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Review

Shared pain: From empathy to synaesthesia

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ABSTRACT

This paper reviews the current literature on "empathy for pain", the ability to understand pain observed in another person, in the context of a newly documented form of pain empathy "synaesthesia for pain". In synaesthesia for pain a person not only empathises with another's pain but experiences the observed or imagined pain as if it was their own. Neural mechanisms potentially involved in synaesthesia for pain include "mirror systems": neural systems active both when observing an action, or experiencing an emotion or sensation and when executing the same action, or personally experiencing the same emotion or sensation. For example, we may know that someone is in pain in part because observation activates similar neural networks as if we were experiencing that pain ourselves. We propose that synaesthesia for pain may be the result of painful and/or traumatic experiences causing disinhibition in the mirror system underlying empathy for pain. We will discuss this theory in the context of a documented group of amputees who experience synaesthesia for pain in phantom limbs.

Contents

1. Introduction

The International Association for the Study of Pain (1994) defines pain as an unpleasant sensory and emotional experience caused by real or possible tissue damage. The neural processes involved in the experience of 'empathy for pain', the understanding of pain in another (other-pain), are not well understood. This review presents a new field of enquiry: synaesthesia for pain (Giummarra and Bradshaw, 2008). Synaesthesia occurs when stimulation in one sensory domain causes a sensation in another

Abbreviations: ACC, anterior cingulate cortex; AI, anterior insula; ASD, autistic spectrum disorders; CIP, congenital insensitivity to pain; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; IC, insula; MEG, magnetoencephalography; MNs, mirror neurons; MNS, mirror neuron system; ROI, region of interest; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SEPs, somatosensory evoked potentials; TMS, transcranial magnetic stimulation.

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domain (for a review, see Rich and Mattingley, 2002). For example, in its most common form, digits, letters or words evoke the perception of a colour (Simner et al., 2006). In the case of synaesthesia for pain, people describe that the empathic response of observing pain in another causes an actual sensation of pain in oneself (Giummarra and Bradshaw, 2008). We expect that synaesthesia for pain and empathy for pain share overlapping neural correlates; however, in synaesthesia for pain these networks may be activated above the level required for conscious perception.

Empathy is the ability to understand the emotional state of others in the context of the self (de Vignemont and Singer, 2006; Decety and Jackson, 2004). This ability allows us to understand and predict the behaviours or emotions of other people (Singer, 2006; Singer et al., 2004) and to respond appropriately in our actions, thoughts and desires towards them (Batson, 1990). Empathy may occur via simulation of another person's state. Neurobiological models of this simulation hold that observing another person's state activates overlapping cortical areas, "mirror systems", as if the observer was in that same state themselves (Decety and Jackson, 2004; Gallese, 2003; Preston and de Waal, 2002). Initial evidence suggesting that empathy for pain may be mediated by mirror systems emerged with the finding that neurons in the anterior cingulate cortex (ACC) fire in response to both pain in the self and the observation of pain in another person (Hutchison et al., 1999). Consequently, research has demonstrated that areas within the "pain matrix" (regions of the brain involved in processing pain to the self; self-pain) become active during the experience of empathy for pain in normal populations (Jackson et al., 2006b).

In this paper, we review current literature on empathy for pain. We suggest that synaesthesia for pain is an abnormal form of empathy for pain, and discuss potential mechanisms that may underlie the experience of another's pain. Specifically, we propose that dysfunctional mirror systems may alter empathic processes by causing the mapping of motor/emotion/perceptual states in a way that exceeds the threshold for conscious experience of those states. Because more cases of pain synaesthesia have been reported in phantom pain patients than any other patient group (see Giummarra and Bradshaw, 2008) we discuss this proposal within the context of amputees suffering from phantom pain; the experience of pain in an absent extremity (Flor, 2002; Flor et al., 2006).

2. Processing pain in the self vs. processing pain in another

While there has been much debate on the neural processes underlying pain perception (see Treede et al., 1999), the way pain is experienced by the individual is influenced by a combination of sensory-discriminative, affective-motivational and cognitive-evaluative factors (Melzack and Casey, 1968; Ploghaus et al., 1999; Price, 2000; Treede et al., 1999). Whereas the sensory-discriminative component of pain allows one to determine where and how intense the pain is in one's body, the affective-motivational component allows one to determine how unpleasant the pain is and to react with a fight or flight response if appropriate (Avenanti and Aglioti, 2006). The cognitive-evaluative component of pain involves higher order processing and its influence over the experience of pain (Melzack and Casey, 1968). For example, attention, expectation and reappraisal may influence how a painful experience is interpreted (Wiech et al., 2008).

