across the 3 groups. However, these models also included additional estimates that modelled the laterality of pain observations (e.g. left hand pain vs right hand pain). As such, at the second level, a fully factorial design was used to model the data with 3 factors in a 3x2x2 design: Pain group (Controls vs Sensory/localisers vs Affective/Generals), Image observations (Pain vs No Pain) and image laterality (Left vs Right). Parameters estimates from regions of interest (ROI) were extracted for each condition using the MARBAR toolbox (Brett *et al.* 2002) and later analysed in SPSS (IBM).

The third set of design matrices was used to model parameter estimates for the ROI analysis of topographic differences and used an identical design to the laterality design matrices however the laterality factor was replaced by the topographic factor (2 Levels: Hand images vs Foot images) in both the first and second level models. As before, parameters estimates were extracted for each condition using the MarsBar toolbox and later analysed in SPSS.

A region-of-interest (ROI) analysis was conducted using 8 regions of the pain matrix and the rTPJ. The coordinates for the anterior cingulate cortex (ACC) and anterior insula were based on the meta-analysis of Lamm *et al* (2011) namely: ACC, x=0 y=12 z=45; left Anterior Insula (AI), x=-40 y=22 z=0; and right AI, x=39 y=23 z=-4 (in MNI space). The location for the rTPJ was based on the mid-point between the anterior and posterior rTPJ subdivisions discussed in Krall's *et al.* (2014) meta-analysis of the rTPJ namely x=54 y-48 z=22 (MNI space). For these regions a 10mm spherical binary masks was applied. By contrast, the somatosensory cortex was defined anatomically rather than functionally using the masks on SPM's anatomy tool box (Eickhoff, *et al.* 2005) for four somatosensory regions (left SI, right SI, left SII and right SII). Parameter estimates (Betas) were

extracted from these regions using the 'MarsBar' tool box (Brett et al. 2002) for Pain > No-pain contrasts. Due to the somatotopic organisation of SI a further more detailed ROI analysis was carried out. Separate hand and foot SI ROIs were selected using a 10mm spherical masks around the left and right hand area reported by Bingel, Lorenz, Glauche, Knab, Glascher, Weiller & Buchel (2004) for physical pain stimulation (left MNI: x=39, y=-30, z=51; right MNI x=36, y=-36, z=48, left and right hand areas were compiled into the same ROI) and the left and right foot area (left MNI: x=-9, y=-39, z=57; right MNI x=9, y=-36, z=66).

The PPI (Psycho-Physiological Interactions) analysis takes seed regions (in our case, standard regions of the pain matrix identified via our whole brain analyses) and correlates activity between these seed regions and all other regions of the brain as a function of a psychological variable (in our case, whether a stimulus depicted pain or not). The PPI models were produced using the Generalized PPI Toolbox (McLaren, Ries, Xu & Johnson, 2012) and included all the same event-related and nuisance regressors as in the original whole-brain GLM. Additionally, the PPI model included one regressor coding the overall BOLD time course of the seed region, and 'Pain Image' regressor coding the PPI interaction term between Pain and No-pain image observation. To examine psychophysiological interactions at the group level, we then specified second-level models similar to those used in the whole-brain GLM of BOLD activations. For each seed region separately, estimates of the PPI interaction terms relating to the 'Pain Image' events regressors were entered into a 3(Pain group: Controls vs Sensory/Localiser Responders vs Affective/General Responders) x 2 (Pain Image: Pain vs No Pain) ANOVA model.

Experiment 2: Vicarious Social Exclusion

Experimental Stimuli

In the second MRI task participants played a novel version of the Cyberball computer game (Mavromihelaki *et al.* 2014), reprogrammed in MATLAB R2014a and Cogent 2000. The current task

differed from Eisenberger's original setup by including a fourth player. Across the task participants view a virtual environment square room in which they see, from a first person perspective, three other human avatars which form (including the participant) a square diamond shape in the room (see figure 3). When the participant choose to throw the ball they would see it move from their position to another avatar would then catch the ball. All movements were animated and fluid so as to mimic the actions of actual people (see Figure 3 for examples of the visual environment). The stimuli was presented in a 600x400 pixel rectangle in the centre of the centre projector screen.

Procedures and Design:

For the Cyberball game participants were told to pass the ball to other players in the game. The rules of the game were such that the participant could only pass to the player to the left or right of them, not to the player opposing them, through use of the button box provided (index finger= left, middle finger=right). The other avatars in the game would then throw the ball to one another or the participants. The two players to the left or right of the participants could throw the ball to all other players in the game, however the avatar opposing the participant view could only through the ball to the left and right, not the participants. This allowed for three block design conditions which included: [1] an 'Inclusion' condition in which all players randomly threw the ball to one another, [2] a 'Self-exclusion' condition in which the participant initially threw the ball away to another player but never received it back from any other player (participant excluded from game), [3] an 'Other-Exclusion' condition in which the participants and two avatars to the player's left and right threw the ball between one another without ever throwing the ball to the fourth avatar who stood opposite the participant, see figure3 for game rules and permitted direction of throws. The task was separated into fifteen 30s blocks, 5 blocks per condition, which were separated with a 20s Inter trial interval in which participants viewed a fixation cross (before each round they were given a 1s written message to 'GET READY'). In each round the participant started with the ball and the 30s timer began when participants first threw the ball to the other players. The task followed a 3 (Vicarous Pain Group) x2

(Round condition: Inclusions vs Self-Exclusion vs. Other-Exclusion) design. The task took approximately 12.5 minutes to complete. See **Figure 3.2** for Cyberball stimuli design.

After participants left the scanner they were asked to complete a manipulation check questionnaire which contained 7 questions. This included three yes/no questions which asked participants: [1] whether or not they thought the game was played unfairly by the other players, [2] whether they thought the player opposing them was treated unfairly by the other players, and [3] whether they thought they themselves were treated unfairly by the other players. For questions 2 and 3 participants were asked to rate on a 5 point Likert scale how much this up set or annoyed them (participants were only asked these questions if they answered 'yes' to questions 2 and/or 3. The final to questions asked participants to respond of a 5 point Likert scale whether they felt like they were playing against a computer or real people (1=computer, 5=real people) and whether they felt they treated the other players like a computer or real people (1=computer, 5=real people). The results of this manipulation check were used to judge whether or not participants should be included in the fMRI analysis.

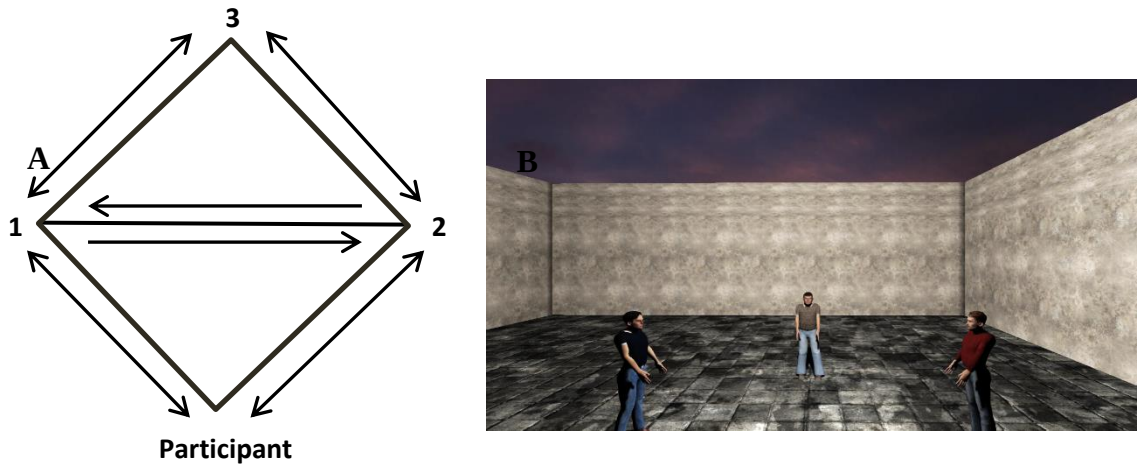


Figure 3.2: [A] shows a diagram of the Cyberball game including all of the possible directions that participants could throw the ball and [B] shows a screenshot of the Cyberball game with a set of screenshots depicting the animation of the ball throwing.

fMRI Analyses

The same statistical threshold was applied to all analyses and consisted of an FDR (False Discovery Rate) of $p<.05$ and a minimum cluster extent of 40 voxels. Statistical parametric Mapping 8 (SPM8, Wellcome trust Centre for Neuroimaging) with the 'MarsBar' (Brett *et al.* 2002) and 'anatomy' (Eickhoff *et al.* 2005) toolboxes was used for the fMRI analysis.

Three sets of first and second level design matrices were created for the fMRI analysis. The first focused primarily on the observations of pain and no pain for the three pain groups. A first level design matrix extracted the parameter estimates for inclusion, self-exclusion, and other exclusion trials (5 trials per condition) using a blocked design with scans that fell over the trial condition. A Markov chain model was used to calculate the number of throws which would be required for tell which condition they were taking part in. After 8 throws by any of the plays in the game the model showed 0.8 probability of predicting the condition which was completed approximately 10 seconds after the begin of the trial. Therefore only the last 20 seconds of each 30 second trial was used in the analysis. At this stage, movement regressors were included in the model as a covariate. This included six ridged body movement regressors were included in the first level models throughout the study which included x3 rotational (roll, pitch, yaw), and x3 translational regressors (X,Y,Z). At the second level a full factorial design was used to model data with 2 factors which included: Pain group (3 Levels: Controls, Sensory/Localisers, Affective generals) and Cyberball condition (3 Levels: Inclusion, Self-Exclusion, Other Exclusion).

The second set of design matrices was used to model the parameters for the ROI analysis which focused on laterality differences for pain and no pain observations between the three groups. The first level model extracted the parameter estimates for the following for conditions: left pain, right pain, left no-pain and right no-pain which each had a total of 16 trials using the event related scans that fell over the image presentation. Movement parameters were included at this stage. At the second level a fully factorial design was used to model the data with 3 factors which included: Pain group (3 Levels: Controls, Sensory/localisers, Affective/Generals), Image observations (2 Levels: Pain vs No Pain) and

image laterality (2 Levels: Left vs Right). Parameters estimates were extracted for each condition using the Marsbar toolbox and later analysed in SPSS.

Results

Experiment 1: Vicarious Pain Perception

Vicarious Pain Ratings

The visual analogue scale generated scores from 1-800, with a higher score indicating higher intensity of vicarious pain. The mean scores, shown in **Figure 3.3**, were analysed using a 2 (Condition: Pain vs. No-pain stimulus) x 3 (Group) ANOVA. There were significant main effects of stimulus ($F(1,37)=68.67$, $p<0.001$, $r=0.64$) and group ($F(2,37)=34.45$, $p<0.001$, $r=0.65$) as well as a significant interaction ($F(1,37)=15.554$, $p<0.001$, $r=0.47$). Within group planned comparisons showed that the Sensory/Localiser ($t(11)=5.217$, $p<0.001$) and Affective/General groups ($t(9)=3.653$, $p=0.011$) showed significantly increased scores during Pain relative to No-pain trials but the controls did not ($t(17)=1.655$, $p=0.155$). Furthermore between group post-hoc tests for pain trials showed that Sensory/Localisers and Affective/Generals showed higher scores than controls, but the two responder groups did not differ from each other. In summary, our two responder groups reported increased levels of vicarious pain for these stimuli during scanning as they had previously done for similar stimuli outside the scanner.

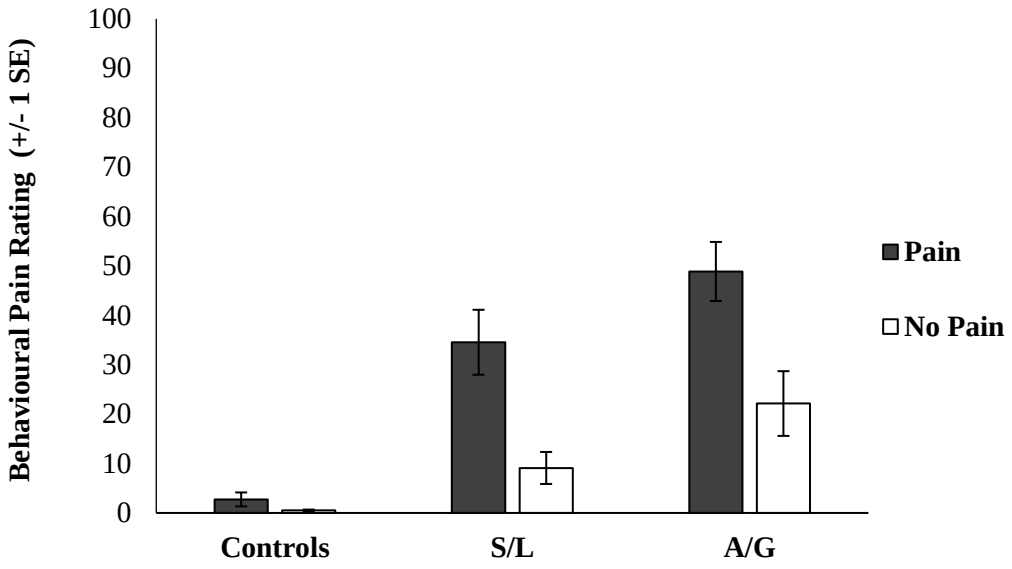


Figure 3.3: Subjective ratings for the pain (filled bars) and no-pain (empty bars) stimuli. A score of 100 indicates a high perception of pain in the participant in response to the observation of pain and a score of 0 represents no perception of pain. Error bars show +/- 1 SEM. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

fMRI results: Whole Brain Analysis

Initially a whole brain analysis was run on the data. We assessed pain vs no-pain within groups and contrasted the effects of the same stimuli between groups. All of the tests were carried out using t-contrasts. **Table 3.2** displays all regions which showed significantly increased differences in pain vs. no-pain activation for the three groups (see also **Figure 3.4**). This analysis shows that all groups display effects in regions associated with the affective processing of pain (anterior insula, and dorsal anterior cingulate extending into the supplementary motor area). However, only the Sensory/Localiser and Affective/General group showed increased activation in the somatosensory cortices which was confirmed by a subsequent ROI analysis.

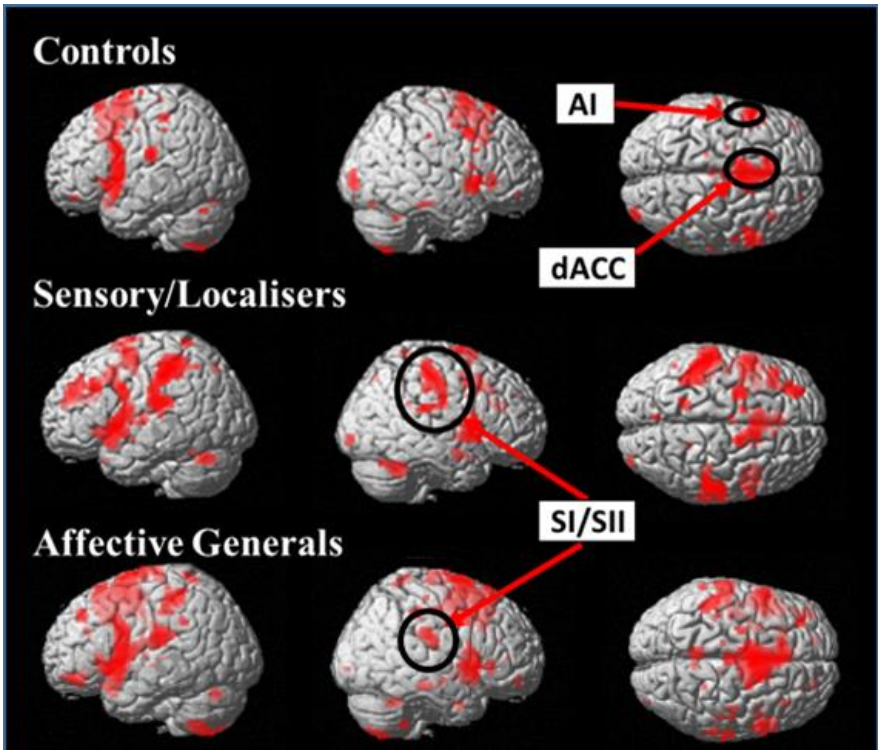


Figure 3.4: Images display within group effects for Pain > No-Pain contrasts for each of the groups. Contrasts use a whole brain $p<0.001$ (uncorrected) with a cluster extent threshold of $k=10$ (this statistical threshold has only been used for figure display reasons and differs from that used in the main analysis). All groups display increased activation in affective pain matrix regions (dACC+AI) but only Sensory/Localiser and Affective/General responders show effects in the primary and secondary somatosensory cortices.

Table 3.2: Regions showing significant within group effects in Pain > No-pain image contrasts. Peak MNI effects are displayed for each effect as well as FDR corrected cluster significance values. S/L = Sensory/Localiser responders; A/G = Affective/General Responders.

Brain Regions	***Lat***	***MNI Coordinates***			***t-score***	***k***	***P(FDR) cluster***
		X	***Y***	***z***			
Controls: Pain > No pain							
Supplementary motor area	L/R	0	3	66	4.89	351	<0.001
	L/R	5	10	59	4.21		
Anterior insula	L	-54	9	-9	4.62	239	<0.001
Inferior frontal gyrus	L	-57	9	27	4.35		
Anterior insula	R	57	12	-3	4.38	54	0.045
S/L: Pain > No pain							
Cerebellum (VI)	R	30	-54	-30	5.48	76	0.011

Primary somatosensory cortex (1/2)	L	-54	-30	51	5.20	361	<0.001
Secondary somatosensory cortex	L	-57	-24	21	4.49		
Inferior Parietal Lobule	L	-50	-33	18	3.92		
Dorsal anterior cingulate cortex	L/R	-3	12	45	5.07	136	0.001
Primary somatosensory cortex (1)	R	57	-27	51	4.76	146	0.001
Primary Somatosensory cortex (3b)	R	54	-18	42	3.79		
Anterior insula	L	-33	12	0	4.51	313	0.001
Parahippocampal Gyrus	L	-21	5	-21	4.47		
Anterior insula	R	51	3	-3	4.40	105	0.003
Dorsal lateral prefrontal cortex	L	-30	45	27	4.31	113	0.002
	L	-20	39	39	3.36		
Precentral gyrus	L	-27	0	60	4.27	64	0.017
Caudate nucleus	R	15	6	6	3.96	69	0.014
A/G: Pain > No-pain							
Supplementary motor area	L/R	0	3	66	5.42	780	<0.001
	L/R	-6	6	60	5.02		
Dorsal anterior cingulate cortex	L/R	3	-3	54	4.34		
Inferior frontal gyrus (Opercularis)	L	-57	9	9	4.95	512	<0.001
Temporal Pole	L	-48	12	-9	4.67		
Anterior Insula	L	-45	3	3	4.43		
Secondary somatosensory cortex	R	-60	-21	19	4.81	143	0.027
	R	21	6	-9	4.56	122	0.026
Periaqueductal grey	R	12	6	3	4.42		
Premotor cortex	L	48	-8	56	4.28	137	0.017
Anterior insula	R	42	3	3	4.21	100	0.035
Secondary somatosensory cortex	L	-63	-24	21	4.13	111	0.029

The differences between groups were explored by assessing Pain vs. No-Pain first level t-contrast betas in a second level one way ANOVA with three groups. **Table 3.3** displays regions showing significant effects (contrasts which did not yield significant effects are not displayed). The responder groups had greater activity than controls in a variety of regions when observing pain, but no effects were observed in the opposite direct (i.e. controls> responders). This included the dorsolateral prefrontal cortex (DLPFC) and cerebellum for both sensory/localiser responders and affective/general. No group differences were observed between the two responder groups suggesting they are broadly similar, at least for the present level of statistical power. Notwithstanding this similarity, we demonstrate later that the groups differ in their connectivity profile. See **Figure 3.5** for between group effects.

Table 3.3: Regions showing significant between group effects for Pain vs Pain contrasts in the responder groups relative to contrasts. Peak MNI effects are displayed for each effect as well as FDR corrected cluster significance values.

Brain Regions	***Lat***	***MNI Coordinates***			***t-score***	***k***	***p(FDR) Clusters***
		x	***y***	***z***			
S/L Pain > Controls Pain							
Inferior frontal gyrus	L	-42	24	33	4.03	82	<0.001
Precuneus	L/R	3	-75	51	5.78	251	<0.001
Inferior parietal lobule	L	-36	-54	42	4.69	97	0.005
Dorsomedial Prefrontal cortex	L	-27	51	12	4.82	211	<0.001
Medial Frontal cortex	L	-33	51	24	4.50		
Cerebellum (VI)	R	-33	-57	-30	4.26	56	0.030
Superior frontal gyrus	L	-27	3	63	4.06	41	0.048
Cerebellum (Crus 2)	L/R	-3	-84	-36	4.00	165	<0.001
Cerebellum (Vermis 7)	L/R	0	-75	-24	3.42		
A/G Pain > Controls pain							
Dorsal anterior cingulate cortex	L/R	2	-5	50	5.21	596	<0.001
Supplementary motor area	L/R	4	-1	51	4.62		
Inferior frontal gyrus	R	53	5	10	5.13	116	0.002
Dorsal lateral prefrontal cortex	L	-45	21	30	5.04	89	<0.001
Primary somatosensory cortex (1)	L	-54	-30	54	4.97	178	0.002
Primary Somatosensory cortex (2)	L	-48	-39	51	3.65		
Cerebellum (Crus 1)	L	-42	-69	-24	4.86	197	0.003
Cerebellum (VII)		-30	-78	-45	4.50		
Ventral premotor area	L	54	2	39	4.81	69	0.016
Anterior insula	L	-50	3	-3	4.74	181	<0.001
Anterior insula	R	48	18	-12	4.47	47	0.050
Precuneus	L/R	-5	-55	51	4.45	144	0.032
Thalamus	R	11	4	2	4.29	108	0.029

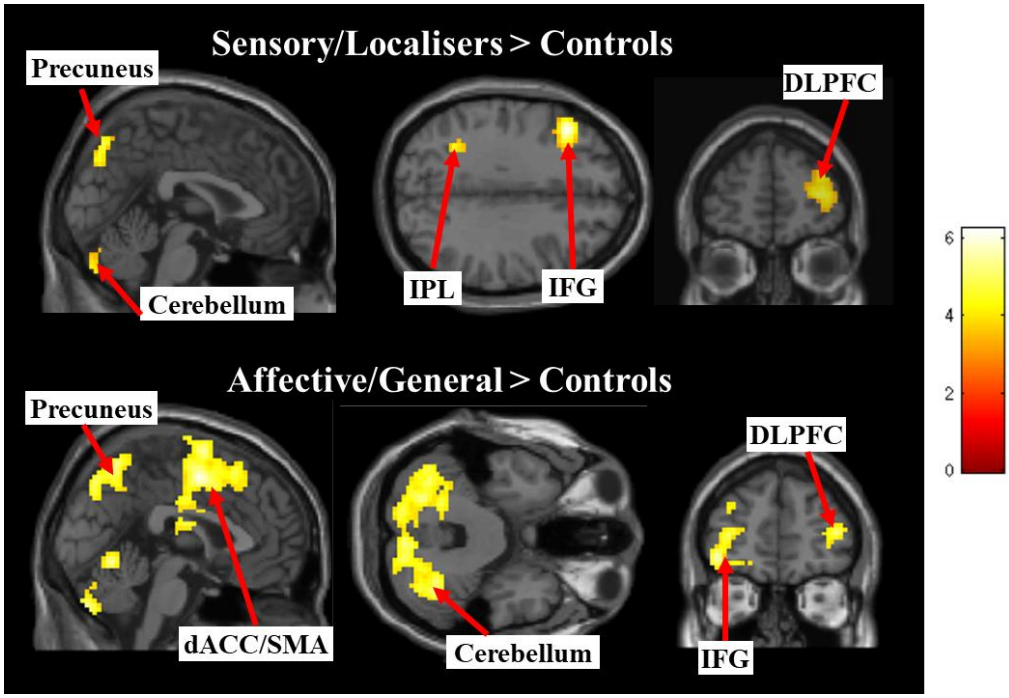


Figure 3.5: Images display between group effects for Pain > Pain contrasts for each of the responder groups compared with controls. Contrasts use a whole brain p<0.001 (uncorrected) with a cluster extent threshold of k=10 (liberal statistical threshold has only been used for figure display).

ROI Analysis

Parameter estimates were extracted from each ROI for contrasts between pain vs. no-pain observations. These parameter estimates show the difference between pain and no pain observations with positive beta values indicating increased activation in the region when viewing pain images. A series of one way ANOVAs assessing differences between the pain groups was run on each ROI. Four regions display significant differences between the groups, including: dACC ($F(2,39)=4.714$, $p=0.015$, $r=0.635$), left SI ($F(2,39)=5.757$, $p=0.007$, $r=0.741$), and right SII ($F(2,39)=5.441$, $p=0.021$, $r=0.704$), additionally left SII and right SI showed an effect of borderline significance (Left SII: $F(2,39)=2.846$, $p=0.076$, $r=0.589$; right SI $F(2,39)=3.114$, $p=0.56$, $r=0.491$). For all significant ROIs the two responders groups had significantly higher signal change relative to controls but they did not differ from each other. Non-significant effects included: the right TPJ ($F(2,39)=2.0440.634$, $p=0.512$,

r=0.156), the left AI (*F*=(2,39)=0.431, *p*=0.653, *r*=0.097) and the right AI (*F*(2,39)=0.761, *p*=0.474, *r*=0.150). See **Figure 3.6.** These effects show that both affective and sensory pain matrix regions show differences in activation between the groups with the two pain responder groups displaying increased differences between pain and no pain observations relative to controls.