Areas of the brain involved in these processes underlying pain perception are centrally located in the pain matrix (Melzack and Casey, 1968). The pain matrix includes the thalamus, contralateral primary somatosensory cortex (S1), secondary somatosensory cortices (S2), insula (IC), ACC, and prefrontal areas (Apkarian et al., 2005; Peyron et al., 2000; Treede et al., 1999). While some of these individual regions (e.g. the ACC and the anterior insula, AI) are involved in processing the affective component of pain (Peyron et al., 2000; Rainville, 2002), others regions (e.g. the somatosensory cortices) may be more involved in processing the sensory component of pain (Bushnell et al., 1999; Hofbauer et al., 2001; Ingvar, 1999; Porro et al., 1998). Activation of the pain matrix is not exclusive to the experience of pain in response to noxious stimuli in the self, but it is also activated in phantom pain (Willoch et al., 2000), social rejection (Eisenberger et al., 2003) and empathy for pain (for a review, see Jackson et al., 2006b).

While empathy for pain is an attractive model for investigating social cognition and mirror systems (Avenanti and Aglioti, 2006; Bufalari et al., 2007) several questions surrounding the experience of empathy for pain remain: does understanding another person's pain require just the affective component or is the sensory component also critical? As discussed in Section 5, most studies investigating activation of the pain matrix in empathy for pain have found overwhelming affective but not sensory activation; however, new techniques have recently found sensory activation. If the experience of empathy for pain does indeed require a sensory component, why do we not always experience the pain we observe in another person?

3. Synaesthesia for touch and pain

"Synaesthesia for touch" (also known as mirror-touch) occurs when the observation of touch causes a tactile sensation in the observer (see Banissy and Ward, 2007; Blakemore et al., 2005; Serino et al., 2008). A mirror system for touch has been identified in somatosensory neural structures (Blakemore et al., 2005; Keysers et al., 2004). While this neural overlapping does not typically result in the experience of touch through observation alone, this is not the case for 'touch synaesthetes'. Similarly, for 'pain synaesthetes', empathy for another's pain results in the subjective sensation of pain. At present, there are few published cases of pain synaesthesia. We will review current studies of synaesthesia for touch and pain and briefly describe potential mechanisms that may underlie these sensory synaesthetic phenomena. First, however, we will qualify our use of the term "synaesthesia" to describe synaesthesia for pain as an empathic process.

While synaesthesia for pain is typically acquired later in life, most reports of synaesthesia are developmental. Ro et al. (2007) suggest that acquired forms of synaesthesia differ from developmental forms of synaesthesia in many crucial ways. First, acquired synaesthetic sensations are often less specific than the sensations experienced in developmental synaesthesia. For example, feeling a tingling sensation in response to sound in acquired synaesthesia (Ro et al., 2007), compared to experiencing specific tastes, such as bread soaked in tomato soup, in response to words in developmental synaesthesia (Ward and Simner, 2003). Second, developmental and acquired forms of synaesthesia tend to involve different sensory modalities. For example, developmental synaesthesia involves the blending of unrelated sensory information, e.g. grapheme-colour (Simner et al., 2006), while reports of acquired synaesthesia include converging representations from different modalities, e.g. sound–touch synaesthesia (Ro et al., 2007), touch–vision (Armel and Ramachandran, 1999) and synaesthesia for pain (Giummarra and Bradshaw, 2008). We feel synaesthesia for pain is a true acquired synaesthesia as vision and pain demonstrate a clear link, as in synaesthesia for touch (e.g. Blakemore et al., 2005).

In the first study of synaesthesia for touch, Blakemore et al. (2005) used functional magnetic resonance imaging (fMRI) to map brain activity underlying both non-synaesthetic and synaesthetic perception of touch. Observing touch activated the tactile mirror system in both synaesthetes and non-synaesthetes, although activation was greater in the case of synaesthesia. This finding suggests that whereas the tactile mirror system is typically activated

below the level required for conscious subjective perception to occur, in touch synaesthetes this activation exceeds the perceptual threshold resulting in conscious perception of touch in the self. The authors suggest that synaesthesia for touch may be due to (1) neural connections directly linking visual and somatosensory regions, or (2) bimodal cells in the parietal cortex being overactive in the perception of touch. Each of these two possibilities is unlikely to explain synaesthesia for touch alone. If (1) is the case, only somatosensory regions would be activated and only in the touch synaesthetes. If (2) is the case, activation would be expected only in the parietal regions comprising bimodal visual-tactile cells.

Banissy and Ward (2007) provided behavioural evidence of the 'reality' of synaesthesia for touch. As synaesthesia for touch had been previously shown to activate the neural regions linked to physical touch (Blakemore et al., 2005), the authors predicted that touch synaesthetes should be unable to discriminate real from synaesthetic touch (Banissy and Ward, 2007). To investigate this hypothesis, touch synaesthetes were asked to report the location of touch to their cheeks or hand. At the same time as being touched they also observed touch to another person in either the same (congruent) or a different (incongruent) location, but were asked to pay no attention to it. Touch synaesthetes were found to make significantly more errors than non-synaesthetic controls in the incongruent condition. This finding confirms that touch synaesthetes experience considerable commonalities between the feeling of actual touch and synaesthetically induced touch. Touch synaesthetes also scored significantly higher on the emotional reactivity index of the empathy quotient measure than non-synaesthetes and other non-touch synaesthetes, suggesting that synaesthesia for touch may be related to a heightened ability to empathise with others in the somatosensory domain (Banissy and Ward, 2007).