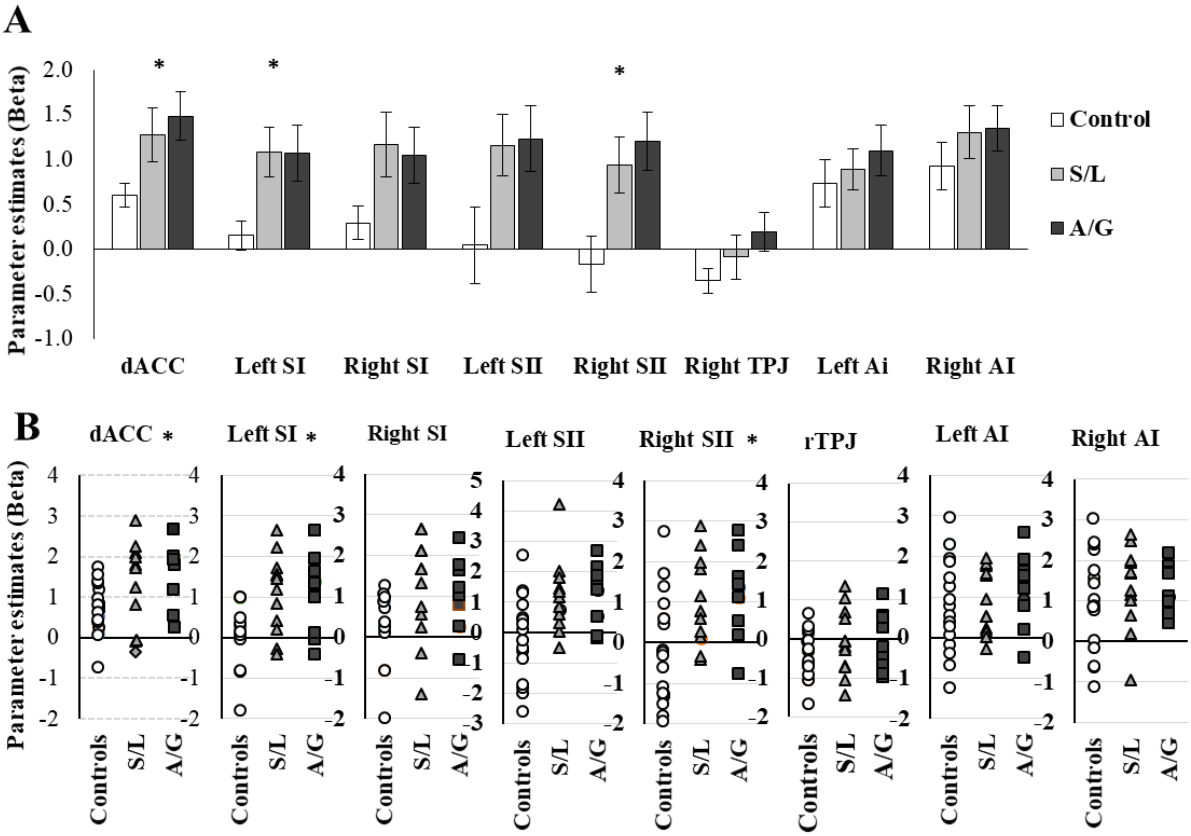


Figure 3.6: [A] Averaged parameter estimate betas extracted from each ROI are displayed for each group. Results of between group ANOVAs are displayed and significant effects are denoted with *(p<0.05). Error bars show +/- 1 SEM. [B] Script plots show the individual beta values extracted for the ROI analyses. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

Due to the somatotopic organisation of S1 a more detailed ROI analysis was carried out. The results are summarised in **Figure 3.7**. A 2 (hand vs foot image) X 2 (hand v. foot ROI) repeated measures ANOVA was run on the data (one for each Group: Controls, Sensory/Localiser, and Affective/General). The Sensory/Localiser group showed a strong interaction of image type X ROI

(F(1,11)=20.40, p=0.001, r=0.63) such that feet images more strongly activated the foot area and hand images more strongly activated the hand area, This pattern was absent in the other two groups (Controls: F(2,17)=0.356, p=0.559, r=0.021; A/G: F(1,9)=0.01, p=0.95, r=0.001). No group showed main effects of image type (Controls: F(1,17)=0.07, p=0.79, r=0.06; Affective/General: F(1,9)=0.39, p=0.55, r=0.04; Sensory/Localiser: F(1,11)=1.65, p=0.22, r=0.12) or ROI (Controls: F(2,17)=0.48, p=0.50, r=0.03; Affective/General: F(1,9)=0.05, p=0.83, r=0.01; Sensory/Localiser: F(1,11)=1.00, p=0.34, r=0.08).

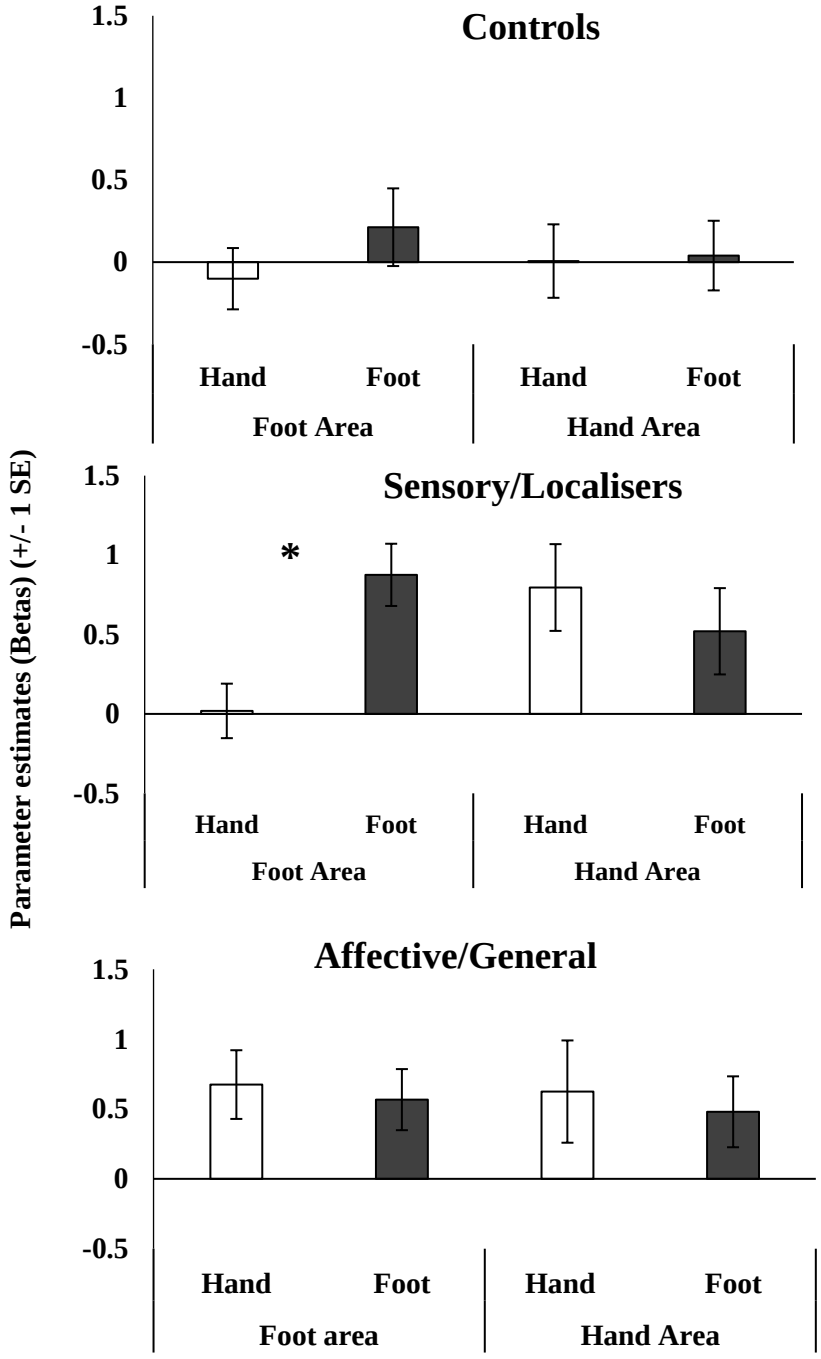


Figure 3.7: Relative activity in SI hand and foot areas (Pain > No-Pain) depending on whether a hand or foot stimulus was shown. Only the Sensory/Localiser group show an interaction of Topographic region*Image condition.

Psychophysiological interaction analysis

We specified five psychophysiological interaction models to test our hypothesis that regions associated with mirror pain activation in the responder group would show differential patterns of functional connectivity depending on whether they viewed pain. Each of the 5 models involved a different seed region that had been identified as showing a significant "pain > no pain" main effect in the aforementioned GLM of BOLD activations. These regions included: the left SI/SII ([-57,-24,21], k = 641), the left AI ([-51,6,09], k = 802), the right AI ([54,12,-3], k = 475), the dACC/SMA ([-3,18,42], k = 641), and the right SI/SII ([54,-21,42], k = 390). BOLD time series data that had been deconvoved for the HRF were entered into first level models to estimate connectivity between the seeds and other regions during the session. The five PPI analyses were investigated by comparing pain vs. no-pain images for each group, and between group contrasts, comparing pain and no pain images across the groups. All contrasts which showed significant PPI effects are displayed in **Table 3.4** which includes directions of effects and the location of significant effects.

For the Sensory/Localiser group, the left and right anterior insula seed regions showed greater functional connectivity (contrasting Pain > No-pain) with the rTPJ. It is to be noted that although we initially hypothesised a role of the rTPJ, this finding emerged from a whole-brain analysis. Seed regions in other parts of the pain matrix (left and right SI/SII and dACC/SMA) showed greater functional connectivity (pain > no-pain) with a region in the left posterior angular gyrus. There were three other PPIs observed in the Sensory/Localiser group (involving retrosplenial cortex and bilateral prefrontal regions). By contrast, for the Affective/General group there were only two observed PPIs when contrasting pain > no-pain (between the left SI/SII seed and dorsal mPFC and left anterior

insula seed and left DLPFC). Control groups did not show any significant PPI effects throughout the analysis.

Table 3.4: Regions showing significant PPI effects for within group contrasts for at the whole group level and for each pain responder group. Effects are displayed for each seed region's PPI analyses and the direction of the effects are displayed. Only contrasts showing significant effects are displayed. S/L = Sensory/Localiser responders; A/G = Affective/General Responders.

		Lat	***MNI Coordinates***			***t-score***	***K***	***p(FDR)***
PPI seed	***Brain Regions***		***x***	***y***	***z***			
S/L Pain >No-Pain								
Left SI/SII	Angular gyrus (IPL - PGp)	L	-39	-75	42	4.77	58	0.050
Right SI/SII	Angular gyrus (IPL – PGa)	L	-36	-75	57	4.31	119	0.002
	Angular Gyrus (IPL – PGp)	L	-45	-72	33	3.93		
Left AI	Retrosplenial cortex	R	9	-60	42	5.02	62	0.028
Left AI	Temporo-parietal junction	R	36	-51	36	5.18	62	0.028
	Intrparietal Sulcus	R	42	-51	45	4.06		
Right AI	Temporo-parietal junction	R	42	-54	45	4.36	66	0.024
dACC/SMA	Angular gyrus (IPL - PGp)	L	-39	-75	42	4.48	218	<0.001
dACC/SMA	Middle frontal gyrus	L	-39	21	48	4.52	106	0.001
		L	-30	9	50	4.25		
		L	-48	18	39	4.25		
dACC/SMA	DLPFC	R	51	30	21	5.53	55	0.021
A/G Pain >No-pain								
Left SI/SII	DMPFC	L	-9	54	15	4.85	78	0.044
	Medial Frontopolar cortex	L	-12	51	5	4.14		
Left AI	DLPFC	L	-42	48	-3	4.64	91	0.003
S/L (Pain – No-Pain) > Control (Pain – No-Pain)								
ACC	DLPFC	R	51	30	21	5.32	44	0.021
Left AI	Temporo-parietal junction	R	42	-51	45	4.89	91	0.003
	Intraparietal sulcus	R	35	-51	35	4.81		
Right AI	Temporo-parietal junction	R	42	-51	48	4.65	60	0.034
	Intrparietal sulcus	R	42	-45	39	3.50		

Experiment 2: Vicarious Social Exclusion

Manipulation checks

Participants were asked: [1] whether they thought that the game was played unfairly by any of the other players; [2] whether they thought they were left out during any other the rounds; [3] whether they noticed the 3rd player being left out of the game during any of the rounds. If participants answer 'no' to all of these questions they were excluded from the analysis. Out of the 41 participants 8 participants did not understand the manipulation, technical faults eliminated 1 participant and 1 participants was excluded as they failed to follow the instructions during the game. This left 32 participants (14 Controls, 11 Sensory/Localisers, and 8 Affective/Generals) in the analysis.

Using a 5 point Likert scale, participants reported no differences in negative affect related to self-exclusion (M=3.066, *S.E*: 0.213) and other exclusion rounds (*M*: 3.100, *S.E*=0.226), $t(30)=0.147$, $p=0.884$. Group differences were also not observed in a 2 (Condition: Self-exclusion vs Other-exclusion) x 3 (Pain Group) in negative affect (Main effect of Group $F(2,28)=2.142$, $p=0.137$, $r=0.400$; Interaction Condition*Pain Group= $F(2,37)= 0.112$,$p=0.894$, $r=0.065$).

Two one way ANOVAs were conducted on the engagement data: Sensory/localisers and affective/general responders were more likely to report a feeling of playing a real person relative to controls ($F(2,30)=5.598$, $p=0.010$; Controls: $M=2.000$, *S.E.*= 0.348, Sensory/localisers: $M=3.33$, *S.E.*=0.224, Affective/Generals: $M=3.000$, *S.E.*=0.40825) and a trend towards significance in terms of whether they treated the other people as real ($t(30)=2.667$,$p=0.094$; Controls: $M=3.000$, *S.E.*=0.325, Sensory/Localisers: $M=3.916$, *S.E.*=0.287, Affective/Generals: $M=3.750$, *S.E.*=0.250). The study therefore provides preliminary evidence that responders have a greater propensity for immersion in virtual/imaginative games.

fMRI results

The data was analysed using a 3 (Round condition: 'Inclusion' vs. 'self-exclusion' vs. 'Other-exclusion') x 3 (Pain group: 'Controls' vs. Sensory/Localisers' vs. 'Affective/Generals') Mixed ANOVA. The data was only analysed 10s after the onset of the round (so that enough time was given

for participants to understand which round they were experiencing) which provided a 20s block for the main analysis. At a whole brain level no regions displayed significant effects in the main effect of 'Round condition', or ' Pain group', or in the two way interaction between Round condition*Pain group.

To further investigate effects of interest a series of contrasts was run on the data. The contrasts of interest included: [1] the differences between 'inclusion' rounds and both exclusions round conditions; [2] the differences between Inclusion rounds and self-exclusion rounds, [3] the differences between Inclusion rounds and other-exclusion rounds, [4] and the difference between self-exclusion and other-exclusion rounds. These contrasts were assessed for all participants and within each pain group. See ***Table 6*** within group effects and ***Figure 9*** for the key effects. Only the contrasts described above which showed significant effects are included in the table.

Table 3.5: Contrasts with significant within groups effects (p<0.05, FDR corrected) for the Cyberball social exclusion task. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

Brain Regions	***Lat***	***MNI Coordinates***			***t-score***	***k***	***p(FDR)***
		x	***y***	***z***			
All Groups: Other-Exclusion > Inclusion							
Dorsolateral Prefrontal cortex	L	-36	42	15	4.69	114	0.008
Anterior Insula	R	39	21	9	4.06	82	0.031
Inferior frontal gyrus	R	57	9	6	4.04	61	0.016
All Groups: Other-Exclusions > Self Exclusion							0.005
Superior Parietal Lobe (medial)	L	-15	-42	33	4.80	374	<0.001
Supramarginal gyrus	L	-57	-35	30	4.30		
Dorsal anterior cingulate cortex	L/R	6	0	39	4.71	81	0.032
Secondary somatosensory cortex	R	69	-12	3	4.73	233	<0.001
Intra-parietal sulcus	L	-21	-63	33	4.06	81	0.032
S/L Resps: Other-Exclusion> Inclusion							
Premotor cortex	R	63	9	18	4.49	75	0.031
Primary somatosensory cortex	R	57	-12	24	4.37	109	0.011
Anterior Insula	R	24	15	-12	4.19	208	0.001
S/L Resps: Other-Exclusions > Self-Exclusion							
Supramarginal gyrus	L	-45	-45	30	4.62	142	0.005
Secondary somatosensory cortex	R	57	-12	21	4.61	77	0.047

Primary somatosensory cortex *A/G Resps: Other-Exclusions > Self - Exclusion*	L	24	-12	21	4.48	170	0.003
Secondary somatosensory cortex	R	66	-18	0	4.99	114	0.043

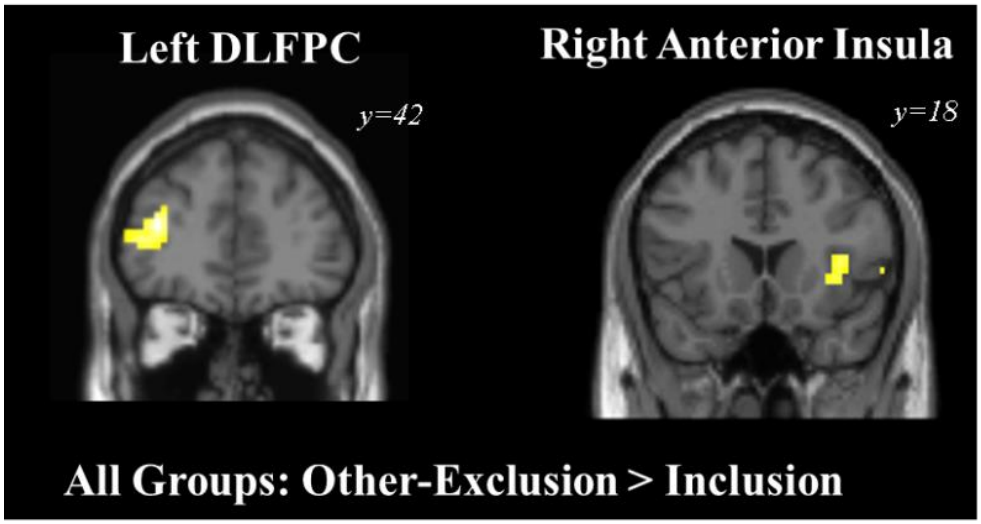


Figure 3.8: Regions with significant effects for other-exclusion > inclusion rounds for all groups (p<0.05, FDR). No significant effects were observed between –self exclusion and inclusion rounds.

Between group contrasts were also observed between the three groups across each of the three conditions. These included: Controls vs Responder (Sensory/Localiser + Affective/General), Controls vs Sensory/Localiser responders, controls vs Affective/General responders and Sensory/Localiser responder vs. Affective/General responders for each of the three experimental conditions (Inclusion, Self-exclusion and Other-Exclusion). None of the contrasts yield any significant between group effects using an FDR corrected threshold of p<0.05 nor when the threshold was made more lenient (p<0.001, uncorrected).

In summary, the analysis of the Cyberball experiment produced somewhat mixed results. Primarily, the results failed to replicate the results of previous fMRI studies assessing self-experienced social exclusion in the Cyberball paradigm (Eisenberger *et al.* 2003). However there was some preliminary evidence for vicarious social exclusion effect in frontal lobe regions which has been observed in similar past studies (Meyer *et al.* 2013; Masten *et al.* 2011) although the lack of affects observed in

the self-experienced social exclusion condition make this effect difficult to interpret. Additionally, the study was underpowered which may explain the lack of expected effects, and no between group effects were observed between the pain groups.

Discussion

When observing people in pain, it is well established that this is linked to activity in a set of regions involved in the physical perception of pain. This is typically attributed to shared representations between self and other (e.g. Decety & Jackson, 2006), which some have also described as a mirror system for pain and somatosensation (analogous to, but separate from, the mirror system for actions; Keysers *et al.* 2010). This system is flexible and heavily modulated by context. There is greater empathy for pain, in terms of degree of activity in shared pain representations, for people who are like us (e.g. in terms of race, Azevedo, Macaluso, Avenanti, Santangelo, Cazzato &Aglioti 2013) and for people we like (e.g. because they previously acted fairly, Singer, Seymour, O'Doherty, Stephan, Dolan & Frith 2006). This contextual modulation is assumed to reflect an interaction between shared representations of pain, and other regions such as the rTPJ, medial PFC, and DLPFC which selectively orient towards either self-relevant or other-relevant properties enabling the observer to 'tune in' or 'tune out' of vicarious pain (Bird & Viding, 2014; Decety & Ickes 2011; Decety & Jackson, 2006). The aim of our study was to assess this general framework from the unique perspective of individual differences in self-reported vicarious pain experiences. Previous research has been largely driven from the assumption that seeing someone in pain leads to an implicit simulation of pain, but not to reportable experiences of pain. Our own research (Grice-Jackson *et al.*2017) , and that of others (Fitzgibbon *et al.*, 2012; Osborn & Derbyshire, 2010), suggests that a significant proportion of people (a quarter to a third) do experience reportable pain-like experiences form observing others in pain. For these individuals it is possible to explore whether the 'standard' findings from the empathy-for-pain literature are driven by this significant minority of participants or do indeed reflect a normative (i.e. universal) response.

In experiment 1, our approach was to take a commonly used image paradigm and stimulus set from the literature (hands and feet in painful and non-painful scenarios) and re-examine it from the perspective of differences between 'responders' who reliably report the pain of others, and 'non-responders', who do not. Our recent research has shown that responders can be classified in two ways, Sensory/Localised and Affective/General, and these were contrasted against non-responder controls. We hypothesised that these groupings may differentially activate regions of the pain matrix that have been labelled as affective/motivational (e.g. anterior insula, mid-cingulate) and sensory/discriminative (e.g. somatosensory cortices). This was not found. In terms of their pattern of activity, the two responder groups were similar to each other but were different to the controls. All three groups tended to activate the anterior insula and mid-cingulate regions (extending into supplementary motor area) when contrasting pain against no-pain. The two responder groups also tended to activate primary and secondary somatosensory cortices when observing pain, which was not found for the controls. There was some evidence that the Sensory/Localiser group did so in a more somatotopic manner (e.g. feet in pain activating the foot area) which was not reflected in the Affective/General group. These findings indicates a pattern of functional activity in the sensory pain matrix regions which delineates the mirror-pain responders from normative controls and provide support for previous fMRI results on mirror-pain responders (Osborn and Derbyshire, 2011), other non-fMRI studies (Fitzgibbon *et al.* 2015) and somatosensory hyperactivity theories of mirror-pain (Banissy & Ward, 2015; Fitzgibbon *et al.* 2012). In normative samples (i.e. that do not separate out responders who report pain), images such as these have been reported to activate the somatosensory cortices (Lamm *et al.*, 2011). As such, raise the possibility that these previous results in somatosensory cortex are driven mainly (perhaps exclusively) by a subset of the 'normal' population who are having pain-like experiences rather than reflecting a normative tendency to implicitly simulate the sensory properties of pain. Further research is needed to clarify this, but it is consistent with our own previous research suggesting that EEG mu/beta suppression when observing pain is linked primarily to responders (in that case, Sensory/Localiser) rather than being a normative tendency (Grice-Jackson et al., 2017).

Beyond these primary findings in the pain matrix the two mirror-pain responders showed more widespread effects than controls. For sensory/localiser responders the left dorsolateral prefrontal cortex (DLPFC), the pre-central gyrus and the cerebellum were active when viewing pain. These regions have been linked with emotional recognition and expression (Moriguchi, *et al.* 2006), empathy (Oschner & Gross, 2005), perspective taking (Decety & Jackson, 2006), motor imagery and sensori motor mirroring (Stappich, *et al.*2002, Molenbergh *et al.* 2012) and Mirror-touch synaesthesia (Holle, Banissy & Ward, 2013). Affective/general within group effects were observed in the periaqueductal grey (PAG) matter, premotor cortex and supplementary motor area (SMA). These regions are known to be involved in normative pain and mirror-pain processing (Peyron *et al.* 2000, Cheng *et al.*2007, Lamm *et al*.2007) and mirror-neuron research (Rizzolatti *et al.* 1996).

Whilst the within group analysis showed a number of pain matrix effects this pattern was not pulled out during the between group effects. However, the results showed a number of widespread increased effects in the two responders, when viewing pain, relative to controls but no such effects in the opposite direction. For both responder groups the left DLPFC, precuneus and cerebellum show significantly increased activity compared with controls which were regions displayed in the within groups analysis. The affective/general group was also shown to display a number of effects in pain matrix regions including the AI, SI/SII and ACC whilst sensory/localiser group showed between group effects in frontal lobe regions which have been previously linked to the mirror-neuron system (Keuken, Hardie, Dorn, Dev, Paulus & Jonas *et al.* 2011) and social cognition (Cheng, Lin, Liu, Hsu, Lim, Hung & Decety 2007), including the inferior frontal gyrus and the superior frontal gyrus. No between groups effects were observed between the two responder groups, again showing a lack of demarcation between the groups. Finally, no between group effects were observed which showed increased activation for controls compared with the mirror-pain groups. The between group ROI analysis with a priori pain matrix regions also showed significantly increased activation for the two responder groups relative to controls in the anterior cingulate cortex, left SI, and right SII, and borderline effects in the Left SII and Right SI. Again, no differences were observed between the two groups with both showing similar patterns of results. These results show some support for the

hyperactivity theories of mirror-pain and touch (Ward & Banissy, 2015) as well as previous fMRI studies of the two conditions (Osborn & Derbyshire 2010, Holle *et al* 2013).

Two further series of ROI analysis were run on the whether the responder groups displayed topographical and laterally specific activation in the primary somatosensory cortex activity. The topography analysis showed that the sensory localiser Sensory/localiser group displayed some evidence of topographic specificity with significantly increased activation during the observation of foot images relative to hand images in foot region of SI. The opposite trend was observed in the hand region however the effect did not reach significance. Previous studies using MEG stimulation has shown that modulation of corticospinal inhibition matches the topography of observed touch in normative samples (Avenanti *et al.*2005, Blakemore *et al.* 2005) but follow-up fMRI studies failed to show SI activation (Jackson *et al.* 2005, Morrison *et al.* 2004). Our results display some evidence for topographic sensitivity in the sensory/localiser group however it should be note the effects observed are relatively mild. Splitting the image analysis by hand and foot reduced the number of images in each condition by half (36 trials p/condition) thus resulting in an underpowered experiment. Future research should specifically focus on these topographic findings with larger trial numbers. The laterality ROI analysis showed no clear effect of SI/SII lateralised specificity, however it did show a main effect of image laterality with right lateralised image displaying increased SI/SII responses relative to left lateralised images across all ROI regions.

The whole brain and ROI analyses reveal a number of common effects across all three groups as well as some specific effects in the responder groups. However, the pain matrix effects were not present across both within-group and between-group analyses and the patterns of effects for the each of the responder groups were somewhat inconsistent and spurious. The PPI analysis of functional connectivity did revealed clear and dissociable patterns. For the control group, we found no significant effects. For the responder groups, there were ten significant effects (all in frontal and parietal regions), primarily for the Sensory/Localised groups. Importantly, many of the same regions emerged via multiple independent analyses (i.e. using different seed regions). We shall discuss the

potential role of the parietal regions (rTPJ, left angular gyrus, precuneus/retrosplenial) and frontal regions (DLPFC, mPFC) in turn.

One region that was hypothesised from the outset to be important was the rTPJ and this region showed greater connectivity to the left and right anterior insula in the Sensory/Localiser group when observing pain (relative to no-pain; and also relative to the same contrast in controls). One function of this region is linked to acting as a switch between self and other based representations such that increased rTPJ activity is linked specifically to suppressing the dominant self-perspective and enhancing the other perspective (Bird & Viding, 2014). The rTPJ is also proposed to simulate social processes (e.g. empathy for pain) that can be externally attributed (Carter & Huettel, 2013). For instance, one study contrasted physically painful stimuli presented concurrently with images of other people in painful or neutral situations (Godinho *et al.,* 2012). Seeing someone else in pain increases the self-reported intensity of physical pain (a normal form of self-other confusion) and this was linked to the same posterior region of the rTPJ that we observed (and not to increased activity in the pain matrix). Moreover, different roles are proposed for posterior and anterior rTPJ (Bzdok *et al.,* 2013; Krall *et al.,* 2014). While both sub-regions are implicated in mirror pain, our previous VBM study showed reduced grey matter in the anterior portion (Grice-Jackson *et al.,* 2017) and the current study implicates the posterior portion. Our explanation of the Sensory/Localised group is that they systematically fail to attribute shared bodily representations to others and this, at least in part, reflects structural and functional differences within the rTPJ coupled with other differences (e.g. in left parietal cortex).

Aside from the rTPJ, other regions were highlighted by the connectivity analysis for the Sensory/Localiser group. A region in the left angular gyrus showed greater connectivity (when observing pain > no-pain) to three seed regions (left and right somatosensory cortices, and the cingulate/SMA region). This parietal region is not the left hemispheric homologue of the rTPJ but is several centimetres posterior to it. This region has been found to be important in several studies relating to agency and body ownership. Long-term gamers who habitually use a certain avatar

activate this region when thinking about (Ganesh, van Schie, de Lange, Thompson, & Wigboldus, 2012) or observing (Lemenager, Dieter, Hill, Koopman, Reinhard, Sell *et al.* 2014) their avatar. Patients with left parietal lobe damage are more inclined to claim agency to third-person perspective hand movements executed by others (Sirigu, Daprati, Pradat-Diehl, Franck, & Jeannerod, 1999), and TMS over this region in healthy controls disrupts agency attribution (Chambon, Moore, & Haggard, 2015). The precise function(s) of this region is uncertain, but one theory is that it computes a mental simulation of the self into alternate spatial scenes and perspectives (Buckner & Carroll, 2007). The precuneus/retrosplenial area was also implicated by multiple independent analyses (Pain > No-pain in both Sensory/Localiser and Affective/General groups, and PPI connectivity to left anterior insula in the Sensory/Localiser group). While this region may also serve a general role in mental simulation/imagery (Cavanna & Trimble, 2006), it has also been hypothesised to have a more specific role in pain. Stimulation of this region in rats has an analgesic effect (Rossaneis, Reis, & Prado, 2011) and, in humans, patients with fibromyalgia have higher resting levels of activity in this region which may arguably reflect an analgesic function (Wik, Fischer, Bragee, Kristianson, & Fredrikson, 2003).

With regards to the frontal lobe, two regions (medial PFC and DLPFC) are noteworthy. The medial PFC region was implicated in the functional connectivity analysis for the Affective/General group. It has been linked specifically to the self-concept (e.g. thinking about one's own characteristics) rather than bodily self (e.g. Mitchell, Banaji, & Macrae, 2005). This particular result needs to be treated with caution given that the region was not implicated by any other analysis. The DLPFC has widespread effects on cognitive control (Duncan, 2010) including empathy (Moriguchi *et al.*2006) and emotion regulation (Ochsner, Silvers, & Buhle, 2012), so it would be unwise to infer a specific role for mirror pain. The region (both left and right) was implicated across multiple analyses. It is important to explore the role of this region, alongside the parietal regions previously discussed, using methods such as non-invasive brain stimulation (NIBS) and combined NIBS-fMRI to examine its causal role on vicarious pain perception.

In experiment 2 an adapted Cyberball paradigm was used to assess vicarious social exclusion in the three responder groups. The original paradigm involved only three players and included rounds in which the participants were either included in the ball tossing game or excluded by the two other players in the game (Eisenberger *et al.* 2003). This experiment showed activation during exclusions in regions that are included in the affective/motivation pain matrix. More recent studies have investigated neural responses to observations others being excluded (Masten, Morelli, Eisenberger 2011) and displayed activation in areas associated with mentalizing and empathy including the DMPFC, Precuneus and temporal pole. When observing participants observed close friends playing the game they activated the affective/motivational pain matrix regions associated with the personal experience of social exclusion and physical pain (Meyer, Masten, Ma, Wang, Shi, Eisenberger & Han 2013).

In the current study no activation was observed when participants were, themselves, excluded from the game (in contrast to the Eisenberger *et al.* 2003). The lack of replication of these results are concerning for the methodology adopted in this study. One of the possibilities for this effect was that the four avatar paradigm used in the study implicitly focused the attention of participants on the avatar facing them rather than their own social exclusion. Another possibility is that the graphical set up meant that the avatars may have had less of an impact on the participants than the cartoon figures used in previous Cyberball studies. When participants observed the avatar facing them (the 'other') a number of regions related to both personally experienced social exclusion and physical pain (AI) and mentalizing and empathy (DLPFC and inferior frontal gyrus). These results show some support for the results observed in studies focusing on people observing others experiencing social exclusion. However, whilst similar these results do not make up the same network proposed in previous studies (Meyer *et al.* 2013).

Effects were also observed between the participant's self-exclusion and observed exclusion rounds including the sensorimotor system and ACC and regions associated with theory mind (i.e. the supramarginal gyrus and inferior parietal lobule). The sensorimotor effect may reflect the fact that

participants were using their hands to press the button more in the other exclusion. The ACC activation may reflect the lack of engagement in self-exclusion rounds and the mentalizing regions may reflect that participants were imagining the social exclusion of the observed avatar. Finally, no between groups effects were observed and within group effects for the mirror-pain responder groups did not display unique patterns of responses. Overall, this experiment shows little support for previous studies and our own hypotheses related to self-experienced social exclusion in the Cyberball game. Some evidence was provided for the observed exclusion hypotheses however they were not consistent with previous studies and no support for the hypothesis of differing social exclusion responses for the pain groups was observed.

To conclude, our research has important theoretical implications for research on empathy for pain (and other shared states). It suggests that greater attention should be paid to individual differences in reportable experiences. These have the potential to distort what is assumed to be a normative response. In particular, activity within the somatosensory cortex when observing others in pain may be primarily (and possibly exclusively) linked to those individuals who report pain when seeing others in pain. Patients with congenital pain sensitivity activate some regions of the 'pain matrix', notably insula and mid-cingulate, when viewing others in pain but notably not the somatosensory cortex (Danziger, Faillenot, & Peyron, 2009). Contrary to our initial predictions, the amount of activity in somatosensory cortices does not seem to strongly reflect the distinction between Sensory/Localised and Affective/General, but they may nonetheless show differences in how these regions are activated (body-part v. whole body respectively).

Our investigation of vicarious social exclusion showed promising findings for the observation of others in pain, with various regions with associations to mentalizing and affective pain processing being highlights, thereby supporting previous research (Masten *et al.*2011; Meyer *et al.*2013). However, when participants were themselves excluded from the round no effects were observed in pain matrix regions, as a result the current study fails to replicate previous Cyberball findings (Eisenberger *et al.*2003). This result may attributed to the alterations in Cyberball methodology used

in the current study or the altered visual representations of the other players in the game. Additionally, no between group effects which would suggest that mirror-pain responder's experiences are not manifested in other kinds of pain.

Hyper-activity within pain matrix regions might be proposed to be both necessary and sufficient for consciously experienced vicarious pain. We previously referred to this as Threshold Theory (Ward & Banissy, 2015) and is based on the notion that all individuals activate, to varying degrees, the pain matrix on seeing pain but only those that do so above a threshold for awareness have reportable pain-like experiences. We do not doubt that this is part of the explanation, however, we question whether it is sufficient. In particular, we argue that it is interactions between the pain matrix and various fronto-parietal regions that give rise to these reportable vicarious pain experiences. This is more clearly the case for the Sensory/Localised group for whom we observed enhanced functional connectivity between pain matrix regions and the rTPJ and left angular gyrus, both of which are implicated in discriminating self from other and bodily perspective taking. The explanation for the Affective/General group is presently lacking and, in some respects, appears to be intermediate between the Sensory/Localised and the non-responder groups. One possibility is that this group reflects differences on autonomic measures (for a model incorporating this see Giummarra & Fitzgibbon, 2015). In summary, our research provides fresh evidence that these individual differences are important to consider methodologically (as they can skew results) and theoretically, as they provide important test cases for current models.

Article III: Behavioural and physiological tests linked to individual differences in vicarious pain perception

Abstract

Mirror-pain responders represent a significant population of interest for the study of empathy, shared representations, and vicarious perception. Their experiences are thought to be related to hyperactivity in somatosensory simulation in response to pain and because of modulated, or diminished, self-other processing. Whilst a novel tool has been developed and neural signatures for the condition have been presented there is still much to learn about the traits and characteristics associated with these individuals and the affective-general subgroup has not yet displayed a unique pattern of results. In this study a set of physiological, behavioural, and questionnaire measures of related traits were run on the two responder groups (Sensory/Localiser and Affective/General responders) and controls. This included the two behavioural measures of social cognition, the 'Control of Imitation' and 'director's task' of perspective taking; two physiological measures, the Skin conductance response (SCR) and Interoceptive awareness; and empathy questionnaire measure. Neither of the social cognition tasks nor the Interoceptive awareness physiological task showed any between group effects. This lack of findings for the social cognition tasks calls into questions some of our assumptions about the link between mirror-pain and cognitive empathy traits. However, the SCR results showed a somewhat unexpected flat-lining of the autonomic nervous system response when viewing pain in only the Affective/General Responder group. This finding could be reflective of an anxiety response bought about by the observation of pain in these individuals; however this is speculative without further research. This finding also represents the first unique response displayed in this subgroup of mirror-pain responders. Additionally, this study displayed a hypothesised link between mirror-pain responders and heightened empathy scores on questionnaire measures.

Introduction

When seeing someone else in pain there is evidence that observers activate neural circuits related to pain – i.e. they have an empathic pain response (Singer *et al.* 2004). Models of empathy link this experience to a process called simulation whereby observations of various states activate the neural regions in the personal experience of that state (Gallese, 1998). For most, this simulation is implicit and non-conscious however, a subset of the population, mirror-pain responders, report conscious bodily experiences of pain during its observation (Giummarra *et al.* 2008).

Previous research has assessed prevalence rates and characteristics of mirror-pain via an online questionnaire tool, the VPQ (Vicarious Pain Questionnaire) (Grice Jackson et al., 2017; **Article I**). This study found that ~30% of the population report common mirror-pain experiences, which is in line with previous reports (Osborn and Derbyshire. 2010). The study also identified two subgroups of mirror-pain responders which were characterised by differences in the quality of their experiences. They included: Sensory/Localisers (19%), who tended to report localised synesthetic experiences using more sensory descriptive terms for their experiences; and Affective/Generals (11%), who tended not to localise their experiences and who used more affective descriptors of their pain.

There currently exists limited understanding of how these different groupings relate to wider cognitive abilities and/or personality traits. Furthermore, very few attempts have been made to assess the physiological characteristics related to mirror-pain, i.e. autonomic nervous system responses and interoceptive awareness. The current study will be split into two sections; experiment one will aim to characterise the two mirror-pain groups previously identified in the VPQ relative to controls by using a battery of social cognition behavioural tasks, and physiological measures which are expected to be linked to mirror-pain and experiment 2 will assess the link between mirror-pan and questionnaire measures of empathy.

Prevalent theories of mirror-pain responders and mirror sensory synaesthesia suggest that the conditions arise out of a two-fold mechanism (Ward & Banissy 2015; Fitzgibbon *et al.* 2012a). The first mechanism is known as 'Threshold theory' and it refers to hyper-activation of simulation systems for somatosensory processing during pain observations. Previous studies have shown increased activity in these groups during pain observations across a variety of neuroimaging measures when compared with controls (Grice-Jackson *et al.* in press, See **Article I**; Fitzgibbon *et al.* 2012b; Osborn & Derbyshire 2010). The second mechanism is known as 'Self-other' theory which states that mirror-pain responders possess diminished or modulated self-other discrimination abilities which results in misattribution or incorporation of other representations to themselves, as such other pain is experienced as self-pain. Self-other processing is a key component of cognitive empathy and social cognition and is considered crucial for vicarious pain processing in typical samples (Jackson & Decety, 2006). A network of neural regions is thought to contribute to this self-other processing including frontal and parietal systems however the right temporoparietal junction (rTPJ) is most frequently associated with self-other discrimination in mirror-pain and vicarious pain literature (Decety & Jackson, 2006; Fitzgibbon *et al.* 2012a). Indeed, our own research has shown decreased grey-matter volume in the region and has shown a functional connectivity between simulation regions and the rTPJ during pain observations.

Few studies have examined the behavioural characteristics of mirror-pain responders. However, those studies that have focused on this have exhibited some interesting findings. Derbyshire's *et al.* (2013) assessment of self-characterised mirror-pain responders showed a number of effects across a series of tests. Specifically, they found that mirror pain responders had faster reaction times during a visual perspective taking task when asked to adopt an avatars perspective. The study also tested mirror-pain responders on the Rubber hand-Illusion paradigm in which participants receive synchronous or synchronous to one of their hands and a rubber hand which is placed next to their own hand (the participant's second hand is occluded from view). The task is a measure of self-other processing and body ownership and typical samples often adopt the rubber hand during the synchronous condition but bodily ownership during asynchronous is highly unusual. However, mirror-pain responders also

showed an increased tendency to adopt ownership of the rubber hand during both synchronous stroke conditions and asynchronous conditions which was considered to provide evidence for the modulated self-other abilities suggested by mirror-sensory theories. Finally, a contextual mirror-pain task showed that those with increased tooth sensitivity were more likely to display mirror-pain when observing cold tooth pain whilst eating ice popsicles. This effect may be display a link between past pain experiences of the observer and the likelihood of them experiencing mirror-pain.

As previously mentioned, diminished self/other control is thought to be a key cause of mirror-pain experiences. Observations of mirror-touch synesthetes, a closely related condition to mirror-pain, have shown impairments in self-other control abilities during a task in which participants had to control for the imitation of another person's body (Santiesteban *et al.* 2015). Past studies observing this regions have showed anodal tDCS stimulation (increased activity) results in an increased ability to control for the imitation of other's hand movements, a key marker of self/other discrimination (Hogerveen, Obhi, Banissy, Santiesteban, Press, Catmus & Bird 2014; Santiesteban *et al.* 2014). This controls of imitation task (Spengler *et al.* 2009) asks participants to raise either their index or middle finger in response to the presentation of a number '1' or '2' respectively. During the number presentation participants are shown either hand completing a congruent finger movement (the same as the number is asking the participants to complete, i.e. a number '1' is presented whilst a hand moving its index finger is presented) or incongruent (in which the opposite finger lift is being presented during the number presentation, i.e. a middle finger movement is displayed during the presentation of a '1'). As this task is considered to be a good marker of self/other discriminations and because it is known to be affected by alterations in rTPJ activity we consider it a highly relevant test for our own mirror-pain responder groups and it will be included as part of our assessment of behavioural measures associated with social cognition. Based on Ward & Banissy's (2015) self-other theory it is expected that the mirror-pain responder groups will be less able to control for the representations of the observed hand and therefore perform more slowly and less accurately than controls.

Perspective taking is an ability trait which has been associated with mirror-pain and self-other representations. It is a key component of cognitive empathy and allows a person to take low-level physical and bodily perspectives (Michelon & Zacks, 2006) and higher level mental perspectives (Frith & Frith, 2006). Critically, previous studies on mirror-pain responders have shown that these individuals find it harder to supress the visual perspective of an avatar when making judgements about the size and locations of objects in visual space which differed from the participant's (Derbyshire, *et al.* 2013). Heightened perspective taking may result in an increased likelihood for the responder to be attuned to the pain of another. Perspective taking is also closely related to self-other representations and discrimination. Viewing pain from the self-perspective is known to increase empathic response (Bach, Fenton-Adams & Tipper 2014) and modulate ERP responses during empathic pain judgements compared with third person perspectives (Li & Han 2010). Additionally, MRI responses in pain related areas (ACC, insula and amygdala) are larger when participants are told to adopt a self-perspective (i.e. 'imagine self' rather than 'imagine other') when observing the pain of others (Lamm, *et al.* 2007). Individual differences in perspective taking are also known to have wide ranging implications for empathic behaviours including the likelihood of people to engage with negatively stereotyped outgroup individuals (Wang, Callaghan, Gooding-Williams, McAllister & Kessler 2014) and the likelihood of giving larger charitable donations (Tusche, Bockler, Kanske, Trautwen & Singer 2016). tDCS induced excitatory rTPJ results in increased accuracy scores on a perspective taking task relative to the sham and cathodal (inhibitory neural effects) tDCS conditions. (Santiesteban *et al.* 2013). This study used the Director's task to assess perspective taking abilities. This task presents participants with a visual scene with a 'director' avatar facing them and a series of objects on a bookshelf. The director asks participants to move the objects and participants are forced to understand that director's visual perspective in order to successfully complete the task. This task will be used to test the perspective taking abilities of the mirror-pain responder groups and it will make up the second part of the behavioural measures of social cognition. We expect to reproduce the findings of previous research into perspective taking and mirror-pain synaesthesia by displaying increased perspective taking scores for the mirror-pain responder groups.

Much of the focus of research into mirror-pain and touch has focused on the behavioural and neurocognitive manifestations of the condition. The current study will attempt to broaden the scope of the literature by including two physiological measures which are thought to be associated with the condition. This will include: Interceptive awareness and Skin Conductive Responses (SCR) to observed pain.

Skin conductance response (SCR) is a sensitive psychophysiological index of changes in autonomic sympathetic arousal that are integrated with emotional and cognitive states (Malik, 1996). Autonomic sympathetic arousal reflects the activity of the autonomic nervous system which is involved in preparing and activating bodily systems in response to environmental stimuli. The anterior insula, a key mirror-pain processing centre, is known to play a key role in autonomic arousal and SCR responses (Critchley, Mathias & Dolan, 2002; Critchley & Dolan, 2002). It is also known to be an important component of people's pain response (Kyle & McNeil 2014) and has been used to assess vicarious responses to the pain of others (Hein *et al.* 2011). Studies investigating emotional contagion and vicarious experiences during the observations of facial expression have successfully shown SCR responses that match the expected autonomic responses of the observed facial expressions (Preston & de Waal, 2002, Levenson & Frieson, 1993). SCR responses to both physical and affective pain will be observed for the pain responder groups relative to controls. Due to the links between the AI, and mirror-pain to SCR it is expected that the mirror pain groups will display greater SCR responses to images of pain relative to controls and the Affective/General group will display higher responses than Sensory/Localisers. Additionally, the two mirror-pain responder groups are expected to respond differently to different types of pain images with Sensory/Localisers showing increased reactions to physical pain and Affective/General Responders showing increased responses to emotional pain images.

Interoception is the monitoring of internal states and the formation of bodily representations of the self, and interoceptive awareness (IA) refers individual differences in one's ability to consciously

monitor these states. Through the use of a heartbeat counting task the right anterior insula has been identified as the key processing region for IA (Critchley, Weins, Rotshein & Dolan, 2004). It has been linked to the neural processing of empathy increased empathic neural processing beings after a period of interoception (Ernst, Boker, Hattenschwiller, Schubacher, Seifritz, & Grimm 2013). Individuals with greater IA abilities display estimated higher pain ratings and compassion when observing the pain of others suggesting that increased cognitive and affective empathy for pain is linked to IA (Grynberg & Pollatos, 2015). Research into body ownership has also shown a link that people with high IA perform better on tests of self/other distinctions, including the Control of Imitation task, thereby implying a link between one's own representations and the formation of other people's (Ainley, Brass & Tsakiris 2014, Tsakiris, Tajadura- Jiminez & Costantini 2011, Suzuki, Golaz, Stephans 2013). Dispositional IA will be assessed and compared for the two mirror-pain groups and controls. Based on the between the insula and mirror-pain and links with self/other distinctions it is expected that the mirror-pain responder groups will displayed higher levels of IA than controls.

Finally, assessments of dispositional measures of empathy will be made for participants who have completed the VPQ. This will include a well characterised empathy measure, the IRI, which can be divided into a number of subscales relating to different aspects of empathy (Davies, 1980, 1983). Due to the strong theoretical links between mirror-pain and empathy and heightened empathy scores observed in individuals with mirror-touch synaesthesia (Banissy *et al.* 2009), it is expected that the mirror-pain responder groups will score highly on the IRI scale, particularly on the perspective taking and personal distress subscales, relative to controls. Additionally, a questionnaire measure of subjective perceived pain sensitivity, the pain sensitivity questionnaire (PSQ), will be taken for each of the three groups (Molenbach *et al.* 2014). The PSQ has been shown to be a good marker of physical pain sensitivity via comparison with actual physical pain sensitivity measures. The pain sensitivity of the observer is thought to be related to empathy for pain, for example, Common painkiller drugs (Mischkowski *et al.* 2016) are known to reduce people's empathy for pain abilities and the content of empathy for pain experiences have been shown to be related to past pain

experiences (Derbyshire *et al.* 2013). It is predicted that the mirror-pain responder groups with display increased perceived pain sensitivity scores. Although empathy is considered foundational in mirror-pain research recent assessments of mirror-touch synaesthetes have called this into questions with this group not displaying the predicted increases in empathy quotient scores compared with controls (Baron-Cohen *et al.* 2016). Indeed, cases of acquired mirror pain have also failed to show increased scores on empathy measures. This study will attempt to assess this issue in the research in relation to mirror-pain responders.

Based on past research into vicarious and mirror-pain and the theories that explain the experiences, the current study makes a set of predictions about how the two pain responder groups will perform on the physiological and social cognition behavioural tasks. These include:

1. *The two responder groups will show increased SCR responses in during the observation of pain images when compared with controls.*
2. *The two control groups will show some differences in SCR responses with Sensory/Localisers showing an increased response to physical pain images and Affective/General Responders showing an increased response to emotional pain images.*
3. *The two responder groups will show differences in interoceptive awareness compared with controls because of the link between mirror-pain and interceptive awareness with the anterior insula.*
4. *The two responder groups will show increased scores on the director's task, which will reflect increased perspective taking abilities, and, decreased performance on the Control of Imitation task, reflecting diminished self-other discrimination abilities.*
5. *The two mirror-pain responder groups will show increased scores on the empathy questionnaires relative to controls.*

Methods

Experiment 1: Behavioural and physiological tests

Participants

81 participants (31 males, 50 females) aged between 18 and 32 years (mean=22.75, S.D= 4.09) took part in all four of the experiments in this article, however only 54 were recruited for the Control of Imitation task (18 males, 36 females) aged between 18 and 32 years (mean=21.65, S.D= 4.09). Participants had previously taken part in the vicarious pain Questionnaire (VPQ), an online questionnaire assessing reports and characteristics of conscious vicarious pain experiences (*see* Grice-Jackson, et al. 2017, **Article I** VPQ). Participants were split between three groups that were classified in the original VPQ 2 step cluster analysis (n=573).

Apparatus

All tasks, apart from the interceptive awareness task, were displayed run on a Dell Optiplex-745 desktop computer with a Dell E771p 16" CRT display. Another laptop computer was used to record the interceptive awareness heartbeat data and to record the SCR data. The heart beat data was recorded using an OEM infra-red heartbeat monitor (Nonin Medical Inc, Plymouth, Minnesota) and the SCR data was recorded using a Biopac MP26 data acquisition system (Biopac system Inc, Goleta, California). The SCR stimuli display program and the perspective taking task were created and run on E-Prime (Version 2 Standard SPI; Psychology Software Inc, Sharpburg, Pennsylvania) and the control if Imitation was script and run on Microsoft Visual Basic. Finally, the online VPQ and dispositional questionnaires were created and run using Bristol Online surveys, which participants could complete on their home PCs.

Procedures and design

In the current experiment participants took part in four tasks. These tasks will be split into two sections: firstly, 'Physiological tasks', which includes [1] an SCR pain-observation task, and an [2] interceptive awareness task; and second, 'Social cognition task, which includes [3] the Control of Imitation task, and [4] the director's task of perspective taking. The session followed the same order of experiments for each participant. The tasks will be described below. Participants who completed the online questionnaire were recruited via an online recruitment city at the University of Sussex (SONA) and were provided with a link through which they could complete the questionnaire on their home computers.

Procedures for physiological task

SCR pain observation task

For the SCR task participants view various types of pain images whilst their SCR response was recorded. A pair of 5 mm surface electrodes were attached to participants' non-dominant hand: one above the thenar muscle and the other above the hypothenar muscle. The stimuli consisted of 120 images presented on the computer monitor. The images were gathered from the International Affective Picture system (IAPS), and various image sharing web-sites. Forty depicted (or implied) people in physical pain (e.g. a needle about to prick someone's arm, or a boy with his mouth open at the dentist); 40 depicted (or implied) people in emotional pain (e.g. an elderly war veteran visiting a graveyard, or a crying child), and the remaining 40 were of neutral content (e.g. people walking, sitting, and reading). See **Figure 4.1** for image examples.

Figure 4.1: Stimuli examples for each of the three image conditions in the GSR task.

The images were randomly organized into four blocks of 30 images, each with an equal amount of neutral, emotional pain, and physical pain images. For ethical reasons, none of the images contained blood or gory content. A sliding VAS scale was used to record participant's subjective responses of pleasantness to each the observed images (1=pleasant, 100=unpleasant). Each image was displayed for 2s, after which participants were displayed with the VAS for a maximum of 3s. Data was not recorded if participants failed to respond within the allotted time.

Interceptive Awareness

This task was adapted from Schandry's (1981) heartbeat counting task and used the heartbeat monitor. The heartbeat monitor was used to count the participant's heartbeat across 6 sessions which lasted between 20s-40s. For each session participants were asked to remain quiet during the 6 sessions and to avoid eye contact with the researcher. During each session participants were asked to count their own heartbeat without receiving feedback from the heartbeat monitor or feeling their wrist/neck for tactile feedback. After each session they were asked to report their heartbeat count for the session and then were asked to make a confidence judgement of their heart beat count using a VAS scale. The

accuracy of their count relative to their monitored heartbeat count was created (interceptive accuracy) as well as a composite score of the accuracy and confidence rating (interceptive awareness). A one way ANOVA was run for group differences in the interceptive accuracy and interceptive awareness scores.

Procedures for social cognition tasks

Control of Imitation

The current task was based on a task previously run by Brass *et al.* (2000). The task consisted of participants viewing short tasks of hand lifting either its middle finger or index finger. The hand videos were rotated across the sagittal and transverse plane relative to the participant's hand to avoid imitation based solely on digit location. A box also appeared as the hand lifted a finger, either a '1' or a '2' for the duration of the video displaying the finger movements. See **Figure 4.2** for stimuli examples. Participants were also asked to place their finger on the keyboard with their right hand index finger on the 'V' key and their right hand middle finger on the 'B' button before each video trial began. Participants were told to lift their finger based on the number presented when the finger was lifted but were told to ignore the actual finger lift (i.e. when '1' is presented participants should lift their index finger from the 'V' button). This allowed for congruent trials, in which the observed hand lift the same finger as the number presented, and incongruent trials, in which the number presented was not matched with the observed hand's finger lift movement. The number of trials varied slight between participants with participants taking part in an average of 59.27 (SD=3.62) congruent and 56.72 (SD=5.76) incongruent trials. Number of hits and misses where recorded as well as the reaction time for their own finger (onset based on the moment that the observed hand began to make a lifting movement). For the statistical analysis a between groups one way ANOVA based on the responder grouping (Controls vs. Sensory/Localiser responders vs. Affective/General responders) was assessed for both the accuracy and RT scores.

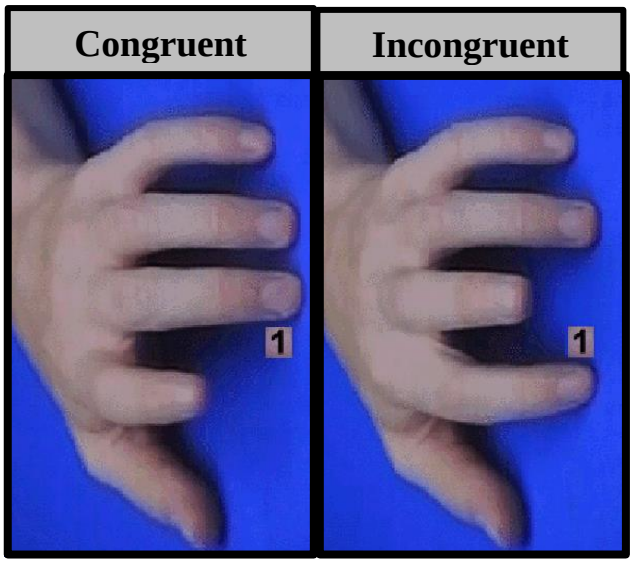


Figure 4.2: Examples of the stimuli used in the Control of Imitation task. In the congruent images a number '1' is presented whilst participants raise their index finger but in incongruent images a number '1' was presented whilst the middle finger was presented. In both trials participants should follow the number and raise their index finger.

Director's task of perspective taking

This task was adapted from Keysar's, Barr, Belin & Brauner. (2000) study. Participants viewed a scene which contained a 'book case' (with a 4x4 square arrangement) with objects on it and a man standing behind the book case (the director). The objects on the bookcase varied but were largely everyday objects, however they varied in size (i.e. participants may see two bowls on the bookcase which were different sizes) and changed from trial to trial. Additionally, some of the squares on the bookcase had barriers which occluded the contents of the square from the director (but not the participants). Participants were asked to adopt the perspective of the director who, during each trial, delivered instructions to the participants which were based on moving the objects from the square it started into another square which was next to its original starting position. See **Figure 4.3** for example arrays. On experimental trials, there was a conflict between the participant's and the director's perspective. For example, if the participant was presented with the array shown in **Figure 4.2**, and

was asked to ‘‘move the large candle up,’’ they should ignore the largest candle they can see, the ‘‘competitor object,’’ (because the director couldn’t see it), and instead move the next largest candle, which is visible to the director. There were two control conditions: C1 and C2. In C1, the director instructed participants to move an object placed in one of the clear slots (e.g., the mug), and therefore there was no conflict between the perspectives of the participant and the director. In C2, an irrelevant object replaced the ‘‘competitor’’ item from the experimental condition, but the instruction remained the same. Accuracy of the selection and movement of the target object and reaction times were recorded. During the final analysis the 2 data from the 2 control conditions was collapsed.

Figure 4.3: Example of director’s trial array. Participants receive audio instructions from the director to move objects from one of the array’s slots to another. See text for description of control and experimental trials.

Experiment 2: VPQ and dispositional questionnaires

Participants

141 participants (Gender: 61 Males, 78 females; Age: Mean=39.75, S.E. =1.02) took part in the VPQ and dispositional measures. Participants were recruited via MTurk, a participant recruitment service

for online experiments hosted by Amazon™, and were paid $1 for their participation. Participants provided informed consent in line with the University of Sussex's ethical guidelines.

Procedures and design

Participants completed the Vicarious Pain Questionnaire (VPQ), Interpersonal reactivity index (IRI, Davies 1983, Davis 1980) and the Pain Sensitivity Questionnaire (Molenberghs, Cunnington & Mattingley, 2012) online using Bristol online surveys on their home computers. The VPQ had participants view a series of 10s pain videos after which they reported whether or not they experienced a sensation of bodily pain as a result of viewing the video. If they provide a positive response they were asked to give details about their pain experiences. The VPQ allowed for classification of participants into 3 Pain groups (Controls, Sensory/Localiser responders and Affective/General responders). A detailed account of the methods for the VPQ as well as a description of the three pain groups can be found in **Article I**. The cluster analysis k-means used to classify these groups was run on this data set (n=144) using the cluster centroids generated during the VPQ analysis presented in Article I, it classified: 94 controls (48.2%), 18 Sensory/Localisers (12.8%) and 29 Affective/General responders (20.6%) The IRI is a 28 item questionnaire assessing four different subscales of empathy which include: [1] the fantasy scale (FS), [2] the perspective taking scale (PT), [3] the personal distress scale (PD) and [4] the empathic concern scale (EC). In the questionnaire participants were asked to rate on a 7 point Likert scale (1=disagree, 7=agree) how much they agreed that a statement (i.e. *"In emergency situations, I feel apprehensive and ill-at-ease"* (PD)) reflected beliefs about themselves. In the PSQ participants read a series of 10 statements describing painful experiences (i.e. *"Imagine you burn your tongue on a very hot drink."*) and rate on a 10 point Likert scale how painful they would expect to find the experience (1=not painful, 10=very painful). The measure aimed at find participant's levels of perceived pain sensitivity, which has been showed to be a good marker of actual physical pain sensitivity (Molberghs *et al.* 2012).

Results

Behavioural and physiological battery (Experiment 1)

This section will split the tasks into two sections. Firstly, 'Physiological tasks', which includes [1] an SCR pain-observation task, and an [2] interceptive awareness task. Secondly, 'Social Cognition tasks', which includes [3] the Control of Imitation task, and [4] the director's task of perspective taking.

Results for physiological tasks

SCR task

81 participants took part in the study but only 68 participants were included in the analysis due to technical issues, outliers and failures to elicit a SCR response in a number of participants. This included: 30 controls, 21 Sensory/Localiser responders, and 18 Affective/General responders.

Subjective reports

Online VAS subjective responses to the images were recoded for each trial and were taken as a measure of image unpleasantness (0=pleasant, 100= unpleasant). Average VAS responses were produced for each condition and were entered into a 3 (Image condition: Neutral images vs affective pain images vs physical pain images) x 3 (Pain group: Controls vs Sensory/Localisers vs Affective/Generals) mixed ANOVA. This analysis showed a significant main effect of Image condition ($F(2,132)=195.353$, $p<0.001$, $r=0.747$) but no main effect of Pain group ($F(2,66)=0.502$, $p=.608$, $r=0.015$) nor an Image condition* Pain group interaction ($F(4,132)=0.141$, $p=0.924$, $r=0.004$) was shown. Post hoc contrasts for the main effect of image condition showed that emotional and

physical pain images showed significant higher unpleasantness scores than neutral images and emotional pain images showed significantly higher scores than Physical pain images. See **Figure 4.4** for means plots.

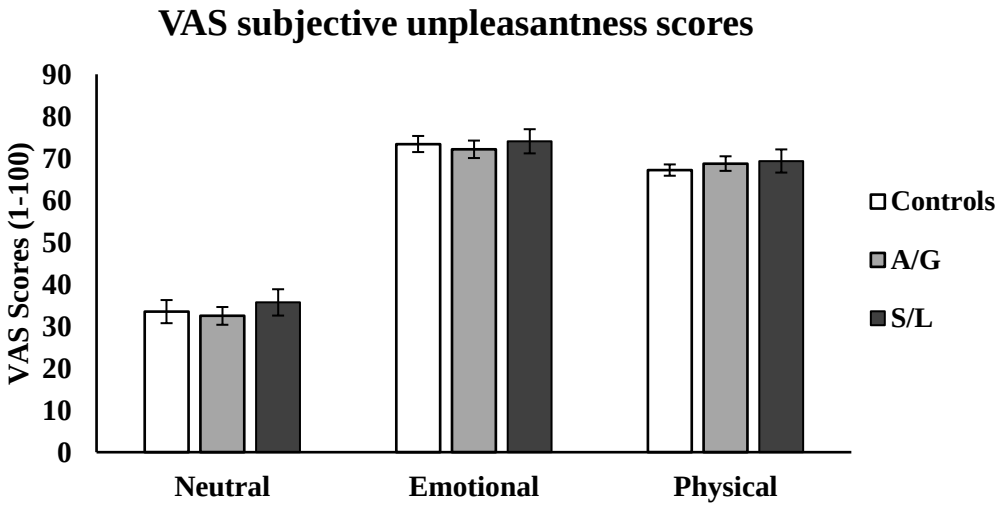


Figure 4.4: VAS subjective ratings for unpleasantness for each of the three image and across each of the three pain responder groups. Scores ranged from 1-100 with higher scores indicating a greater level of unpleasantness experienced in response to the image observations. Error bars represent 1+/- SE from the mean. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

SCR Processing and data modification

Continuous Decomposition Analysis was used to analysis the SCR data which decomposed the SCR data into phasic and continuous tonic activity. The method allowed reliable SCR estimates for short 2s intervals – rather than the longer 10 second intervals used by most SCR studies thereby allowing for the presentation of a higher number of trials. This processing processed raw event related skin conductance responses (measured in nanosiemens). For each participant trials which displayed outlier SCR values were removed from the sample which resulted in 3.4% of the data being removed across all participants. Many of the participants displayed skewed distributions in their SCR values corrected for using a Log10 (SCR+1) transformation. These transformed values were split into the three

conditions ([1] Neutral images, [2] Affective pain images and [3] Physical pain images) and were used for the final analysis. Finally participants were removed from the analysis if observation of the decomposed SCR plots showed that they did not display a typical event related SCR responses of if they displayed a high number of artefacts during the recording sessions.

Log10 SCR responses were entered into a 3 (Image condition) x 3 (Pain group) Mixed ANOVA. This analysis showed a significant main effect of Image condition ($F(2,132)=18.361$, $p<0.001$, $r=0.981$), a non-significant main effect of Pain group ($F(2,66)= 2.525$, $p=0.088$, $r=0.489$) and a significant Condition*Group interaction ($F(4,132)=3.641$, $p=.014$, $r=.751$). Between groups Bonferroni post hoc comparisons showed no significant differences between the groups across all conditions and at each level of the conditions apart from a borderline significant between Controls>Affecftive/General responders when viewing emotional pain images (Controls vs Sensory/Localiser: Average $p=1.00$, Neutral $p=0.74$, Emotional $p=1.00$, Physical $p=1.00$; Controls vs Affective/Generals: Average $p=0.16$, Neutral $p=1.00$, Emotional $p=0.06$, Physical $p=0.12$; Sensory/Localisers vs. Affective/Generals: Average $p=0.15$, Neutral $p=0.46$, Emotional $p=0.16$, Physical $p=0.25$) . However, when comparing across the conditions using Bonferroni corrections for within each group a number of effects were observed. Controls showed the expected levels of performance on the SCR task with emotional pain images ($p=0.001$) and physical pain images ($p=<0.001$) showing significantly higher SCR responses than neutral images as well as increased SCR responses for physical images compared with emotional images ($p=0.010$). Sensory/Localiser responders showed a borderline significant increase in physical pain images compared with neutral images ($p=0.069$) but no significant increase in emotional pain images compared with neutral ($p=0.980$) or physical images compared with emotional images ($p=0.127$). The borderline significant trends this group was somewhat similar to the control group however the effects were reduced by increased SCR responses in the neutral image condition. The most surprising results were displayed in the Affective/General were no significant effects were observed between neutral images and physical ($p<0.911$) or emotional ($p<0.807$) images or between physical and emotional images ($p<0.187$). These results that the two responder groups show reduced pain>no-pain SCR effects and that this is most pronounced in the Affective/General

group who display a flatlining of the SCR response across the pain and no-pain conditions. See **Figure 4.5** for the SCR analysis means plots.

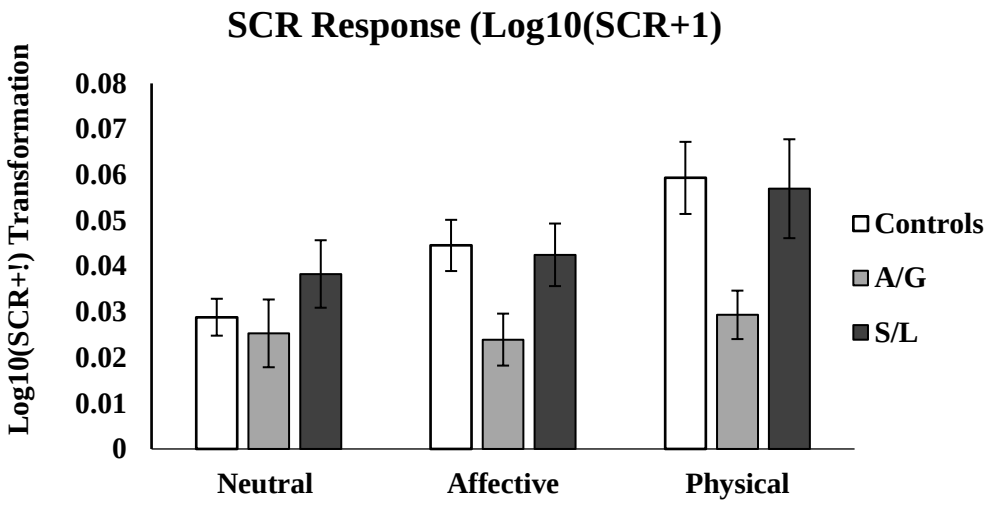


Figure 4.5: Average event related SCR responses for each of the three image conditions and across each of the three responder groups. Raw Skin conductance data was decomposed using CDA procedures. Due to the skewed distribution in the data at the individual level a Log10 (SCR+1) was applied to the data. Higher values indicate a higher GSR response to the stimuli. Error bars represent 1+/- SE from the mean. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

Interceptive awareness

The interceptive awareness task included 81 participants which included 38 Controls, 25 Sensory/Localiser responders and 18 Affective/General responders. Interception was measured using the Mental Tracking Method of heartbeat perception (Schandry, 1981). This task produced two measures; the first Interceptive sensitivity was a measure of accuracy of heartbeat counting and was calculated as: 1/3Σ (1-(|recorded heartbeats – counted heartbeats| /recorded heartbeats). Scores ranged between 0 and 1 and higher scores indicate higher interoceptive sensitivity. The second, Interceptive awareness was calculated as a composite measure of interoceptive awareness and the confidence scores given after each heartbeat counting session.

For each measure a one way between groups ANOVA was used to assess difference between the three pain responder groups. No significant effects were observed between the groups for either the interoceptive sensitivity measure (F(2,79)= 1.35, *p*=0.267) nor in interceptive awareness measure (F(2,79)=1.360, *p*=0.264). See **Figure 4. 6** for means plots for both measures.

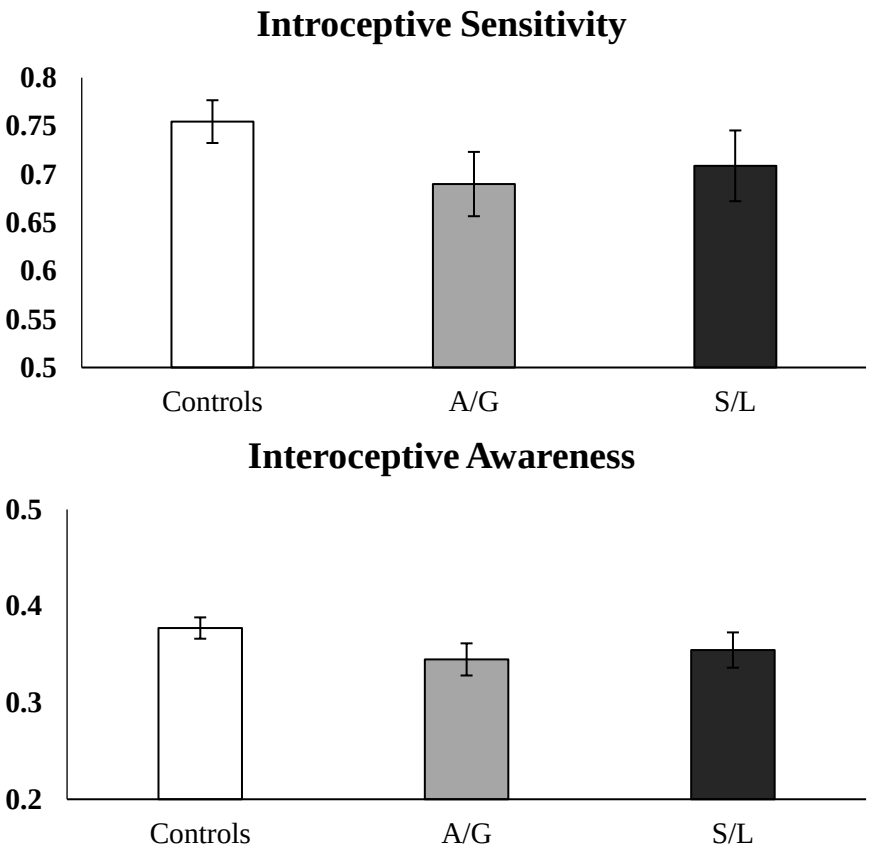


Figure 4.6: Interceptive sensitivity and interceptive awareness scores for each for the three groups. No significant effects were observed between the groups. Error bars represent 1 +/- SE from the mean. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

Results for social cognition tasks

Control of Imitation: Selecting the self-perspective

Of the 54 participants that took part in the Control of Imitation task 6 participants were excluded because they misunderstood the task instructions of because their mean accuracy or mean RT scores exceeded 2 SDs from the mean. This resulted in 17 Controls, 18 Sensory/Localisers pain responders and 13 Affective/General pain responders being included in the main analysis.

Initially accuracy scores during the task were assessed using a 2 (Condition: congruent trials vs incongruent trials) x3 (Pain group: Controls vs Affective/Generals vs Sensory/Localisers) mixed ANOVA. Accuracy was based on whether participants followed the numeric instructions presented on the screen next to the hand (1= raise index finger, 2= raise middle finger). During congruent trials the observed hand raised the same finger as the numeric instruction and during incongruent trials the hand raised the alternate finger from the numeric instruction meaning participants had to control for imitative behaviours during this condition. If participants raised their finger a number of times during the trials, their first response was taken as their accuracy score. Percentage correct values were produced for each condition relative to the total number of trials for each condition. This carried out to do small differences in the number of trials for each participant.

The ANOVA showed a significant main effect of Condition ($F(1,45)=16.777$, $p<0.001$, $r=0.979$) but no main effect of Group ($F(1,45)=1.187$, $p=0.317$, $r=0.243$) nor a significant Group*Condition Interaction ($F(2,45)=0.328$, $p=0.722$, $r=0.098$. The significant main effect of condition was driven by lower accuracy scores for the incongruent condition meaning that all participants struggled to control for imitation however this was not influenced by the pain group they were a member of (see **Figure 4.7** for means plot).

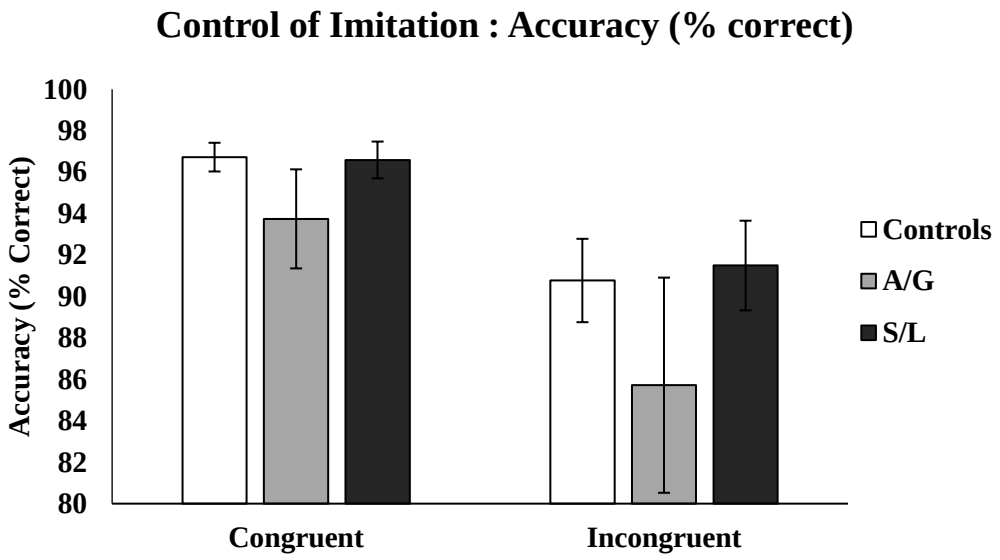


Figure 4.7: Control of Imitation accuracy scores for incongruent and congruent Control of Imitation conditions taken as a percentage correct from the total number of trials for each condition. Error bars represent 1 +/- SE from the mean. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

Reaction times

Reaction times during the Control of Imitation task were also observed. The reaction time measure counted the difference between the onset of the numerical instruction and the time they lifted their finger in response to that instruction. Again, if they raised their finger multiple times during a trial the first response was taken. Rather than assessing both congruent and incongruent RTs, individuals composite RT measure was produced by subtracting the RTs in the congruent trials by those in the congruent trials (Santiesteban *et* 2012), as it was expected that incongruent RTs would be greater than Congruent RTs. A One way between groups ANOVA was carried out on the Incongruent minus Congruent RT , however no significant effect was observed, $F(1,47)=0.520$, $p=0.599$ (See **Figure 4.8** for RT means).

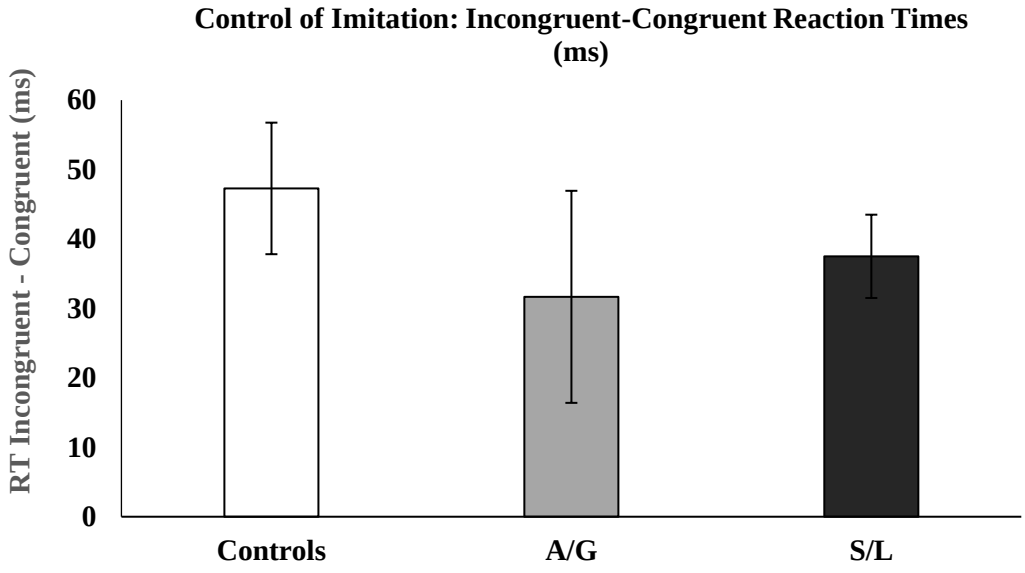


Figure 4.8: Control of Imitation reaction time in milliseconds for each pain responder groups. RTs are expressed as the difference between Incongruent and congruent trials. It was expected that incongruent trials would display higher RTs than congruent trials positive scores would indicate that participants struggled with the trials in which they had to control for imitation relative to those in which they did not. Error bars represent 1 +/- SE from the mean. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

Director's task: Selecting the other person's perspective

The director's test of perspective taking included initially included 81 participants, however 22 participants were excluded because the failed to understand task instructions or because they produced accuracy and reaction times scores which were over two SDs from the mean. This resulted in 24 Controls, 19 Sensory/Localiser responders and 15 Affective/General responders.

Accuracy during the task was measured by how well participants followed the instructions from the director and included two trials types: [1] Controls trials: in which both participants and the director had a good view of the object that the director asked the participant to move. Here participants were correct if they moved the object into the box that the director asked them to. [2] Experimental trials: in

which the director gave a description and instruction to move an object but the most appropriate object to move was occluded from the director's view by the bookcase (i.e. the director may ask to move a 'small candle,' whilst the director could see a candle there was an additional smaller candle that only the participant could see. Here participants were correct if they moved the object which the director could see rather than that which was occluded (i.e. taking the director's perspective). The overall count of correct responses for each condition was used in the analysis as all participants completed the same number of trials (36 was the highest possible score for each condition).

A 2 (Condition: experimental vs controls) x 3 (Pain groups: Controls vs Sensory/Localisers vs Affective/Generals) was carried out on the accuracy score data. This analysis revealed a main effect of Condition ($F(1,56)=41.577$, $p<0.001$, $r= 0.478$) but no main effect of Pain group ($F(2,56)=0.395$, $p=.676$, $r=.111$) nor a significant Condition*Pain Group interaction $F(2,56)=0.103$, $p=0.902$, $r=0.065$. The main effect of condition was driven by lower accuracy scores in the experimental condition. This means that participants did perform worse when they had to take the director's perceptive however this was not affect by their pain group membership. See **Figure 4.9** for accuracy means plots.

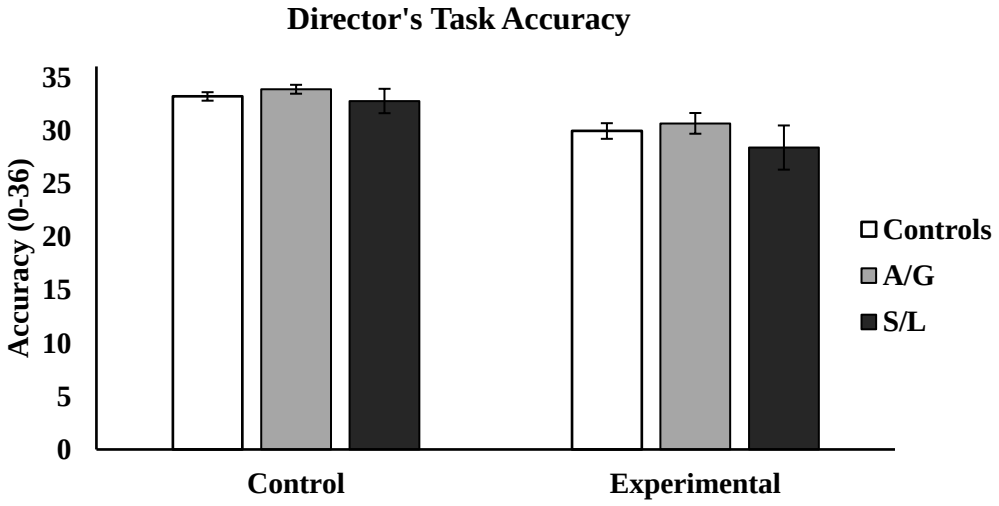


Figure 4.9: Accuracy scores for control and experimental conditions across each of the three pain groups. Accuracy values are expressed as a raw count of the correct responses out of a maximum for

of 36. Error-Bars represent 1+/- SE from Mean. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

Reaction times

Reaction time scores were taken during the task. These RTs were based on the amount of time that participants took to click on the square that they wanted to move the object to relative to the offset of the director's instruction. For each participant's trial RTs which lay 2 SD away from the individual's mean were excluded when summarising their data. Due to the large amount of inter-subject variability and the expectation that RTs for the experimental condition would be lower than the control condition RTs were expressed as percentage of change in the control condition relative to the experimental condition. Higher percentages would indicate that an individual's RTs during the experimental trials were smaller than the control trials indicating that they struggled more with the condition. The percentage change RT score was entered into a one way between groups ANOVA to assess differences between the groups and showed there to be no significant effects, ($F(1,56)=1.299$, p=-.281). See **Figure 4.10** for means.

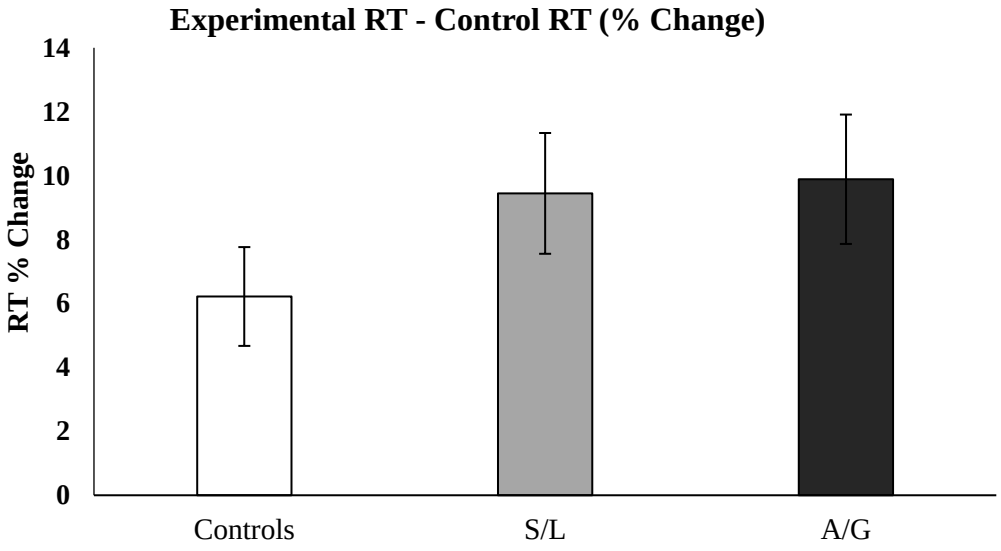


Figure 4.10: Director's task reaction time scores for each of the three groups. Because of the high amount of inter-subject variability in the raw values RTs were expressed as % of change from the control condition to the experiment condition. This direction of change was chosen as higher RTs were expected in the experimental condition. Therefore higher scores indicate that participants struggled more with the experimental trials relative to controls trials. Error bars represent 1 +/- SE from the mean. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

Results: VPQ and dispositional questionnaires (Experiment 2)

141 participants took part in an online questionnaire in which they completed the VPQ and were subsequently group into one of the three pain groups as well as the IRI empathy questionnaire (Davies 1983) and the Pain sensitivity questionnaire. The VPQ results showed some consistency in terms of prevalence with the results of **Article I**. Overall the two pain responder groups made up 33.4% of the sample (the remaining 66.7% of the sample were controls) which is relatively close to the 30% prevalence rate highlighted in **Article I.** However in **Article I** the Sensory/Localiser responders had an approximately twofold increase prevalence rate relative to Affective/Generals. In the MTurk data this trend is reverse with Affective/Generals showing a prevalence rate of 20.6% relative to the 12.8% for Sensory/Localisers.

The IRI was broken up into its four subscales which included: [1] Fantasy scale (FS), [2] Empathic concern, [3] Perspective taking and [4] Personal distress. All measures (including the PSQ) were measured using a 10 point Likert scale. Higher scores on the IRI indicated higher subscale empathy levels and high scores on the PSQ indicated increased perceived pain sensitivity.

Five between groups one way ANOVAs were carried out on each of the five measures to assess between group differences. The five ANOVAs were Bonferroni corrected to account for multiple comparisons. A borderline significant effect was observed in the Fantasy scale ($F(2,140)=2.651$,

p=0.074, r=0.519) however Tukey post hoc tests showed no significant effects. A significant effect was also observed in the Empathic concern scale (F(2,140)=4.873, p=0.009, r=0.762) and post hoc tests showed that Sensory/Localiser responders scored significantly higher than controls however no other effects were observed. Additionally, a significant effect was observed in the Perspective taking subscale (F(2,140)=8.752, p<0.001, r=0.968) with post hoc tests showing that Sensory/Localiser responders score significantly higher than controls and that Affective/General responders also scored significantly higher than controls. None of the other variables showed significant effects (IRI Personal distress: F(2,140)=0.941, p=0.393, r=0.210; PSQ: F(2,140)=1.241, p=292; r=0.267). See **Figure 4.11** for means plots for the significant IRI subscales.

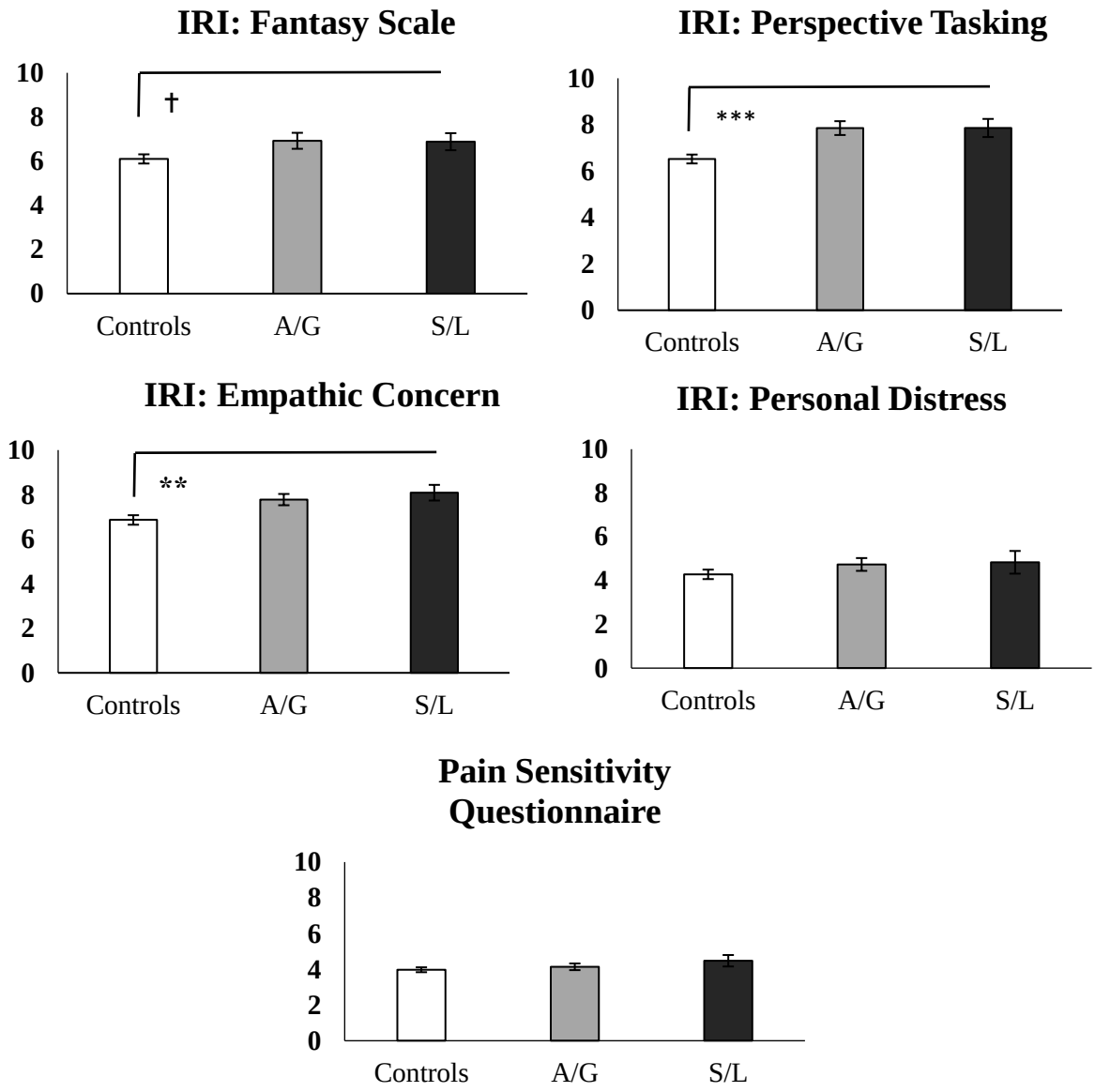


Figure 4.11: Personality measure means for variables which showed significant effects between the pain responder groups and include 3 subscales from the interpersonal reactivity index. Values ranged between 1-10, on a Likert scale, with higher scores representing higher empathy levels within the subscale. Error bars show 1+/- SE from the mean. † = borderline significance * <0.05, **<0.01, ***<0.001. S/L = Sensory/Localiser responders; A/G = Affective/General responders.

Discussion

This study sought to investigate whether individuals who reported common mirror-pain experiences showed modulated performance on a series of behavioural and physiological tasks when compared with controls. In experiment 1, two mirror-pain groups, Sensory/Localisers and Affective/Generals, and a group of controls took part in two social cognition behavioural tasks, including the Control of Imitation task and the director's task of perspective taking task; and two physiological tasks, including the SCR task and the heartbeat counting task of interoceptive awareness (IA). In experiment 2 a separate group of participants carried out the VPQ and took part in two dispositional questionnaires relating to empathy and perceived sensitivity to physical pain.

Our first hypothesis predicted increase SCR responses for the mirror-pain responder groups and the second hypothesis predicted the two mirror-pain responder groups would differ based on the type of pain image displayed. This prediction was not reflected in data, instead the SCR task showed that the control group displayed an expected pattern of results of increased autonomic arousal in the emotional and physical pain image conditions relative to the neutral image condition and all groups showed the expected VAS unpleasantness scores on response to the pain observations. However both responder groups did not show the same pattern of responses. Instead they displayed reduced pain > no-pain SCR meaning they did not produce an increased SCR response during the pain images compared with neutral images. For the Sensory/Localiser group there was a trend towards significance for the normative pattern which physical pain images resulting in increased SCR responses compared with neutral images however there was no difference between neutral images and Emotional image images. This was likely due to an increased SCR response in the neutral image condition. However, the Affective/General group displayed more pronounced reductions in the pain>no-pain SCR effects to the extent that this group displayed a flat lining of SCR responses with no changes across the three conditions, remaining at the level of neutral image observations in controls throughout.

This SCR result was somewhat surprising and counterintuitive. One possible explanation of the flat lining observed in the Affective/General group may relate SCR poor sensitivity in high anxiety individuals whilst they carry out stressful or anxiety inducing tasks. Individuals with high trait anxiety

have been shown to produce similar SCR flattening to that observed in the current study when presented with anxiogenic stimuli (anxiety inducing stimuli) (Navateur, Buisine & Gruzeller, 2005). These findings also extended to other physiological autonomic nervous system measures such as cardiovascular activation (Jezova, Makatsori, Duncko, Moncek & Jukabek, 2004). These studies suggest that high trait anxiety is associated with a hindered ability to regulate autonomic responses to anxiety inducing stimuli. Similar findings have been observed in conditions which are linked lower emotional regulation abilities such as Autism Spectrum Disorder (ASD) (Panju, Brian, Dupuis, Anagnoustou, & Kushki, 2015), alexythemia (Fanz, Schaefer & Scheider, 2003), depression (Schwerdtfeger & Rosenkaimer 2011), and attention deficit disorder (Herpertz, Wenning, Mueller, Qunaibi, Sass & Herpertz-Dahlmann, 2001). Alternatively, SCR flat lining is explained via a protective/defensive mechanism meant to reduce the disruption due to high levels of activation (Ray *et al.* 1977; Harley, 1973).

It may be the case that Affective/General responders possess high pain related anxiety which produces this flat-lining of SCR responses. During Giummarra's *et al.* (2015) development of the Empathy for Pain Scale (EPS) the researchers noted that mirror-pain experiences were associated with this heightened anxiety when witnessing pain however they were unable explain how this related to key empathy and mirror-pain theories. Our Vicarious pain Questionnaire (VPQ) may have reflected this high pain related anxiety by identifying this group of Affective/General responders (Grice-Jackson *et al.*2017, **Article I**). Their use of affective pain descriptors such as 'nauseating' and 'fearful' may reflect this anxiety. In turn, this pain related anxiety may be producing this SCR flat-lining that has been linked to high anxiety individuals and those who display poor emotional regulation. Currently this is conjecture, and the effect requires further research. Initially it will be important to investigate whether this group does display increased trait or pain specific state anxiety through the use of generalised anxiety measures, such as the GAD7 (Spitzer, Kroenke, Williams & Lowe 2006), and behavioural measures of pain specific anxiety. Furthermore future physiological tasks should manipulate the levels of intensity in pain related anxiogenic stimuli to assess whether SCR flat-lining is modulated in line with the levels of anxiety in pain images. This SCR result is particularly

important as it is the first effect which has been uniquely observed amongst the Affective/General group. Previously, we have observed a unique pattern of mu rhythm EEG responses in the Sensory/Localiser group and common VBM effects across the two responder groups (Grice-Jackson *et al.*2017).

The anxiety related explanation described for the Affective/General may also explain the reduced pain>no-pain SCR effects observed in the Sensory/Localiser group however observations of the results seem to indicate that this lack of effects was due increased SCR responses in the neutral condition. Their responses to the Emotional and Physical pain images were very similar to those observed in the control group. The increased responses observed in the Neutral condition may have been related to a pain observation anticipatory response which has been observed during the anticipation of physical pain (Bradley, Silikowski & Lang, 2008). At this point it is not clear whether the flatling is a result that is completely unique to the Affective/general group or whether both responders display this trend with the Affective/General group displaying a more pronounced flat lining.

The third hypothesis predicted increased IA across the two pain responder groups. However, our results showed no between group differences between mirror pain responder groups and controls. This may be because trait-based IA abilities are related to internal bodily representations rather than interpersonal factors, which are important for mirror-pain. Studies have shown that when participants are asked to actively engage in periods of IA they perform higher on empathy task (Grynberg and Pollatos, 2015); however these findings may not be related to dispositional factors. Indeed, Ainsley *et al.* (2015) failed to show any association between participant's IA and interpersonal factors including empathy and perspective taking. As mirror-pain is thought to be related to these interpersonal factors it may follow that mirror pain is not closely linked to dispositional IA abilities, which represents internal bodily awareness. An alternate explanation for the null results is the type of task we used. The heart beat tracking task is considered to be a less objective measure of IA than measures which relate to the tracking of external stimuli in relation to heartbeat monitoring, i.e. heartbeat discrimination

tasks (Brener & Kluvitse 1988). Recent comparison of the two tasks shows them to be dissociable and distinct from one another (Garfinkel, Minati, Gray, Seth, Dolan & Critchley 2014). It may be the case that our analysis relies too heavily on a single task and should incorporate a broader range of IA tasks, such as the heartbeat tracking task, before discounting its link to mirror-pain.

Past research has suggested that self/other distinction are important for mirror-pain and vicarious sensory experiences (Ward & Banissy 2013, Fitzgibbon *et al.* 2012) and that perspective taking is central to these abilities (Santiesteban *et al.* 2013). Hypothesis four therefore predicted between group differences in the Control of Imitation and director's task, however, across both tasks no between groups differences were observed; our mirror-pain sample showed no differences in perspective taking or Control of Imitation compared with controls.

The Control of Imitation task is a well validated task for assessing spatial imitation of other people's movements (Brass *et al.* 2005, Spengler *et al.* 2009) with links to the rTPJ (Santiesteban *et al* 2013). Given the links between mirror-pain and the self/other discrimination and the rTPJ, highlighted by previous work (Fitzgibbon *et al.* 2012) and our own VBM study (Grice-Jackson *et al.* 2017), we had expected to find differences in performance on the Control of Imitation task. As the Control of Imitation task mainly focuses on motor representations it may be the case that the Control of Imitation task does not access the sensory representations relevant to vicarious sensory experiences. Motor simulation is known to be processed in different regions than somatosensory simulation (Keysers *et al.* 2004). There is also some debate as to whether the rTPJ plays a role in task specific or domain general self/other distinctions, or whether it reflects general attentional processing (Sowden & Catmur 2013; Krall *et al* 2014). If the rTPJ plays a task specific role in attentional shifting between self and other it may be the case that rTPJ function is only relevant to mirror-pain responders when participants are involved directing in sensory empathy. Our VBM study indicated that mirror-pain between group effects lie in the anterior portion which differ from the more posterior coordinates usually used in Control of Imitation studies (Brass *et al.* 2005; Splenger *et al.* 2009, Sowden & Catmur 2013). It may be the case that the observed rTPJ effects in past Control of Imitation studies

relate to this functional dissociable region relative to the one important for mirror-pain. Data collection for the Control of Imitation experiment in this study had a smaller sample size than the other three experiments which may have resulted in an underpowered analysis.

With regards to the director's task, given that the ability to distinguish between one's own and another another's perspective is key for successful performance of the director's task (Santiesteban *et al.*2013) it was surprising that no between group differences where observed in this study. This may because the director's task is a PT measure more well suited to cognitive perspective taking (Decety & Cowell, 2014) and may also be solved by theory of mind abilities (Santiesteban *et al.* 2013) rather than the embodied self/other distinctions that is important for mirror pain. Additionally, the task director's task was a relatively repetitive one in which one could easily attain high scores once they had properly theorised the manipulation, and those did not do so would struggle throughout. Therefore the measure may not be sensitive to distinguishing between those that understood the manipulation and those who actually possess increased perspective taking abilities.

Our final hypothesis predicted increased empathy scores for the mirror-pain responder groups with the aim of addressing the debate raised by Baron-Cohen *et al* (2016) who failed to display links between empathy and mirror-pain synesthetes. Experiment 2 recruited a large online sample who took part in the VPQ online questionnaire which split participants into the three pain responder groups (using the two step cluster analysis in **Article I**). The prevalence of mirror-pain remained broadly similar to that observed in **Article I**, ~30%, however the ratio of Sensory/Localisers and Affective/Generals has switched in this sample with a 2:1 ratio of affective generals to sensory localisers observed in this case. Whilst it is encouraging that the VPQ highlights comparative similar proportion of mirror-pain responders despite the differences in samples and recruitment methods it is clear that more still needs to be learned about the distribution of characteristics within the groups. The results of the dispositional measures analysis broadly met our expectations with significantly increased scores across two IRI scores related to self/other representations and vicarious experiences, perspective taking and empathic concern. These results support previous findings of increased empathy scores

observed in mirror-sensory synesthetes (Banissy *et al.* 2009) whilst countering the results displayed in Baron-Cohen *et al* (2016). This indicates either that mirror-pain differs from mirror-touch synaesthesia with the former displaying closer ties with empathy than the latter; or, that that there is increased support for the link between mirror-sensory synaesthesia more generally. No hypothesised differences were observed in the PSQ as was expected, it may be the case that mirror-pain responder's experiences are less related to general pain sensitivity and more so to specific pain observations related to their own personal experiences as indicated by Derbyshire *et al.* (2013).

Overall, the current study has had limited success in profiling the characteristics of mirror-pain responders. For most of the hypotheses no significant effects or trends in the data were observed. Despite this, the study has revealed a unique pattern of SCR responses for the Affective/General group. Our previous assessments of this group have shown little dissociation them and Sensory/Localisers, with EEG for the Affective/General responders similar to controls and VBM data similar to the Sensory/Localiser responders. Here, we have observed a flat lining of SCR data across both emotional and physical pain image observations and neutral images. This flat lining could be related to pain-specific anxiety of general anxiety levels which results in a flat lining of the autonomic arousal system in response to pain image observations. Finally, we displayed increased scores for the Perspective taking and Empathic concern on the IRI subscales for both mirror-pain responders relative to controls.

Article IV: Investigating the causal link between the right temporo-parietal junction and somatosensory hyperactivity during pain observations

Abstract

Prominent theories which seek to explain the mechanisms behind mirror-pain experiences suggest that these conscious vicarious experiences arise out of an interaction between hyperactive somatosensory process and modulated processing in self-other regions. Additionally, a number of studies assessing vicarious pain processing in typical individuals have highlighted self-other processing as a driver of the hyperactive empathic simulation response. The right temporo-parietal junction (rTPJ) has been identified as a key candidate for these processes and has previously been highlighted in our own structural and connectivity analyses of MRI data in mirror-pain responders. However, it is not known how this region and its self-other capabilities interact with activity in the somatosensory cortices (SI/SII). In this study we attempt to investigate the potential for a causal link between the two regions by stimulating the rTPJ with theta burst transcranial magnetic stimulation (TBS) and observing the Electroencephalogram (EEG) responses to observations of pain. Typical individuals, not mirror-pain responders, were chosen for this sample as it was expected that stimulation of the rTPJ would produce the effects of visual pain stimuli on somatosensory evoked potentials that has been displayed in previous studies assessing EEG responses in mirror-pain responders. The results showed that the EEG responses were not modulated by the either the observation of pain, nor by the stimulation of the rTPJ. The lack of modulation as a result of observing pain was of concern as previous EEG studies have observed this effect; and the lack of somatosensory modulation calls into question the potential for a unidirectional mechanism of causality in mirror-pain theories. This suggests that the mechanisms underlying mirror-pain may be more complex than the simple afferent modulation from the rTPJ to SI/SII. Alternatively, self-other processing may rely on other regions than just the rTPJ; our previous fMRI connectivity analysis indicates that a self-other network, which includes the rTPJ and ventral prefrontal regions, may drive

mirror-pain. Future stimulation studies perhaps should consider network based-approach rather than focusing on the influence of a singular region as this will provide a more holistic view of the influence of self-other processing on mirror-pain activity.

Introduction

Stimulation models of empathy suggest that the observed motor, sensory, or emotional states of others activate corresponding representations and neural processes in an individual observing that state (Preston & de Waal, 2002; Gallese 2003; Decety & Jackson, 2004). Indeed, the discovery of so called 'mirror neurons,' which show overlapping during the observation and execution of states, provided evidence for empathy researchers that the processing of observed states relies on implicit simulation (Rizzolatti, Fogassi & Gallese. 2001; Carr *et al.* 2003; Wicker *et al.* 2004). Initially, simulation research has largely focused of action and emotion mirroring; however, more recently simulation approaches have been applied to research into pain and touch (Jackson & Decety 2006; Keysers *et al.* 2004). In the present research, we use TMS to try to induce an increase in the level of empathy for pain as measured through modulations of an electrophysiological measure (somatosensory-evoked potentials).

The standard approach in the neuroscience literature on empathy for pain has been to present participants with images of pain and to record (e.g. using fMRI) the level of activation in brain regions that are also responsive to physical pain. In doing so fMRI research has consistently shown simulation in affective-motivation pain processing regions (Lamm *et al.* 2011) with the anterior-cingulate cortex and anterior insula receiving particular attention (Jackson *et al.* 2006; Singer *et al.* 2004). However, sensory-discriminative regions of the pain matrix, which is made up of the primary and secondary somatosensory cortex, shows less consistency in their activation across the majority of fMRI research (Lamm *et al.*2011). Transcranial magnetic stimulation (TMS) has been used to elicit motor evoked potentials (MEPs) and has shown significant modulation of normal corticospinal responses during the observation of others in pain (Avenanti *et al.* 2005). This MEP modulation has

shown muscle specificity which matches the observed pain (Avenanti *et al.* 2008) and is influenced by trait and state empathy levels of the observer (Avenanti *et al.* 2008) as well as implicit biases that they hold, i.e. racial biases (Avenanti *et al.* 2010).

EEG has also been used to show modulation of somatosensory evoked potentials (SEPs) during the observation of pain, which is indicative of somatosensory modulation (Bufalari *et al.* 2007; Martínez-Jauand *et al.* 2012; Meng, Jackson, Chen, Hu, Yang, Su & Huang, 2013; Valeriani *et al.* 2008). Additionally, these studies have shown that early SEP components, originated in the primary somatosensory cortices, display this simulation based modulation. In these studies tactic stimulation is applied to the hand or vagal nerve of the participants and the event related potentials are observed when participants observe the other experiencing pain or touch. Laser evoked potentials have also been used to assess later stage pain specific ERP components using similar methods (Valeriani *et al.* 2008; Meng *et al.* 2013). These studies show that observed pain effects the cortical processing of physical touch/pain, but the key mechanism and brain region responsible for the modulation is not revealed by this research.

Self-other processing is thought to be a key component in mechanisms of vicarious pain which plays a mediating effect on simulation through excitatory or inhibitory processes. Decety & Jackson (2006) suggest that self-other control and awareness is required in empathy for pain to assign representations of the self and other to incoming visual pain stimuli in order to facilitate an appropriate response in the observer. De Vignemont (2013) argues that the sharing of bodily representations which exists in vicarious pain cannot be achieved without a 'whose' system for assign ownership of observed pain to the self or another. These processes have been shown to influence the degree of affective pain matrix simulation depending on how close/similar the victim of observed pain is to the observer, or, how much like the self they are (Cheng *et al.* 2010). Additionally, in the case the person is less like the other, such as when they are of a different race (Avenanti *et al.* 2010), or when a context demands that the observer thinks of the other less like themselves, such as when a doctor treats a patient (Decety, Yang & Cheng, 2010), these self-other processes are thought to inhibit simulation responses.

One of the brain's key processing centres for self-other representations in the right temporo-parietal junction (rTPJ) has been of particular interest for theories which explain empathy for pain and mirror-pain (Decety & Jackson, 2004; Jackson & Decety 2006). The region has been associated with a number of social cognitive and interpersonal functions which are associated with vicarious pain, including: Mentalizing (Frith & Frith 2004), Bodily perspective taking (Arzy, Thut, Mohr, Michel & Blanke, 2006), Moral beliefs (Young, Camprodon, Hauser, Pascual-Leone & Saxe 2010) and Theory of Mind (Decety & Lamm 2007). fMRI studies show that the region is activated when asking participants to imagine representations of the self and other people (Decety *et al.* 2007) and is more active when thinking about others than the self (Ruby & Decety, 2004). When the region is stimulated with excitatory stimulation (tDCS) participants showed increased performance on self-other tasks (Santiesteban, *et al.* 2013) and the opposite has been found when it receives inhibitory TMS stimulation (Catmur & Sowden, 2013). Additionally, TMS rTPJ disruption has been associated with out of body experiences/illusions which are characterised by a loss of bodily self-representations (Blanke, Ortigue, Landis & Seeck, 2002; Blanke *et al.* 2005).

Research into mirror-pain responders and mirror-sensory synesthetes has identified the region as a component of the mechanism which results in conscious experiences of mirror pain. Behavioural assessments of this group have shown diminished self/other control in perspective taking takes and increased ownership in the Rubber Hand Illusion, both of which rely on self/other control (Derbyshire *et al.* 2013). It is suggested that the condition may be characterised by abnormal plasticity of self/representations mediated by the rTPJ, or, self-other merging (Bufalari, Porciello & Aglioti, 2015). Our own neuroimaging studies have repeatedly highlighted the region with decrease grey-matter volume observed in the region for mirror-pain groups (Grice-Jackson, Critchley, Banissy and Ward, *in press*, **Article I**) as well as a connectivity network between pain matrix regions and the rTPJ (Grice-Jackson, Critchley, Banissy & Ward, *in prep*, **Article II**). Key theories of mirror pain suggest that the experience arises out of hyperactivity in somatosensory simulation systems, known as threshold theory, and out of modulated self-other processing in the rTPJ (Ward & Banissy, 2015;

Fitzgibbon *et al.* 2012, Banissy *et al.* 2009). It is thought that these groups display diminished self-other capabilities which results in a merging of self-and other representations which influence the somatosensory simulation responses and contributes to conscious mirror-pain experiences.

Despite theories of both vicarious pain and mirror-pain predicting links between the self-other processing in the rTPJ and responses to observed pain, little is known about the mechanisms that underlie this link. fMRI studies into vicarious pain have displayed its activation during pain observations (Decety & Jackson 2006) and connectivity analysis have displayed a mirror-pain network with the rTPJ (**Article II**) however these studies do not describe a causal link and do not explain how the region affects pain processing. The mirror-pain theories essentially state that the experiences arise out of exaggerated normative processes, hyperactivity in simulation systems and that this arise out of diminished self-other processing (Ward and Banissy 2015; Fitzgibbon *et al.* 2012).

Based on this explanation, modulating the processing of self-other regions (rTPJ), should affect the somatosensory simulation response. Additionally, based on Decety & Jackson's (2004) model of empathy, modulating self-other processes in the rTPJ is expected to alter neural processes of empathy for pain in neurotypical individuals. In this study we will attempt to address these points by assessing the casual link between the rTPJ and somatosensory simulation during observations of pain. This will be achieved by using theta burst TMS stimulation to inhibit activity in the rTPJ; and by measuring the resulting impact on the somatosensory cortices using EEG to assess somatosensory evoked potentials (SEPs) whilst participants view pain. The study will be run a neurotypical sample as past studies have displayed modulated SEPs when viewing pain in these groups and because it is expected that their rTPJ self-other process will already be operating at a typical level.

In effect we expect that the rTPJ stimulation will produce the diminished/inhibited activity which is predicted in mirror-pain responders meaning that the mirror-pain neural mechanisms may be

replicated in our neurotypical sample. A number of specific hypotheses have been generated for this study:

1. *Regardless of rTPJ stimulation, the SEP components will show distinguishable modulation when participants observe pain compared with a static hand and no visual stimuli.*
2. *Stimulation of the rTPJ will result in modulated SEPs during the pain observation trials but not in a static hand or control trial. This modulation will reflect increased vicarious activation of the sensorimotor system when observing pain and will show a causal link between the system and the rTPJ.*

Methods

Participants

Fifteen healthy participants (8 males, 7 females) aged between 19 and 26 years (mean=26.6, S.E= 1.37) volunteered to take part in the study. All participants self-reported being right handed, had normal or corrected vision and were naïve to the purpose of the experience. Furthermore participants had previously taken part in the Vicarious Pain Questionnaire (VPQ), an online questionnaire assessing reports and characteristics of conscious vicarious pain experiences (*see* Grice-Jackson *et al.* 2017, **Article I** *VPQ*). All participants were classified as non-responders, meaning that they did not commonly experiences conscious vicarious pain. Participants provided written and informed consent in accordance with paid £10 p/ hour for their participation in the study. The study's procedures were reviewed and approved by the University of Sussex's (C-REC) Ethics Committee.

Apparatus

EEG data was recorded on ANT neuro's 'Advanced Source analysis 4.7.11' using an ANT neuro waveguard™ original 64 electrode 10-10 system cap and amplifier and 4 external electrodes used for eye blink detection. Theta-burst TMS was carried out using a Magstim™ Rapid^2 magnetic stimulator unit and a 70mm Magstim alpha flat coil and neuro-navigation was carried out using an ANI Polaris™ 3D optical tracking system and Visor™ 2.1 tracking software. Structural MRI images (used for neuro-navigation) were acquired form a Siemens Avanto (Clinical Imaging Sciences Centre, University of Sussex) 1.5 T MR scanner using a T1-weighted MPRAGE sequence (TR = 2730ms, TE = 3.57ms, FOV = 240 x 256 x 192 mm, voxel size=1x1x1 mm). SEP touch stimulations were delivered using a Digitimer concurrent electrical stimulator (DS7A) which were attached to the participants are with a digitimer D185-HB4 electrode cable and a Velcro strap. Stimuli was presented using Matlab 2014a with Psychtoolbox 3.0 on a 19" Dell monitor and EEG data was analysed using Matlab 2014a with EEGLAB™ and ERPLAB™ toolboxes. Two Dell Precisions T3500 PCs were used for EEG recording and stimuli presentation and a HP PC was used for neuro-navigation.

Visual Stimuli

Participants were presented with 6s video clips depicting pain or no pain experiences to another person's hand. Videos were presented in the centre of a dark screen in a 600x400 rectangle. The videos were taken from previous SEP studies on empathic pain and touch processing (Martinez-Juauad, *et al.* 2012; Bufalari *et al.* 2007) and included three condition: [1] a 'baseline' condition depicting a static 3 static hashtags in the centre of the screen, [2] a 'no-pain' condition depicting a palm facing down, non-moving hand in the centre of the screen and [3] 'pain' condition in which a palm facing down hand was being injected with a needle. To reduce habituation, there were three points of syringe contact on the hand and three syringe colours which varied randomly across trials. In all pain trials the person holding the needle was not shown in the video and the hand was oriented in a way that would be unnatural for the participants own hand (from the side of the image) to reduce visual identification of the observed hand with their own bodily image. For all pain videos the point of contact for the needle began within 1s of video onset. See **Figure 5.2** for examples of the stimuli.

SEP stimulation

SEPs were chosen as a measure of somatosensory simulation a number of studies have shown it is a reliable measure of neural simulation for pain and touch (Martinez-Juaund *et al.* 2012; Bufalari *et al.* 2007). Additionally, the resulting event related potentials (ERPs) are a highly temporally specific and sensitive measure which allows for the identification of well-established somatosensory components. These components are based on the scalp location and latency from stimuli onset and can be used to make inferences about the regions and processes underlying the potentials. In this case particular attention was placed on the early components known as P45 and N80 as they have been highlighted in previous SEP studies for pain and touch (Martinez-Juaund *et al.* 2012; Bufalari *et al.* 2007; Meng *et al.* 2013).

Non-painful electrical stimulations, which delivered tactile sensations, were delivered to the participant's right hands simultaneously with the observations of the 6 second videos. SEP procedures were based on previous studies which used stimulations to illicit somatosensory components (Bufalari *et al.* 2007; Martinez Juaund *et al.* 2012). Stimulations were applied to the medial nerve and was attached using a Velcro strap which was tightened to prevent movement of the electrode. Prior to the experiment a comfortable level of stimulation was determined by testing and increasing the mA level of the stimulation slowly until the tactile sensations were clearly distinct and discernible but were comfortable and non-painful. All participants' electrical stimulations fell between 40 and 70 mA. During the experiment electrical stimulations were delivered in trains of 5 pulses (100ms duration p/ pulse) which began 1s after the video's onset with a gap of 1s between the onsets of each stimulation. Overall participants received 1,200 electric stimulation p/ session split equally across the 3 conditions.

Theta Burst TMS

Theta-burst stimulation (TBS) will be used to inhibit the activity of the rTPJ and in a control site, for comparison. TBS is an effective method of inhibiting localised cortical activity by using high frequency bursts of TMS over a relatively short period of time with effects lasting for longer periods of time than traditional single pulse TMS. It is estimated that 40 seconds of TBShas effects lasting for approximately 30 minutes after simulation (Huang, Edwards, Rounis, Bhatia, Rothwell 2005). Critically, this method of simulation allows for an EEG cap to be fitted prior to stimulation so the SEP measures can be taken immediately after stimulation. The stimulation site for this study was based on the centre point between anterior and posterior rTPJ deriving from a Krall *et al.* (2015) identification of rTPJ anatomy and was located with structural MRI guided neuro-navigation. A comparisons/ control site (Pz: based on EEG 10-10 system) was also selected to assess the modulation effects of rTPJ stimulation.

A total of 600 pulses within 40 s were administered, involving three pulses at 50 Hz repeated every 200 ms (5 Hz; Huang *et al.* 2005). The stimulation intensity was set to 40% of maximum stimulator output (MSO). A fixed stimulation protocol was chosen as individual resting motor thresholds are not representative of parietal thresholds (Chang, Liu, Chen, Liu & Duyn2013; Stewart, Walsh & Rothwell 2001). Furthermore, a fixed intensity ensured a more consistent spatial spread of TMS effects in subjects' brains not influenced by differences in individual motor thresholds. It is estimated that this stimulation would produce effects for between 30 and 40 minutes.

Two stimulation sites were used across the two sessions and include an rTPJ stimulation site and a control site. The rTPJ stimulation was at x=57, y=-52, z=14 MNI location which was based on a previous article meta-analysis assessing the role and function of the rTPJ (Krall *et al.* 2014). For each participant the rTPJ MNI site was corrected for the diffidence between the normalised scan and the participant’s scan to produce a personal unwarped rTPJ site. The control site was the Pz the electrode placement system on the EEG cap. This is a midline site over the posterior parietal cortex was chosen because of the lack of proximate regions with functions related to rTPJ functions or somatosensory processes and because the site is with 5cm of the rTPJ experimental site.

Procedure

The study took place over 2 counterbalanced experimental sessions (split by at least 7 days) which was based on the stimulation site used (rTPJ vs Control site). The procedure for each session was identical apart from the stimulation site. During each session participants were sat in a faraday-cage lab and the EEG cap and external electrodes were applied with electrode gel until electrical impedance was reduced to 5kΩ. The electrical stimulator was then attached to the arm and the appropriate level of stimulation was determined. For the rTPJ stimulation site neuro-navigation was then carried out using structural MRI scans and a 3D camera to determine the location of the rTPJ. The control site was localised using the previously applied EEG cap however the neuro-navigation was still carried out so that suspicion as to the experimental site was not raised to the participant. Finally the TMS coil was placed above the stimulation site; for all participant the coil was placed within 1mm of the target site and angle so that the centre point of the coil maintained contact with the scalp with only the EEG cap in between. The position of the coil was maintain by using an adjustable stand and by placing participants in a chin rest. The theta burst stimulation was then applied and a 5 minute gap was left between the end of the TMS stimulation and the beginning of the experiment.

During the experimental session participants were displayed with the 6s video and baseline trials which were split by a 1s intertribal interval which displayed a fixation cross. During each trial the train of 5 electrical was delivered 1s after the onset of the trial. Trials were organised into 8 blocks, each containing 10 pseudo-randomized mixed condition trials. This resulted in 240 video trials (80 p/ condition) and 1,200 electrical stimulations (400 p/condition). Overall the experimental session lasted for approximated 30mins. See **Figure 5.1a** for trial and **5.1b** block setup for each experimental sessions. Once the experiment was completed the equipment was removed and participants were given the opportunity to wash their hair and after the last session were fully debriefed and paid for their participation.

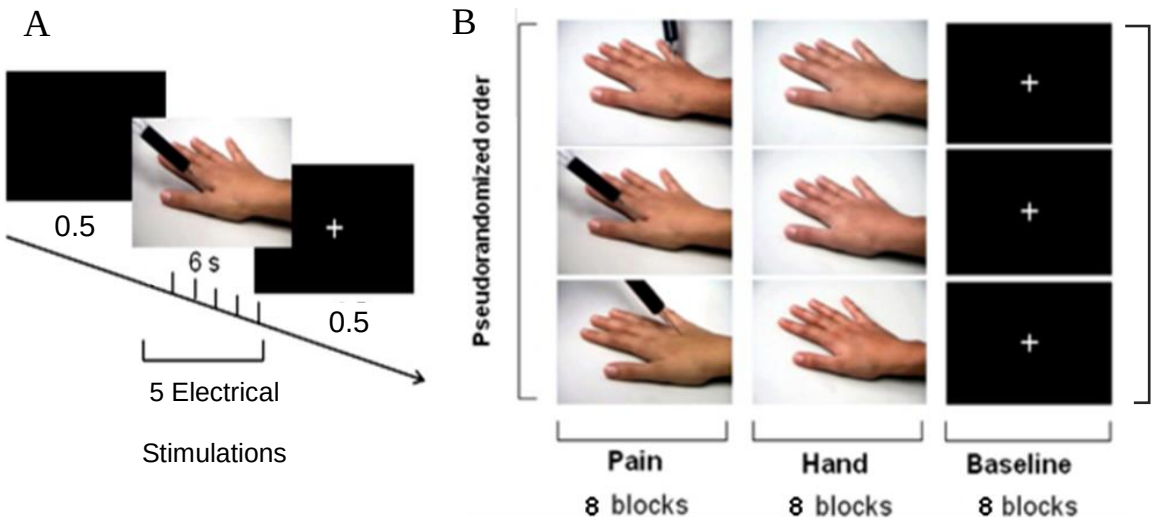


Figure 5.1: [A] Trial setup for each video presented to participants, [B} block setup for experimental sessions. Static images show examples of the stimuli used for each condition. Participants carried our two experimental sessions for the study which differed only in the location of the theta burst TMS stimulation.

EEG Processing and Analysis

Once collected EEG was resampled to 500 Hz and referenced to the mastoid ear electrodes. A high filer of 30 Hz and low pass filter of 0.1HZ. Bad channels were removed and interpolated and epochs were extracted -100 to 300ms relative to the onset of each electrical somatosensory stimulation and were grouped into the pain condition based on the video stimulation that was observed during the stimulation. Artefact detection was carried using a 100uv moving average and 100uv step-like detection and participants were removed from the analysis if they had an artefact rejection rate of over 25% of trials. Once ERP data was averaged electrodes were selected for the main analysis based on the maximal peak responses for the following two somatosensory components of interest: [1] P45, a positively polarized component between a 35 and 55ms time window; and [2] N80, a negatively polarized component between a 70 and 90ms time window. Three of the most maximally responding electrodes were selected and interpolated for each component which were to be used in the main analysis.

For the main analysis two 2 (Stimulation site: rTPJ vs. Control site) x3 (Video condition: pain vs no pain vs. baseline) repeated measures ANOVAs were carried out for each of the somatosensory components. Follow-up planned comparisons were then carried out to assess pain vs no pain comparisons with each stimulation site condition, pain vs pain and no-pain vs no-pain conditions between the stimulation sites.

Results

Somatosensory evoked potentials (P45 & N80) were identified by visually inspecting the ERP and by assessing the peak latency of the two components after the onset of tactile stimulation. Visual inspection of the ERP showed that electrodes surrounding the facial muscles and those in frontal areas displayed a large number of artefacts, likely due to muscle movements and blinking rather than neural activity. As a result these channels were removed leaving the following channels for the main analysis : Fz, F1, F2, F3, F4, Cz, C1, C2, C3, C4, C5, C6, CPz, CP1, CP2, CP3, CP4, CP5, CP6, Pz, P1, P2, P3, P4, POz, PO1, PO2. Of the four bands of channels only C, CP and P displayed P50 and N80 components, and observations of the large peak P50 and N80 components showed that C3, CP3 and P3 displayed the strongest components. These three channels were averages across one another to create a channel, known herein as the 'Sensorimotor' channel, which was used in the main analysis. Mean amplitude across the P45 and N80 time windows was used as the measurement variable in this analysis and time windows for the analysis were selected by observing the latency of peak activity across two time windows in the Sensorimotor channel; 20-80ms positive peak for P45 and 60-160ms negative peak for N80. The P45 peak lay at approximately 60ms after tactile onset and 130ms for the N80 component. The mean amplitude was calculated using a 50-70ms time window for the P50 component and 120-140ms for the N80 component (+/- 10ms the peak amplitude). See **Figure 5.2** for scalp maps of the SEP components at P45 (60ms) and N80 (130ms) across the three visual conditions (Baseline, Hand, Pain).

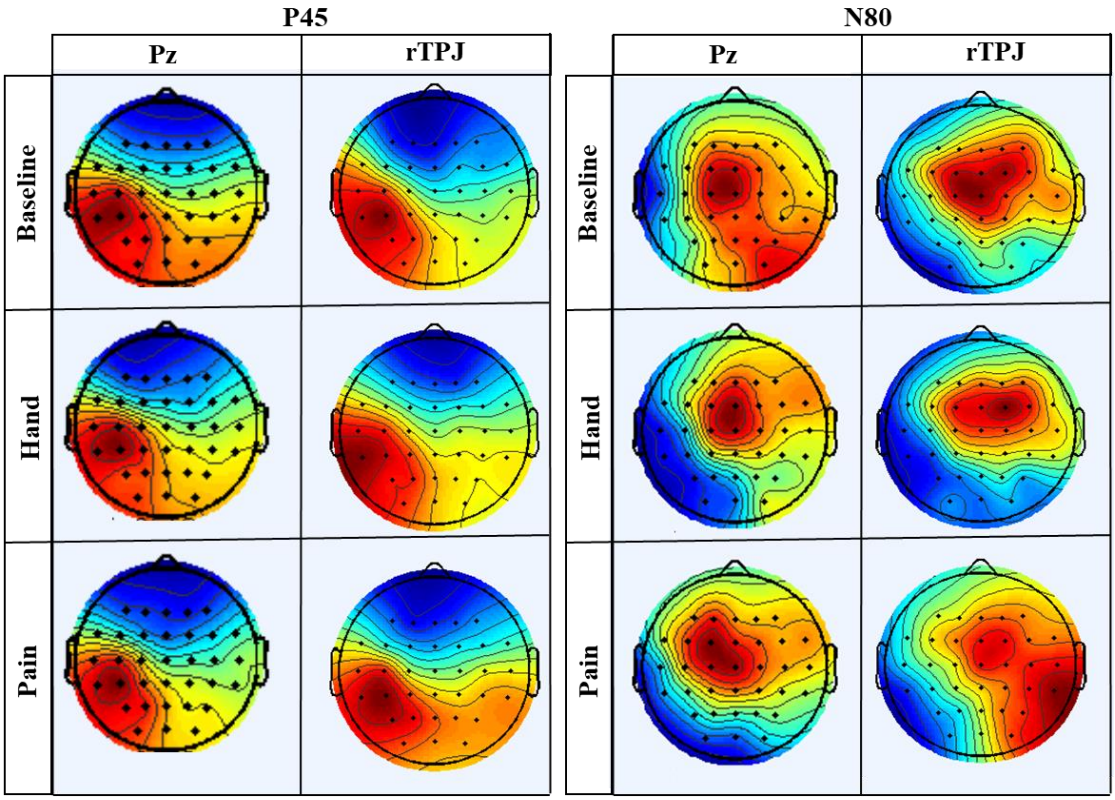


Figure 5.2: Scalp maps for P45 (60ms) and N80 (130ms) components across Pz and rTPJ stimulation conditions and the three visual stimuli conditions. Dark blue represents -1uv and Dark red represents +1uv.

Two separate 3 (Condition: Baseline vs Hand Image vs Pain Image) x 2 (TMS site: Pz vs. rTPJ) within group ANOVAs were run on the data, one for the P45 component and another for the N80 component. **Figure 5.3** shows the SEP components for the Pz and rTPJ stimulation conditions.

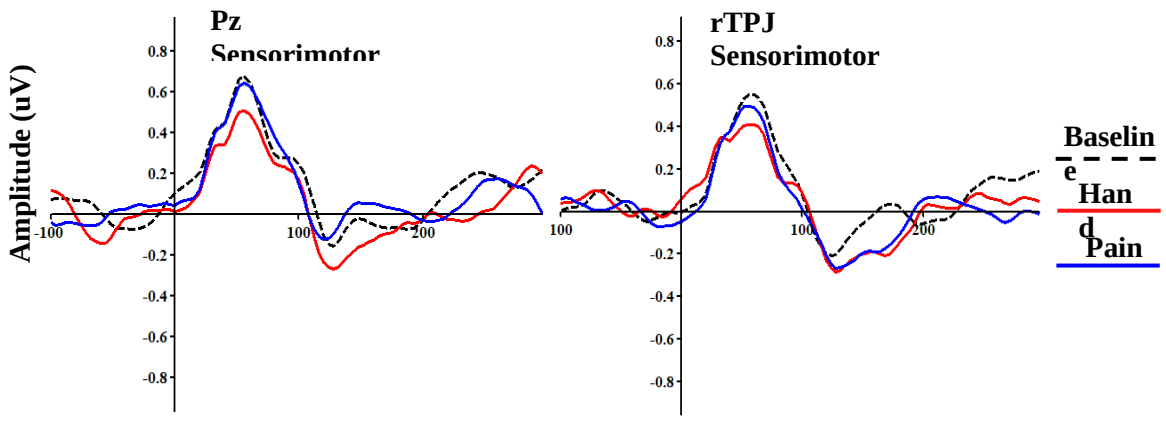


Figure 5.3: Grand average ERP waves for the Somatosensory evoked potentials across the Pz and rTPJ TMS stimulation sessions. The x axis measures time in ms and the zero point of this axis represents the onset of the somatosensory and visual stimuli and the y axis measures the amplitude at +/- 1 uV. The dotted line displays the Baseline (no visual image condition), the red line shows the hand image condition and the blue shows the pain image condition.

The P45 ANOVA showed no main effects of Image condition ($F(2,22)=2.541$, $p=0.102$, $r=0.454$) or TMS electrode site ($F(1,22)=0.714$, $p=0.416$, $r=0.121$), nor an interaction of TMS site*Image condition ($F(2,22)=0.117$, $p=0.890$, $r=0.066$). The N80 ANOVA also showed no main effects of image condition ($F(2,22)=1.424$, $p=0.262$, $r=0.272$) or TMS site ($F(1,22)=0.810$, $p=0.387$, $r=0.131$), nor an interaction of TMS site*Image Condition ($F(2,22)=0.688$, $p=0.513$, $r=0.151$). Observations of the ERP wave in the Sensorimotor channel shows that the tactile stimulation did successfully illicit a P45 positive component and N80 negative component. However, the ANOVAs show that neither the observation of pain images (Image condition) nor the TMS stimulation of the rTPJ (TMS site condition) modulated the SEP responses across either component. See **Figure 5.4** means plots for the two ANOVAs.

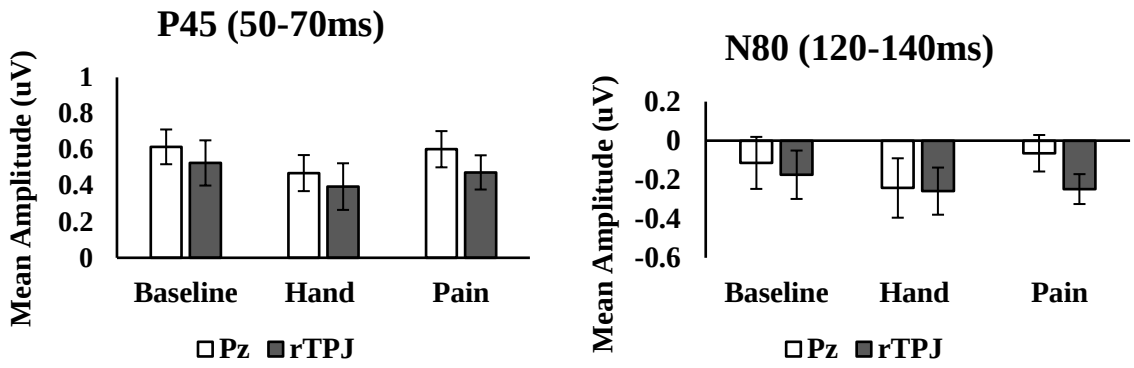


Figure 5.4: Bar charts displaying the means and Standard errors (1 +/-) for the P45 (left) and (N80) components which made up the two 3 (Image condition: Baseline vs. Hand Image vs. Pain Image) x2 (TMS stimulation site: Pz vs. rTPJ) ANOVAs in this study.

Discussion

The results of the current study did not successfully meet the either of the hypotheses which were: [1] to display modulation of SEP based on the presentation of pain images compared with no pain images, and, [2] to display modulation of SEPs based on stimulation of the rTPJ stimulation compared with a control site.. Specifically, no evidence of SEP modulation was observed between the visual conditions (Static hand and Pain) and the baseline condition (Hypothesis 1); and no SEP modulation was observed based on the TMS stimulation site for any of the visual condition stimuli conditions (Hypothesis 2). However, the study was successful in eliciting P45 and N80 SEP components over the somatosensory cortices in the contralateral hemisphere to the tactile stimulation, thereby validating the EEG methodology.

The failure to establish hypothesis 1 is of particular concern for the current study as a number of previous ERP studies have displayed significant modulation of SEPs when participants view hands being touched or having pain inflicted on them (Bufalari *et al.* 2007; Martinez-Juaund *et al.* 2012). It is possible that the theta burst TMS stimulation used had more holistic inhibitory effects resulting in an overall reduction in activity which included the simulation effects which would normally produce

the subtle SEP modulation that it highlighted in these studies. This appears to have been the case in recent rTMS stimulation studies which assessed the effect of rTPJ stimulation on out of body experiences (Daltrozzo, Kotchoubey, Gueler & Karim 2016). This study showed reduction in out-of-body experiences after stimulation in both rTPJ and control site simulation which the authors attributed to the general reduction of cortical stimulation caused by rTMS stimulation. To investigate this possibility the current study could have included a sham session in which no stimulation would be delivered, thereby more closely replicating the previous SEP studies which showed modulation effects.

Another possibility for the lack of SEP modulation is that the current study did not have enough trials to produce powerful enough SEPs to distinguish these subtle simulation effects. Both Martinez-Juaund *et al.* (2012) and Bufalari *et al.* (2007) collected data from over 1500 trials per condition (Static hand, Hand being touched, Hand in pain) compared with the 400 trials per condition used in this study. This is idea is further supported by the more typically shaped SEP components generated across these two studies. Alternatively, the effects of earlier studies may have emerged later in the later stages of the experiment due to habituation of the somatosensory stimuli. This lack of distinct SEPs caused by a lack of trials is likely to increase the influence of variability and noise which are present during the course an EEG recording whilst dampening the subtle neural effects of interest. The number of trials in the current study was heavily restricted because of the length of time in which TBS is considered to be effective in inhibiting the cortex. Based on a study investigating the effect of TBS on motor evoked potentials the time period of maximum inhibitory effectiveness for stimulation is approximately 30 minutes (Huang, Edwards, Rounis, Bhatia & Rothwell 2005). To ensure that there was enough time between the stimulation offset and the beginning of the EEG recording a maximum task period of 24 minutes was selected which resulted in 1,200 trials which utilised the same trial design as previous SEP studies. Additionally, the ERP generated by this study display relatively low voltage outputs (0.5-0.8uV) compared with previous studies (i.e. P45 are most commonly >1uV (Martinez-Jauand *et al.* 2012; Bufalari *et al.* 2007)). This may have been caused by the relatively low number of trials or by a lack of intensity in the somatosensory stimulation. Our

procedures followed that of previous somatosensory stimulation in past SEP studies by delivering perceptible but non-painful touch to the vagal nerve on the wrist however participants may have indicated that they were comfortable with the somatosensory stimulation when it was not actually strong enough to generate large SEPs which may have affected the results of the study.

The current study also had a relatively high amount of excluded trials based on the occurrence of eye blinking and other artefacts which may have been the result of increased blink caused facial nerve irritation bought on by the theta burst TMS. This loss of trials further diminished the power of SEP components. In this study we could have utilised Mu rhythm suppression as an EEG based dependant variable as was the case in **Article I** (Grice-Jackson *et al. in prep*). However, this was not selected because the results of that experiment indicated mu rhythm suppression was only present in the Sensory/Localiser responder group and that effects found in previous studies which utilised this method may have been driven by undetected mirror-pain responders (Cheng *et al*, 2008; Yang *et al.* 2009). The current study utilised only neurotypical participants and therefore an EEG method which demonstrated somatosensory stimulation in controls was selected.

The use of SEPs as a dependant variable for measuring mirror-pain itself may have been flawed. SEPs are focused on tactile processing, not pain processing; the latter is known to illicit activation in a different and more widespread network than the former. It may then have been more appropriate to used Laser-evoked potentials (LEPs) as the inducing stimulus. LEPs work under a similar principal to SEPs however thermal heat is used to illicit sensations of pain and pain related neural processes in participants (Ohara, Anderson, Lawson, Lee & Lenz, 2006). LEPs have displayed modulation of the resulting ERPs during observation of pain videos and more appropriately illicit the more widespread networks associated with pain (Valleriani *et al.* 2008). Although this is appealing for the current study it should be noted that SEPs have been successfully used to assess somatosensory modulation across a number of studies there and therefore could have considered as more robust than the more rarely implant LEP approach.

Our EEG/TMS experiment also failed to establish hypothesis 2, that rTPJ stimulation would affect SEP modulation. Beyond the fact that hypothesis 1 was not established, no rTPJ stimulation was observed in either of the components of interests over and above the visual stimuli factor. These results indicate that the rTPJ does not have a directly afferent causal role in sensorimotor simulation which is contrary to a large body of research in related fields. A number of previous TMS stimulation studies have shown a causal link between the rTPJ and processes related to perspective taking (Wang, *et al.* 2014), Theory of mind (Krall *et al.* 2015), moral judgement making (Young *et al.* 2010), Control of Imitation (Sowden & Catmur 2013). Based on these links between empathy and the rTPJ it was expected that there would be a relationship between the region and mirror-pain simulation. However, when assessing its relation to mirror-pain, rTMS stimulation of the rTPJ has not yielded significant casual effects (Vandenbroucke, Bardi, Lamm, & Goubert 2015). This study used vibrotactile stimulation techniques to assess vicarious errors when observations of pain and tactile stimulation were incongruent. The study showed that rTPJ stimulation was ineffectual in modulating the number of vicarious errors by participants. It showed that rTPJ stimulation may not specifically affect low-level affective simulation processes compared with higher level cognitive processes studied in rTMS studies assessing empathic processes. The SEP components represented in the current study are reflective of low level and early simulation responses. A previous pain related stimulation study employing tDCS showed links between the region and empathic pain. The authors used empathic responses to facial expressions which could be conceived as a more high-level and socially based empathic process (Coll, Tremblay & Jackson 2017). In order to test this idea the current study could have included a separate high-level empathy task which has been shown to be influenced by rTPJ stimulation however time limitations on the rTMS stimulation prevented this.

The results of this study do not rule out the potential for links between the rTPJ and mirror-pain response. Instead, they could indicate that the relationship between the rTPJ and somatosensory simulation for mirror-pain is more complex than the causal, unidirectional approach assessed in this study. Past research has repeatedly shown that the rTPJ is implicated in mirror-pain and vicarious pain response and (Jackson & Decety 2006, Coll *et al.* 2017) our previous assessment of the rTPJ in

mirror-pain responders indicate that region is linked to their experiences In **Article I** structural MRI results show that the region possesses reduced grey matter volume in responders compared with controls (Grice-Jackson *et al.*2017); and **Article II** shows that there is a significant degree of connectivity between regions showing vicarious activation for pain and the right temporo-parietal junction (Grice-Jackson *et al. in prep*). It would therefore be short-sighted to reject the rTPJ and mirror-pain links outright.

It may be the case that the hyperactivity and self/other processes interaction in a multidirectional approach or that they are influenced by another region. Alternatively, it may be the case that the processes underlying mirror-pain are a result of multi-sensory conflict for tactile stimuli and that the rTPJ is involved in process the higher processes related to this conflict. The secondary somatosensory cortex has been highlighted as a key region processing multisensory information related to vision and touch (Keysers *et al.*2010). Research on animal populations indicates that SII has distinct sub regions related specifically to integrating multisensory information (Manzel & Brath, 2005; Brett-Green, Paulsen, Staba, Fifková & Barth 2004). Indeed studies assessing mirror-touch synaesthesia have also highlighted the SII (Holle *et al.*2013), as have mirror-pain studies (Osborn & Derbyshire 2010). The fMRI analysis in **Article II** has shown effects which span across the primary and secondary somatosensory cortex. Multisensory conflict is thought to influence and change self-other representations (Tajadura-Jiménez, Grehl & Tsakiris 2012); and, it is thought that the rTPJ may more involved in detecting multisensory conflict rather than resolving (Papeo, Longo, Feurra & Haggard 2010). This may indicate that the rTPJ is involved invoking the high-order empathy responses which result from an interaction between simulation regions which undergo multisensory conflict. It should be a priority in the mirror-pain literature to develop studies to assess the possible mechanisms underlying the rTPJ/sensorimotor mirror-pain link. This study has shown that a unidirectional rTPJ to sensorimotor link is unlikely however it does not test for a multi-directional or mediatory relationship.

The past studies of the rTPJ have also shown that the region displays functionally distinct sub regions. As mentioned in the in the introduction, the region as a whole displays seemingly distinct functional

roles related to spatial attention and social interactions (Krall *et al.* 2016). Using MRI activation likelihood estimation to assess task related conjunction for fMRI studies on attention and social interaction tasks, the rTPJ has been shown to display functionally distinct regions related to spatial attention, in the anterior portion, and social interaction, in the posterior portion (Krall *et al.* 2014). Due to the focus on social interaction, particularly empathy and theory of mind, in mirror-pain research, the current study could have specifically targeted the posterior rTPJ to assess the specific effects of the rTPJ social interaction functions on SEP modulation. However, this approach would have made assumptions of the functional relationship between the rTPJ and simulation regions which were unjustified, i.e. it may be the case that the attention based processes have an effect on somatosensory simulation. Many of past studies which have found modulation effects of TMS stimulation on social interaction processes have not specifically targeted the posterior region (Sowden & Catmur 2010; Santiesteban *et al.*2013); furthermore, Krall *et al.* (2015) study only focused on social interaction studies related to the false belief task. This task is related to high-level empathy processes and has little to do with self-other distinction or mirror-pain/touch, thus, the findings may not relate to the processes most related to the current study.

Based on the connectivity analysis conducted in **Article II** it may also be possible that the current study did not account for all of the necessary region associated with self-other control (Grice-Jackson *et al. in prep*). This connectivity analysis showed that the Dorsal-lateral prefrontal cortex (DLPFC) and Dorsomedial prefrontal corex (DMPFC) are also involved in the connectivity network associated with mirror-pain simulation responses. The DLPFC has widespread effects on cognitive control (Duncan, 2010) including empathy (Moriguchi *et al.* 2007) and emotion regulation (Ochsner, Silvers, & Buhle, 2012); and the DMPFC is thought to be link to self-concepts and representations (Mitchell, Bariati & Macrae). These regions, with the rTPJ may make up a network of regions responsible for the self-other processing involved in vicarious/mirror pain. By looking at a single region within this network we may have not sufficiently affected the network so as to modulate sensorimotor simulation. Future research should take a network based approach by stimulating a number of regions within this self-other network and assessing the impact of their impact on sensorimotor stimulation.

In conclusion the current study failed to establish a causal link between the rTPJ and processing during pain observations. This finding indicates the link between the rTPJ and somatosensory simulation regions (which have been highlight in our previous studies on mirror-pain responder) may be more complex and further research is required to understand this important relationship. However it should be note that the lack of rTPJ stimulation effect could be attributed to the methodological approach used in this study, therefore the causal link should not be discounted completely. Additionally, the study failed to replicate previous findings of SEPs modulation during pain observations compared with static hand and baseline visual conditions. This could represent methodological issues related to SEP data collection or to the general inhibitory effects of theta burst stimulation itself.

Discussion

In this final section I will firstly summarise and expand on the findings reported in this thesis and assess the degree to which the empirical research achieved the objectives set out in the introductory chapter. We will then discuss the methodological limitations of the research presented and suggest possible amendments which may inform others conducting research in the field during their experimental design. This will be followed by a discussion of the contributions and implications of the research programme to the extant literature on mirror-pain experiences and empathy for pain more generally. Beyond that, I will discuss the current findings in the context of the major theories and debates present in the literature on mirror-pain and empathy. Finally, I will cover some of the questions yet to answer in the field as a series of suggestion for future research.

1. Summary of findings

The empirical projects described in this thesis set out to achieve three primary goals: (1) identifying and characterising a population of mirror-pain responders; (2) assessing the brain regions and networks underpinning mirror-pain experiences; and (3) testing neurocognitive models of mirror-pain and empathy theories. The first of these objectives was initially approached as its findings were expected to highlight the population of interest for this thesis – mirror-pain responders – who were identified through the development of the 'Vicarious Pain Questionnaire' (VPQ – **Article I**). **Figure 6.1** displays a summary of the research findings associated with the three groups (Controls, Sensory/Localiser pain responders, and Affective/General pain responders) presented in this thesis and displays the major findings associated with each one. Overall, the findings display a more distinctive profile for Sensory/Localiser responders and a less distinctive profile for Affective/General responders. It is not clear whether the two groups differ significantly on the neural patterns associated with their subjective experiences or whether they exist on the same spectrum as mirror-pain.

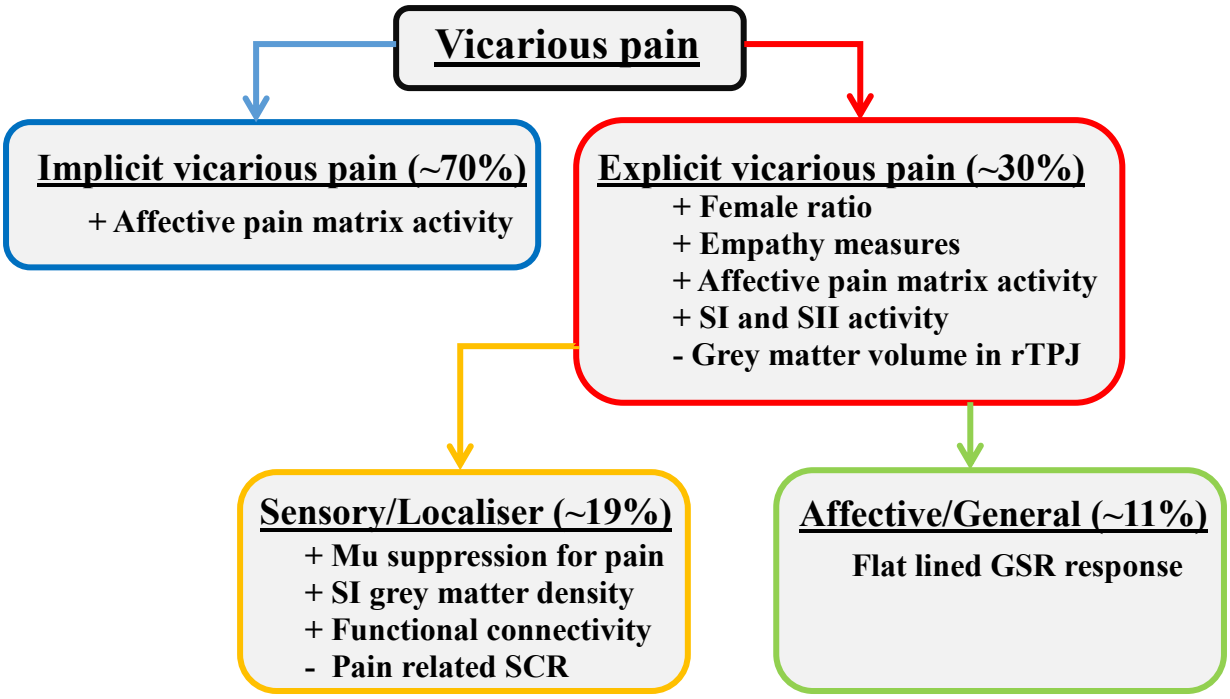


Figure 6.1: Major research findings associated with controls, mirror-pain responders, Sensory/Localizer responders and Affective/General responders across the empirical projects described in this thesis

The online questionnaire (VPQ) recruited a large sample of participants and asked them to report their subjective experiences of mirror-pain during the observation of a series of pain videos. In doing so the tool displayed a prevalence rate which was consistent with previous studies of a similar nature (Giummarra *et al.* 2015; Osborn & Derbyshire, 2010). The high prevalence rate was surprising as the VPQ was designed to be a more stringent measure for highlighting mirror-pain responders than previous studies (which had used criteria such as having a single localised vicarious pain response; Osborn & Derbyshire, 2010). The k-means cluster analysis displayed for the first time that mirror-pain experiences are not homogeneous and that inter-individual differences in participants' subjective reports can be used to categorise responders into two groups: Sensory/Localiser responders and Affective/General responders. The former reported feeling sensations on a particular point on their own bodies, often in the same location as the observed pain, and used descriptors which highlighted the sensory aspects of pain. The latter did not tend to localise mirror-pain experiences to a point on their bodies and used descriptors which focused on the affective components of their pain. Aside from

this difference the two groups reported a similar number of mirror-pain experiences and reported similar levels of mirror-pain regularity in their daily lives. Due to the discovery of these two groups our aims were adjusted to include a separated characterising of the traits and neural patterns underlying their subjective experiences.

A series of behavioural, physiological and questionnaire measures were also used to characterise the two mirror-pain responder groups (**Article III**). These measures assessed a number of characteristics and traits related to mirror-pain and empathy, including: visual perspective taking, self-other control, interoceptive awareness, and empathy; all of which were thought to be related to mirror-pain. This study showed no effects unique to either mirror-pain responder groups across the majority of measures (visual perspective taking, self-other control and interoceptive awareness). This finding was unexpected as the measures used were thought to be highly related to mirror-sensory experiences and previous studies had shown effects on similar measures (self-other control: Santiesteban *et al.* 2013; visual perspective taking: Derbyshire *et al.* 2013). The only measure to display a mirror-pain responder group effect was the IRI measures of empathy. This result showed that both of the mirror-pain responder groups showed increased scores on the perspective taking and empathic concern subscales but no differences were observed between the two groups. This result provides evidence for a hypothesised link between empathy and mirror-pain responders in both of our responder groups.

The second major aim of the study was to identify neural regions and networks associated with mirror-pain responders. Here, the primary aim was to establish a neural basis for the experiences of the population that was highlighted by the vicarious pain questionnaire. **Article I** did so by using EEG to assess somatosensory oscillations, known as Mu rhythms, and Voxel Based Morphometry (VBM). This study found decreased grey matter volume in both pain responders which was taken as initial evidence for the involvement of self-other neural regions in mirror-pain processing (Ward & Banissy, 2015; Fitzgibbon *et al.* 2012). Furthermore the study highlighted a number of effects unique to the Sensory/Localiser pain responder group including increased suppression of Mu rhythms when viewing pain images relative to no-pain images - an effect not observed in controls of

Affective/General responders – and increased grey matter volume in the somatosensory cortices. This result is consistent with hyperactive sensory-discriminative pain region processing during pain observations for this group as hypothesised by Ward & Banissy's (2015) Threshold theory.

Our fMRI results also showed that both mirror-pain responder groups showed increased activity in both sensory-discriminative and affective motivational pain matrix regions where controls only showed increased activity in affective motivational regions (**Article II**). The affective motivational simulation displayed across the three groups is consistent with previous fMRI studies on typical controls (Jackson *et al.* 2006; Singer *et al.*2004, Lamm *et al.* 2011). Critically, the sensory-discriminative activation observed in the two pain responder groups provides some evidence for the hyperactivity of these regions in these groups which may contribute to their vicarious experiences, and is thus consistent with previous fMRI studies of mirror-pain responders and mirror-touch responders (Holle, *et al.* 2013; Osborn & Derbyshire, 2010). These results however were not significant at a between-group level and thus should be taken with some caution. Whilst they are in line with previous results the findings are relatively weak and further investigation is required to establish this effect.

The fMRI study assessed neural networks associated with mirror-pain by using a Psycho-Physiological Interactions analysis (PPI) (**Article II**). This analysis assessed the connectivity between active regions during the observation of pain relative to no pain and only showed significant effects for the Sensory/Localiser responder and Affective/General groups, but not for controls. For the Sensory/Localiser groups these results showed a network of connectivity between both sensory discriminative and affective motivational pain matrix regions, and self-other regions, primarily in the temporo-parietal junction (TPJ) and angular gyrus; however, affective motivation regions also showed connectivity with the dorsolateral prefrontal cortex (DLPFC), an area associated with multisensory integration and social cognition (Godinho *et al.* 2012). The Affective/General responders also showed connectivity between sensory/discriminative pain matrix regions (SI and AI) and the dorsolateral and dorsomedial prefrontal cortex (DMPFC). The DMPFC is associated with higher-level empathic

process such as theory of mind but is particularly associated with the self-referential processes involved in empathy and the formation of self-representations (Gusnard & Rafcle, 2001). These findings provide evidence of networks for higher-level empathic and self-other networks for mirror-pain responders and provide some evidence for a slight difference between Affective/General and Sensory/Localiser responders, with the former displaying more connectivity effects with 'self' focused processing regions whilst the latter displays more connectivity with 'other' focused regions. To our knowledge this study represents the first attempt to assess connectivity networks in research associated with mirror-pain responders.

Aside from this connectivity effects, the majority of our findings have only showed unique effects for the Sensory/Localiser group whilst the Affective/General group have shown effects similar to Sensory/Localisers in some measures (fMRI **Article II**, VBM **Article I**), and similar to controls in other measures (Mu Rhythms, **Article I**). However, our assessment of skin conductance responses (SCR) showed that Affective/General responders showed a flat-lining of their skin responses whilst Sensory/Localisers and controls performed similarly by showing increased levels of SCR during observations of pain images (**Article III**). SCR is associated with autonomic nervous system responses to pain (Kyle & McNeil, 2014) and has been shown to be sensitive to empathic responses to facial expressions (Levenson & Friesen, 1993). Consequently, it was expected that the pain responders groups would show increased SCR response and thus the flat-lining was a surprising response. We hypothesised that this effect may reflect an anxiety response to observations of pain as previous studies have associated this kind of effect with trait and state anxiety (Panju, *et al.* 2015; Navateur *et al.* 2005). As these findings were not hypothesised they are highly preliminary and further research is required to understand the effect more fully.

The final major aim of this research was to investigate major theories of empathy and mirror-sensory synaesthesia on pain responders and controls, including theories of simulation (Gallese & Goldman 2003), threshold theory (Ward & Banissy 2015), and self-other theory (Fitzgibbon *et al.* 2012). A number of our findings supported the concept that mirror-pain responders display hyperactivity of

sensory-discriminative pain matrix regions (**Article I**, **Article II**) for mirror-pain responders; however, these findings were largely focused on sensory-discriminative pain matrix responders who showed a far more distinctive pattern of effects. Causal evidence for threshold theory was observed in the Mu rhythm study (**Article I**) in which observations of pain resulted in somatosensory simulation in only the Sensory/Localiser responders. Additionally the group displayed structural effects associated with this hyperactivity. Both of the mirror-pain responder groups showed correlational fMRI effects which were somewhat indicative of this hyperactivity; however, the Affective/General group did not show strong or unique neural pattern associated with this theory.

The VBM effects (**Article I**) and connectivity analysis effects (**Article II**) both indicated that self-other processing is associated with both affective motivational and sensory-discriminative simulation in the mirror-pain responder groups, however, the behavioural self-other control results failed to highlight significant effects. Overall these show that there is evidence for neural underpinning of self-other processing. Casual evidence for the theory was not highlighted in this study. **Article IV** aimed to resolve this issue by attempting to establish a causal link between processing in self-other regions and somatosensory mirror-pain responses. To do so, theta burst TMS stimulation was used to modulate activity in the right temporoparietal junction (rTPJ) in control participants. Somatosensory evoked potentials, which have been used to assess somatosensory responses in controls (Bufalri *et al.* 2007), were then observed to assess the modulatory effects of rTPJ stimulation. This study failed to show significant findings of self-other region stimulation on the somatosensory processing thus indicating that a causal link from the rTPJ to the somatosensory cortex does not cause hyperactive vicarious processing for controls. It may be the case therefore that the link between these two regions is more complicated than a simple one-to-one connection, or that other processing regions within the self-other network have more of a role, and that affecting the rTPJ alone is not sufficient for modulating somatosensory activity.

2. Methodological limitations

In this section I will review some of the methodological issues faced during the course of the empirical research in this thesis and suggest alternatives and adjustments to the methods for future research.

In our behavioural and physiological battery of experiments few significant effects were displayed, despite the measured traits having been closely associated with mirror-pain and mirror-touch in the past, e.g. visual perspective taking (Derbyshire *et al.* 2013). The task chosen in **Article III** for perspective taking was not the same as that used in the Derbyshire *et al'*s. study, which focused on visual and spatial perspective taking exclusively. The director's task used in **Article III** also assesses visual perspective taking; however, unlike Derbyshire's *et al* measure, the perspective of the director is fixed, and thus participants can learn the rules of the game relatively simply. It therefore may be the case that the study was confound by participants' problem solving abilities and the degree to which they understood the task, rather than their focusing on visual perspective taking. Should this study be replicated, researchers should consider using a method that uses a changing visual perspective so that participants cannot simply learn the rules of the task in order to perform well. Secondly, the choice of interoceptive awareness (IA) task may have been insufficient for assessing the measures as it has been somewhat discredited in recent years. The heartbeat tracking task we used is considered to be a less objective measure of IA than measures which relate to the tracking of external stimuli in relation to heartbeat monitoring, i.e. heartbeat discrimination tasks (Brener & Kluvitse, 1988) with recent comparisons of the two tasks showing them to be dissociable and distinct from one another (Garfinkel *et al* 2014). It may be the case that our analysis relies too heavily on a single task and should therefore incorporate a broader range of IA tasks before discounting its link to mirror-pain.

In the fMRI study one of the major issues faced was that of underpowered statistical analysis (**Article II**). Both within-group and between-group analyses showed some degree of underpowered analysis. This issue was most prevalent in the between-group analysis. As a result the study relied to a greater extent than ideal on small volume correction and Region of Interest (ROI) analyses. Whilst it was felt that these were justified based on a priori hypotheses they reflected a need for more data. With

regards to the within-group power issues, the selection of trials was based on Osborn and Derbyshire's 2010 study; whilst this was sufficient for pain versus no pain comparison, when the stimuli was split between image laterality and topography the result data did not yield enough power. This was expected to some degree, however it had significant implications for the analyses. Research should increase the number of trials in similar studies so that each broken down stimuli condition has at least 32 trials, as was the case with the pain and no-pain conditions. The underpowered analysis in the between-group studies was likely due to a lack of participants in the mirror-pain responder groups, particularly in the Affective/General group. Recruitment for the study began prior to the breaking down of the mirror-pain responders into the two subgroups and was initially setup to be 20 controls versus 20 mirror-pain responders. When the analysis was broken into the two subgroups the between-group analyses for these groups was underpowered and extra data collection was not possible due to restrictions of the number of participants we could recruit.

Finally, the TMS study presented a number of methodological challenges. This was to be expected as it was the most experimental and untested of the research projects attempted. Firstly, the choice of stimulation sites should have increased in order to accommodate other self-other processing regions as discussed earlier in this discussion Additionally, the location of the rTPJ stimulation could have been adjusted to specifically assess the anterior or posterior portions of the region as the two portions have slightly differing functions (Krall *et al.* 2015). The study could have also used a different dependant measure of somatosensory activation. SEPs were selected as they allow for the investigation of the source of somatosensory modulation based on the latency of the affected components (earlier components relate to S1 processing and later components relate to SII processing). Whilst this insight would have been useful it may have been the case that the measure focused on components that were too early in the temporal response to be affected by rTPJ processing. As such, a less temporally acute measure such as Mu rhythms could have been adopted. Mu rhythms were successfully used in **Article I** to assess pain versus no-pain activation in Sensory/Localisers and therefore is a good future candidate for a dependant variable. Finally the study could have adopted behavioural measures in addition to the neuroimaging dependant variables. Previous stimulation studies of the region have

shown significant effects of the stimulation (Santiesteban *et al.* 2013) and therefore measures such as self-other control or the director's task of perspective taking could have been used as markers for the impact of TPJ stimulation. Without this, it is unclear whether the lack of findings result from theoretical reasons or because the stimulation was not effective. The main motivation behind not including these measure was the lack of a test time window that theta burst stimulation provided.

3. Contribution to literature

One of the major contributions of this thesis to the literature is the development of the vicarious pain questionnaire (VPQ) which fulfils the aim of screening mirror-pain populations, assessing the prevalence of the condition, and highlighting characteristics of pain responders' subjective experiences (**Article I**). Previous studies have developed screening methods to highlight mirror-pain responding, including Osborn & Derbyshire's (2010) screening tool and the Empathic Pain Scale (Giummarra *et al.*2015). Whilst insightful, these tools had some issues: Osborn and Derbyshire's tool provided little information about the participants' experiences and was fairly liberal and arbitrary in its classification of mirror-pain responders; whilst the EPS did not actually evoke mirror-pain experiences during the assessment, but instead relied on reports of past mirror-pain experiences. The VPQ provides an easily-administered online test that uses participants' actual mirror-pain experiences as well as their reports of past experiences and their regularity. A major advantage of the VPQ is that it asks participants to report details of the subjective mirror-pain experiences they reported during pain observations, which includes subjective descriptors and reports about the location of their experiences on their own bodies. Additionally, with the application of a two-step k-means cluster analysis, this questionnaire allowed for bottom-up categorisation based on input variables that related to participants' subjective experiences of mirror-pain. This tool may be used and adapted in the future by researchers to assess mirror-pain and mirror-sensory synaesthesia. The ability to not only highlight but also profile participants based on their experiences will be highly valuable for making predictions about the experiences of these individuals.

A related contribution of this thesis was the highlighting of inter-individual differences in mirror-pain responder groups. Previous studies of mirror-sensory groups have largely treated them as a homogenous group, whereas the VPQ and k-means analysis allowed for the classification of mirror-pain responders based on differences in the way they experienced mirror-pain. This resulted in two distinct groups based on their subjective experiences, Sensory/Localisers and Affective/General responders. Research into mirror-touch synesthetes has highlighted inter-individual differences relating to the location of their vicarious touch (Banissy & Ward 2007). Here, respondents were classified into specular, i.e. feeling vicarious pain as if the observed touch was mirrored on their own body, or anatomical, i.e. where vicarious touch is felt on the same anatomical location as the observed touch. The same attempt to assess individual differences in mirror-pain responders has not been made up until this point. This approach is promising for future research as assessing the implications of individual differences can offer more depth to investigations of the phenomena and can allow different neurocognitive predictions based on the subjective reports. Further measures may be added to the VPQ to allow for an even greater expression of these individual differences. So far the questionnaire has focused on qualitative descriptors and localisation reports, and so a number of other measures can be developed to further classify these groups.

The findings in this thesis have also made a contribution towards developing a neural pattern associated with mirror-pain, particularly with regards to the underlying connectivity networks. Previous fMRI studies have shown that mirror-pain responders display both sensory-discriminative and affective general pain matrix activation in response to pain observations (Osborn and Derbyshire, 2010) and studies on mirror-pain amputees have displayed evidence for the hyperactivity of sensorimotor regions during pain observations (Fitzgibbon *et al.* 2010). Findings from **Articles I** and **II** report results that are highly consistent with these findings by displaying activity in the somatosensory cortices for both pain responder groups and increased Mu rhythm responses in Sensory/Localiser responders. **Article I** goes beyond previous results by displaying structural markers of mirror-pain in the somatosensory cortices and rTPJ. This VBM technique has not been applied to mirror-pain responders in the past; however, similar findings to those present here have been shown in

structural MRI analysis of mirror-pain respondents (Holle *et al.* 2013). Additionally, this thesis presents the first attempt to assess the connectivity networks associated with mirror-pain. Both affective and sensory pain matrix regions showed increased connectivity with regions that process self and other representations during vicarious pain. These findings contribute to and support theories of mirror-sensory synaesthesia and mirror-pain which suggests that the condition occurs out of an interaction between neural simulation and modulated self-other processes (Fitzgibbon *et al.* 2012).

Another contribution from this thesis is the use of SCR to assess the activity of the autonomic nervous system in response to pain observations. This tool has previous been used to measure first-hand nociceptive stimulation and pain in typical samples and was to shown to be a sufficiently sensitive measure (Storm, 2008). However, the SCR methods used in **Article III** are the first which attempt to measure ANS activation in vicarious responses in either typical samples or mirror-pain responders. The results showed a most striking, and somewhat counterintuitive, finding of a flattening of responses in the Affective/General group and evidence for reduced pain related SCR effects in the Sensory/Localiser group. One possible explanation of this flat-lining may be related SCR's lack of sensitivity towards high-anxiety individuals whilst they carry out stressful or anxiety-inducing tasks. Past observations of children with ASD have shown that blunted SCR responses to anxiety-inducing tasks can be predicted by whether or not the participant had high trait anxiety (Panju *et al.* 2015). This finding also extends to typical individuals who display high trait anxiety, with low SCR responses being observed in high anxiety individuals when emotional auditory task distractors were added to a basic word-searching task (Navateur *et al.* 2005). Affective/General responders may display substantially higher levels of contextually-specific anxiety related to the observation of pain, which may result in SCR responses that mimic the responses of high anxiety individuals. This unexpected finding may have implications for the way we view mirror-pain. As of yet, most research in the field has focused on the respondent adopting and incorporating representations of others, which causes physical sensations in the viewer's body, This finding could suggest that for some respondents the experience of mirror-pain may be related to self-referential experiences, such as anxiety. This

hypothesis is based on this an unexpected finding and would require specially designed methodologies to test it in the future.

4. Implications for debates and theories

Previous studies of vicarious pain processing in typical individuals has been somewhat divided as to whether sensory-discriminative pain matrix regions are activated during the observations of pain. The majority of fMRI studies fail to show activation of these regions (Singer *et al.* 2004; Jackson, *et al.* 2006) whereas a number of non-fMRI papers (MEG, EEG, TMS) do show effects in such regions (Avenanti *et al.* 2009, Cheng *et al.* 2008; Yang *et al.* 2009). In **Article I** Mu rhythms highlighted that only the Sensory/Localiser responders displayed sensorimotor activation during pain observations. These individuals were also found to represent approximately 18% of the population. Using modelled data it was shown that this 18% had the potential to drive a sample of typical controls and undiagnosed sensory/localiser responders to significance based on the results of previous EEG studies which presented increased mu rhythm suppression. This may indicate that the non-fMRI findings which displayed sensory discriminative simulation for the general population may be driven by undiagnosed mirror-pain responders, and that sensory-discriminative simulation to pain is not the norm for typical controls.

The use of consistent terminology in mirror-pain research is lacking to some degree. Largely terminology has been developed fairly organically and independently across the small number of research groups working in the field. There is a relatively good consensus in the use of the terms vicarious pain, empathy for pain, and mirror-pain. Vicarious pain tends to refer to the normative neural processes underlying observations of pain (Avenanti *et al.* 2008, Avenanti *et al.* 2009, Bufalari *et al* 2007), empathy for pain is commonly used when referring to simulationist accounts of vicarious pain (Singer *et al.* 2004; Decety & Jackson 2006; Lamm *et al.* 2011) and mirror-pain refers to the non-normative conscious experiences of pain when observing it (Giummarra *et al.* 2008; Osborn & Derbyshire 2010; Fitzgibbon *et al.* 2012). More controversial is the use of the term synaesthesia in the

field. The related condition of mirror-touch synaesthesia has come to adopt the term based on the multi-sensory integration component in mirror-touch and synaesthesia has also been used to describe mirror-pain by Fitzgibbon *et al.* (2012) where it was called mirror-sensory synaesthesia. This is associated with non-normative cross-modal neural processing which is often developmental (Baron-Cohen 1996). Other researchers have been more cautious in the use of the terms in mirror-pain and mirror-touch. Rothen & Meier (2014) state that the term is not appropriate because mirror-pain and touch [1] rely on a social component, [2] have predictably match responses between observations and experience, [3] reflect normative processes. Mirror-pain researchers such as Osborn & Derbyshire (2010) and Giummarra *et al.* (2015) have used the term mirror-pain responders. This term has been used when highlighting individuals through large scale prevalence tests. These studies often do not have a thorough diagnosis meaning it may be misguided to use the term synaesthesia for this group. Additionally, mirror-pain research indicates that the experience may be to some degree malleable based on factors such as past pain experiences (Derbyshire *et al.* 2013). Due to these factors the current thesis has avoided using the term mirror-pain synaesthesia and has adopted mirror-pain responders to characterise the group of interest. The current thesis also focuses on using terms conscious and non-conscious, and, implicit and explicit when referring to mirror-pain experiences (See **Figure 6.1**). This is because the theories underlying thesis suggest that mirror-pain reflects abnormal processing in normative cognitive mechanisms related to simulation and mentalizing networks.

The empirical work in this thesis is heavily influenced by simulation and shared representation models of empathy for pain (Based on Decety & Jackson, 2004, Lamm *et al.*2011). The increased mu rhythm responses observed in **Article I** and the fMRI effects in pain matrix regions in **Article II** are considered to be examples of shared representations of observation and experience for pain in action. Whilst these simulation theories have for a long time been dominant within the field, recent evidence has presented a challenge by suggesting that empathy for pain relies on a range of cognitive and emotional mechanisms which are separate from egocentric pain processing (Hooker, Verosky, Germine, Knight & D'Esposito 2008).

This debate was investigated using fMRI, machine learning and multivariate pattern analysis to highlight networks of regions associated with personally experienced pain and vicarious pain. When assessing self-experienced pain Wager, Atlas, Lindquist, Roy, Woo & Kross (2013) used this methodology to highlight a Neurological Pain Signature (NPS) made up of the dACC, insula and somatosensory cortex. Activation in this network is showed to be highly predictive and specific for personally experienced pain. The same approach was then taken with observations of pain and a Vicarious Pain Signature (VPS) was highlighted (Krishnan, Woo, Chang, Ruzic, Gu, Lopez-Solá, Jackson, Pujol, Fan & Wager, 2016). Rather displaying a VPS which displayed overlap with the NPS, as would be expected in a shared representations account, this study showed a double dissociation between VPS and NPS regions with little overlap between the systems. Whereas the NPS showed regions classically considered to be part of the pain matrix the VPS highlighted regions which have been associated with cognitive empathy and mentalizing systems such as the rTPJ, STS and DMPFC (Frith & Frith, 2005). Krishnan *et al* (2016) therefore showed that whilst a neural signature for vicarious pain is observable it is not similar to that displayed during actual pain experiences as would be expected simulation theories. Interestingly, the other study also showed that the VPS mentalizing neural signature displays a degree of somatotopy as can be observed within the somatosensory cortex during actual pain. The implications of this finding are significant for the current thesis as they call into question the simulation upon which much of this work is theoretically based. However, it should be noted that this paper largely focuses on simulation within the ACC and insula pain matrix regions. Although these regions were highlight in the fMRI study (**Article II**) the key findings within the thesis fell within somatosensory regions of regions within the mentalizing system described in this study. Kirshan *et al* suggest that the lack of somatosensory findings in previous mirror pain studies (i.e. Lamm *et al.* 2011) are indicative of the lack of simulation however **Article I** and **II** of this thesis show that mirror-pain responders do display vicarious activation within regions that Wager *et al.* (2013) linked to the NPS.

It may be the case that whilst normative vicarious pain processing relies on a unique neural pattern within the VPS, however the mirror-pain responders in our study may recruit a regions within the NPS which elicits their conscious vicarious pain experiences. Additionally, it should be nted that a number of key findings in this thesis do highlight regions within the mentalizing VPS such as the DMPFC and rTPJ. Whilst the research may have been motivated by simulation theories observations of neuroimaging results has implicated this system as a key driver of mirror-pain experiences.

Another key debate in the literature is that relating to the specificity of neural regions for pain processing. The neuro-matrix or pain-matrix has for a long time been considered a reliable guide for understanding the neural processes associated with pain (Melzack 2000, Peyron *et al.* 1999). More recently however this principle has been called into question with a number of researchers questioning the degree of specificity that this collection of regions displays for pain (Iannetti & Mouraux 2010). The researchers note that regions within the pain matrix do not respond with specificity to nociceptive pain and that they are active during a range of salient sensory information. The two regions most commonly associated with pain processing are the dorsal ACC and the insula. A highly controversial findings using the meta-analytical tool neurosynth[tm] went sofar as to claim that the dACC is selective and specific to pain processing (Lieberman & Eisenberger 2015). However, this result was widely criticised on the basis of emerging results which linked its activation to a range salience and survival responses (Wager, Atlas, Botvinick, Chang, Coghill, Davish, *et al.* 2016). They claimed that the reverse inference analysis used with neurosynth did not highlight these emerging findings or non-specificity. Additionally, it has recently been shown that the insula does not display specificity to pain with local-field potential fMRI techniques showing that non-painful stimuli influences insula activity (Liberati , Klöcker, Safronova, Ferrão Santos, Vaz, Raftopoulos & Mouraux 2016). Considering that these key regions show a lack of specificity for pain it may be misguided for the research in this thesis to continue using the pain matrix as a guiding principle for vicarious pain processing. However Wager's *et al.* (2016) Neurological Pain Signature (NPS) recently showed that a system of regions which include the dACC and Insula are closely associated with pain processing. Therefore, whilst these regions are not uniquely associated with pain it seems to be the case that integrated activation

amongst these regions is required for the processing of pain. As a result, we use activity in these regions cautiously when making inferences about vicarious pain processing but continue to use the pain matrix as a neurological guide especially where activation amongst a number of NPS regions is present.

A recent study on mirror-touch synaesthesia has suggested that the condition is not linked to increased empathy and that it is present in autistic spectrum disorder (ASD) individuals, a condition marked by impaired empathy abilities (Baron-Cohen *et al.* 2016). This finding represents somewhat of a challenge to the literature on mirror-sensory synaesthesia as much of it is built on the assumption that empathy is the driving component behind the phenomena. However, previous studies of the groups have shown links to empathy with mirror-touch synaesthtes displaying heightened emotional skills and modulated social skills (Banissy & Ward, 2007). The current thesis did show links between mirror-pain responders and empathy using the IRI questionnaire with increased scores being displayed in the perspective taking and empathic concern subscales (**Article III**). This choice of questionnaire was different to that used by Baron-Cohen *et al.* (2016) who used the empathy quotient. This does provide a link between mirror-pain and empathy, although our behavioural results do not show the same support, with a lack of findings being displayed on measures assessing component parts of empathy such as the Control of Imitation task (self-other control) and the director's task (perspective taking). This inconsistency in our findings indicates that the reliance on empathy as a foundational construct for mirror-pain and mirror-touch needs further research in order to establish it, and possible adjustments to the way we view empathy and mirror-sensory experiences may be required.

Article IV of this thesis attempts to display a causal link between the rTPJ, a self-other control region and somatosensory modulation during pain observations through the use of TMS. This study did not provide evidence of this link, thereby bringing the prediction of self-other theory into some question (as the rTPJ is thought to be a key processing region for self-other control in the mirror-sensory research) (Fitzgibbon *et al.* 2012; Ward & Banissy, 2015, Holle *et al.* 2013). **Article III** also failed to

show effects of control for imitation, a behavioural test of self-other control. However, the connectivity results of **Article II** indicate that self-other processing regions including the TPJ, DMPFC and DLPFC are part of a connectivity network associated with mirror-pain experiences. These conflicting results mean that future studies will have to consider the mechanism of self-other control on mirror-pain experiences. It may be the case that a simple one-to-one causal link does not sufficiently explain the influence of self-other processing and that other mechanisms need to be considered. Alternatively researchers may have to reconsider the importance of self-other control for mirror-pain research.

5. Future Directions

Whilst this thesis has made a number of contributions to the literature it has also raised a number of additional questions and laid the groundwork for future research. One of the most obvious questions is related to the profile of Affective/General mirror-pain responders. The results of the VPQ indicated that these individuals had a qualitatively different experience of mirror-pain relative to Sensory/Localisers. However, the experiments involving the two groups in this thesis showed a far less consistent pattern of neural and behavioural responses for this group. Where the Sensory/Localiser group showed a number of clear and hypothesised effects, the Affective/General group showed effects that were, in some cases, indistinguishable from Sensory/Localiser responders and, at other times, from controls. The only unique findings for this group were unexpected, as in the case of the SCR responses, or only slightly different from Sensory/Localisers, as in the connectivity analysis. At this point it is difficult to judge whether the Affective/General group's differing qualitative experience is manifested uniquely in their neural activity or whether they exist on the same spectrum as Sensory/Localiser responders, but with less extensive activation. Future research should attempt to establish this question by assessing measures in which possible dissociations between the two responder groups could occur. A promising direction for this study lies in the self-referential versus other-referential basis of the two groups' experiences.

Another interesting aspect of mirror-pain is related to contextually specific experiences and the association between mirror-pain and past pain experiences. Investigations into affective-motivational pain matrix responses to pain observations have revealed that such responses are downregulated in physicians compared with controls (Cheng *et al.* 2008). The researchers claimed that the increased experience of pain observations in their work meant that doctors were able to inhibit normal empathy for pain responses. This therefore shows the impact of past experiences with pain, and the context within which individuals observe it. Mirror-pain responder amputees are hypothesised to have acquired their mirror-pain because of their traumatic pain experiences, and observations of pain are thought to trigger the sensations (Fitzgibbon *et al.* 2009). Furthermore, Derbyshire *et al* (2013) have shown that people with past experiences of tooth sensitivity displayed increased levels of mirror-pain when observing others experiencing pain when eating an iced popsicle. This finding indicates that mirror-pain may be a more malleable experience than previously thought and it could depend on context and past experience. To further test the past pain hypothesis, it may be useful to profile participants based their past pain experiences and to assess whether these experiences make it more likely that the individual experiences mirror-pain. Furthermore it may be useful to assess the neural basis of this effect. It may be the case that salience-processing regions such as areas in the affective-pain matrix (Legrain *et al.* 2011) may modulate the levels of vicarious pain processing. Additionally, research into mirror-pain has hypothesised and presented some evidence for the concept of increased empathy for those similar to oneself (De Vignemont, 2012; Avenanti *et al.* 2009). It may also be useful to investigate whether the frequency of mirror-pain response may be heightened when observing pain in loved ones or in situations where increased empathy is required, i.e. seeing a vulnerable individual in pain.

As previously mentioned, one of the major benefits of the VPQ and one of the promising lines of future research in the field relates to inter-individual differences based on subjective experiences of mirror-pain. The VPQ highlights two groups of mirror-pain responder based on responses to two of the items in the questionnaire, these being the localisation of pain, and qualitative pain descriptors. In order to gain a deeper understanding of the inter-individual differences it is important that new items

are developed and added to the VPQ. In mirror-touch research a recent study has highlighted the lived experiences of mirror-touch synesthetes via a qualitative analysis of interviews with these individuals (Martin, Cleghorn & Ward, 2017). In doing so the researchers were able to understand the daily experiences of these groups, particularly with regard to their experiences of empathy and social functioning. Applying a similar qualitative method to mirror-pain responders could provide interesting insights to their experiences, particularly with regards to inter-individual differences. Based on this qualitative approach, new questionnaire measures could be developed and validated which could be fed into the VPQ thus providing greater potential for analysing these individual differences.

Finally, with regards to the issue of self-other processing discussed in the previous section future repetitive transcranial magnetic stimulation (rTMS) work should attempt to incorporate other areas within the self-other network into the trial design. These studies may include stimulation of the DLPFC/DMPFC as well as the rTPJ to assess which component parts of this network are responsible the mirror-pain experiences. Additionally, other kinds of stimulation should be considered as rTMS only has inhibitory effects. Previous studies using transcranial direct current stimulation, which has executory as well as inhibitory effects have shown modulations of performance on tasks related to empathy and self-other control (Santiesteban *et al.* 2013).

6. Conclusions

This thesis represents a significant progress in the systematic investigation of the experiences and neural underpinnings in mirror-pain responders. The current programme of research has furthered the development of an effective questionnaire tool for the screening and characterisation of mirror-pain responders, and in doing so has highlighted differences in inter-individual experiences within mirror-pain responders. Additionally the research has developed our understanding of the neural processes involved in mirror-pain, which has applications to our understanding of empathy for pain processing more generally. The results are of theoretical interest in extending our current knowledge of empathy

for pain, mirror-experiences and neural mechanisms underlying simulations, and they raise a number of interesting pathways for future research. Furthermore, they encourage debates around the importance of self-other processing in mirror-pain, the connectivity networks underlying the experiences of mirror-pain, and inter-individual differences in subjective reports. In addition, this research may be used to inform methodological practices for future studies and may have implications for improving our understanding of embodied empathy.

Appendices

Appendix 1: Supplementary materials for Article I

Vicarious Pain questionnaire:

All videos of pain presented to the participants can be found at the following URL: https://www.youtube.com/channel/UCT8goTgWGRsu14NjVaPCSGw/videos.

[Section1] After each video participants were asked the following questions (note: questions labelled with '*' were only asked if participants responded with a 'yes' to quest 1):

1. Did you experience any bodily sensation of pain whilst observing the person in pain?
2. Please rate how painful this experience was for you (Likert scale,1= Very Mild Pain, 10= Highly intense pain). *
3. Did you feel this pain in a specific location or was it a more general bodily feeling? *
    a. General bodily experience
    b. Localised to the same point as the observed pain.
    c. Localised but not to the same point as the observed pain.
4. How unpleasant did you find the experience of watching this video? (Likert scale 1= not unpleasant, 10= Highly unpleasant)
5. Looking back on your experiences of vicarious pain please choose any of the following adjectives to describe the type of pain you experience. (Select as many as you feel necessary to describe your past experiences or experience of watching the videos). [Note: these were presented as a random list to participants and not grouped in this way] *

Table 1: Full list of response questionnaire pain descriptor responses present in the VPQ.

Sensory Descriptors:	Affective Descriptors	Cognitive Evaluative Descriptors
Tingling	Nauseating	Brief
Stinging	Aversion	Constant
Sharp	Wincing	Rhythmic
Dull	Fearful	
Soreness/Aching	Terrifying	
Stiff/Tight	Sickening	
Shooting	Torturing	
Throbbing	Gruelling	
Burning	Vicious	
Numbness	Suffocating	

In addition to the video based questions, participants were also asked a number of single item dispositional questions [Section 2]. The wording for these is as follows:

1. Would you say you have a high or low physical pain threshold? i.e., highly sensitive to pain or not very sensitive to pain. (1=no at all sensitive to pain, 10= highly sensitive to pain).
2. Do you consider yourself an empathetic person? (1= not at all empathetic, 10= highly empathetic).
3. Do you consider yourself an emotionally sensitive person? i.e. are you easily upset? (1= Not emotional, 10= highly emotional)
4. Are you made uncomfortable by the sight of, your own or another person's, blood? (1= No discomfort, 10=absolute discomfort).

Participants were also asked to questions about their past experiences with vicarious pain [Section 3]: These items are as follows (note: questions labelled with '*' were only asked if participants responded with a 'yes' to question 1):

1. Have you ever noticed feeling a sensation of pain whilst observing another in pain in your past or everyday life?
2. How regularly do you experience vicarious pain? (0= hardly ever, 10= very regularly) *

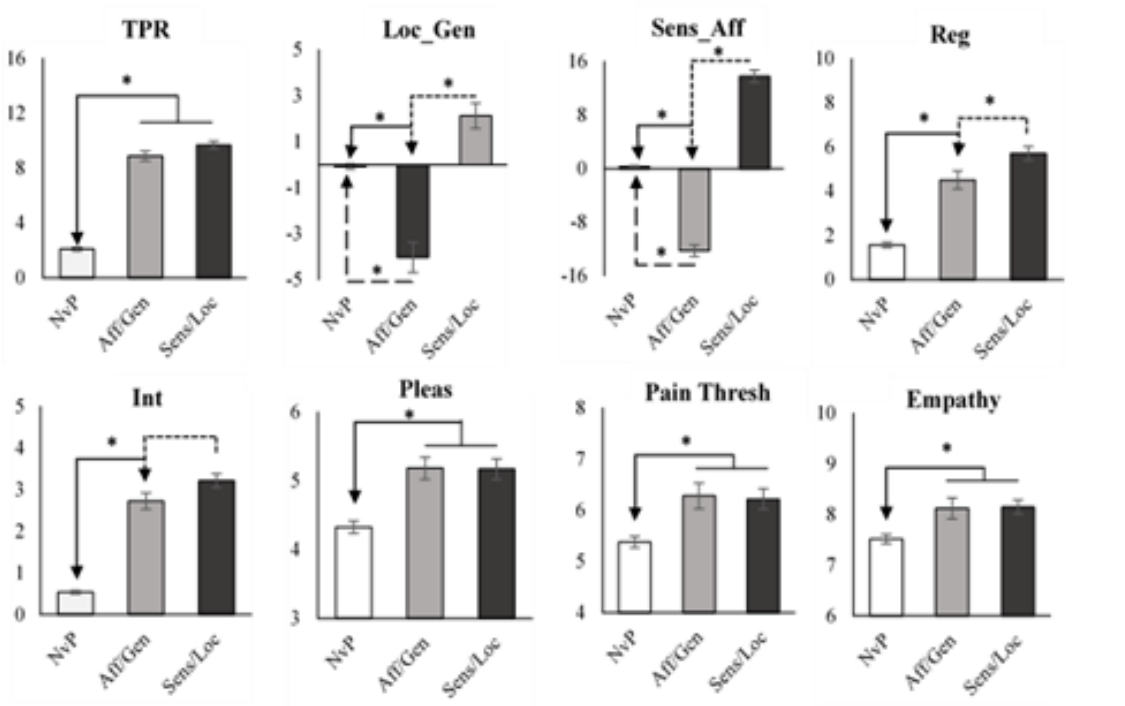
3. Do you feel as if you vicarious pain experiences are helpful, or a hindrance to your everyday life? (-5=hindrance, 5=helpful) *
4. Do you experience vicarious pain more for loved ones/ friends or is it an indiscriminate sensation (i.e. happens for everyone you see in pain)? (1= Happens for everyone, 10= only happens for loved ones).*
5. Based on your the description for pain synaesthesia given at the beginning of this questionnaire and your experience of watching the videos, do you feel as if you may potentially have pain synaesthesia (note: participants were given a short description of vicarious pain synaesthesia before this item)?

Supplementary Results:

Study 1: The Vicarious Pain Questionnaire (VPQ)

Table 2: Demographics of participants based on groups. Gender is cross tabulated with cluster group, observed frequencies are presented with percentages brackets. Mean age is represented for each group with standard error in brackets.

		Controls	Aff/Gen Responders	Sens/Loc Responders
Gender	F:	286 (65.29)	57 (13.01)	95 (21.68)
	M:	108 (80.59)	10 (7.46)	16 (11.94)
Age		20.15 (0.19)	20.88 (0.47)	20.79 (0.73)



***Supplementary Figure 2*:** Displays bar graphs for a variety of variables on the vicarious pain questionnaire (see Supplementary methods for VPQ for question wording of these items/measures). TPR=Section 1, Ouestion 1; Loc_gen= Section 1, Question 3; Sens_aff= Section 1, Question 5; Reg = Section 3, Question 2; Int = Section 1, Question 2; Pleas = Section 3, Question 4; Pain thresh: Section 2, Question 1; Empathy= Section 2, Question 2.

Study 2: Planned comparisons for EEG suppressions Mixed ANOVAs

Within group planned contrasts for the ~10Hz mu-alpha and ~20 Hz rolandic-beta oscillations showed that only the sensory/localiser group displayed significantly greater suppression during pain observations relative to no-pain (mu-alpha: Sensory/Localiser= *pain* = -4.03, *no-pain*=-3.04, t(7)= 3.35, *p*=0.015, *d=1.184)*, Controls= t(17)=0.11, *p*=0.911, *d=0.026*, Affective/General = t(6)=1.61, *p*=0.152, *d=0.608*. beta: Sensory/Localiser= *pain*= -1.82, *no-pain*=-0.93, t(7)=3.81, *p*=0.009, *r=d=1.347;* controls= t(17)=0.21, *p*=0.84, *d=0.049*, Affective/General: t(6)=0.16, *p*=.877, *d=0.060*). Between groups planned comparisons for pain and neutral images showed that sensory/localiser displayed increased mu suppression for pain observations relative to both groups and across broth frequency ranges (Mu-alpha: Sensory/Localiser>Affective/General *p*=0.04, Sensory/Localiser> Controls *p* =0.01;

rolandic-beta: Sensory/Localiser>Affective/General p=0.02, Sensory/Localiser>Controls p=0.01). No significant effects were observed in Affective/General vs. controls across any comparisons.

Study 2: Analyses of EEG electrode clusters

We aimed to establish that the mu/beta oscillations that we observe (both during vicarious perception and when performing movements) are consistent with a sensori-motor origin by showing that they are maximal over central sites relative to neighbouring sites. A source analysis was not possible without more electrode coverage. We assessed the difference between and beta oscillations between the central (somatosensory) electrodes (C3+CZ+C4), the frontal electrodes (CF3+CFZ+CF4) and posterior electrodes (CP3+CFZ+CF4). For this analysis pain and no-pain condition were collapsed across one another as the current analysis focused on the origin of the oscillations rather than difference between the image conditions. A one-way repeated measures ANOVA was carried across the three positions (Frontal vs. Central vs. Posterior) for both alpha and beta oscillations. For alpha oscillations there was a significant effect of electrode position, $F(2,45.316)=7.851$, p=0.003, r=.873 (Greenhouse-Geisser). Post-hoc comparisons showed that the central electrode positions (M=-1.94, S.E=0.36) differed significantly from both the frontal electrode positions (M =-1.45, S.E. =0.34; $t(31)=5.734$, p<.001) and posterior electrodes (M=-1.52, S.E=0.29; $t(31)= 2.653$, p=.012) and that there was no differences between frontal and posterior electrodes ($t(31)=0.469$, p=.64). Across the beta channel the one-way ANOVA revealed no differences between the 3 electrode positions ($F(2, 45.11)=0.084$, p=.911, r=.64; Greenhouse-Geisser). Furthermore, alpha and beta oscillations were observed during the hand movement task which showed a similar pattern scalp distribution to the image observation task. For the alpha frequency band a borderline significant one-way ANOVA effect was observed, $F(2,62)=2.957$,p=.059. Post hoc tests showed that the central alpha band displayed the greatest mu suppression (M=-1.24, S.E=0.15) when compared with the posterior channels (M=-0.92, S.E. 0.11; $t(31)=-3.202$, p=.003) and a borderline significant difference compared with frontal channels (M=-0.95, S.E=0.20, $t(31) =1.706$, p=.098), no effect was observed between frontal and posterior electrodes ($t(31)=0.17$, p=.863). The beta oscillations showed a significant one-

way ANOVA effect, F(2, 62)=3.338, *p*=.044, *r*=.600, with central electrodes (M=-0,95, S.E. 0.09) showing increased suppression relative to posterior electrodes (M=-0.76, S.E.=0.11; *t*(31)=2.76, *p*=0.009), but not frontal electrodes (M=-0.88, S.E.=.0.09; *t*(31)=0.99, *p*=0.326) and no effect was observed between frontal and posterior electrodes (*t*(31)=1.46, *p*=.15). As the data from the image observations and hand movement show a similar pattern, with central electrodes displaying the maximal mu suppression (rather than posterior electrodes), it is unlikely that the observed suppression in alpha and beta oscillations originate from an occipital (visual alpha) source and are more likely to display somatosensory processing.

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