Recently, Serino et al. (2008) experimentally induced something akin to synaesthesia for touch in non-synaesthetes. They examined the way in which a persons' perception of sub-threshold stimulation to the face was affected by simultaneously observing touch to his or her own face, to another person's face or to an inanimate object. Perception of sub-threshold tactile stimuli was increased when participants observed touch to another's face, but was strongest when the observed touch was directed to the participant's own face. These results suggest that by manipulating perceptual thresholds in the mirror system for touch, something similar to the behavioural qualities of synaesthesia for touch can be induced in non-synaesthetes.

Investigating the frequency and the features of synaesthesia for touch, Banissy et al. (2009) administered a questionnaire on synaesthesia to a student population. In this questionnaire, participants were asked to rate how strongly they agreed with the question 'do you experience touch sensations on your own body when you see them on another person's body?'. Almost 11% of all participants gave a positive response to this question and were contacted for further enquiry including the presentation of a series of videos depicting touch. In response to these videos, 2.5% of all participants experienced a tingling somatic sensation on the matching part of their body. Further, in response to videos that, for instance, depicted a needle to a hand (painful stimuli), the sensation was both different and more intense then that to touch alone. To investigate the authenticity of these potential mirror-touch synaesthetes, the touch synaesthetes underwent the paradigm discussed above by Banissy and Ward (2007). Compared to non-synaesthete controls, nine of the potential mirror-touch synaesthetes demonstrated faster reaction times when the condition was congruent compared to non-congruent and/or demonstrated more errors, thereby determining the prevalence of mirror-touch synaesthesia to be 1.6% of all participants.

The results of these mirror-touch synaesthetes were then compared to those of previously reported mirror-touch synaesthetes ($n = 12$). As no difference was found between groups in reaction time or error type, the groups were pooled ($n = 21$) to determine characteristics of the experience. They found that for the majority of mirror-touch synaesthetes, the experience is elicited for observed bodies and not for inaminate objects, but some did experience a tactile sensation to the observation of an object being touched. While some experience the sensation in the finger-tip that is touching the object, others experience being touched on their own body spatially corresponding to the touch on another's, and some even experience spatial congruity for both bodies and objects. They also found that the majority report a specular frame of reference, like looking in a mirror, while the minority report an anatomical frame of reference, where, for instance, observed touch on someone's right thigh causes the sensation on their own right thigh.

Overall, research into the mirror system for touch supports the idea that sensory synaesthesia is due to increased sensitivity in the same neural networks that process sensation in synaesthetes and non-synaesthetes. That is, in non-synaesthetes the observation of touch causes neural activation that is below a threshold necessary for consciously perceived experience (Blakemore et al., 2005). In synaesthetes, however, this perception appears to be activated above the threshold of conscious perception resulting in the perceptual effects observed in sensory synaesthetes as reported by Banissy and Ward (2007). We propose that similar mirror system mechanisms may be involved in synaesthesia for pain. Synaesthesia for pain, however, differs from touch synaesthesia in one major respect: while mirror-touch synaesthesia has been documented from birth (developmental), synaesthesia for pain has only been reported following trauma (acquired).

The first case reported to exhibit a relationship between observed and "real" pain was anecdotally described by Bradshaw and Mattingley (2001) in a man with hyperalgesia who felt pain when he observed his wife in pain. No investigations could be done as the man's condition was described by patient's wife following his death. The patient's wife reported that the pain appeared to be qualitatively similar to her husband's own hypersensitivity to touch: "*If I slightly knocked my finger, spontaneously showing him, he would immediately grasp his own finger and say "don't do that" (meaning not to show him); he actually felt it*".

Eight cases of lower limb phantom limb patients have reported that their phantom pain is triggered by observing, thinking about, or inferring that another person is in pain (Giummarra and Bradshaw, 2008; Giummarra et al., 2006). Patients described these experiences when asked "does anything trigger or cause your phantom limb sensations or phantom limb pain to emerge or change?" One amputee, RB, reported that he experienced strong, painful "electric" impulses in his phantom foot when he observed sutured wounds. Another amputee, AR, reported that he felt pain, at first in the stump and then in the phantom, when he observed someone cut or hurt themselves, while NN reported his phantom foot "going crazy" when he heard a gruesome story. Finally, GD experienced synaesthesia for pain in his stumps when he observed experiences he associated with pain, such as walking barefoot. See Box 1 for an overview of known characteristics of synaesthesia for pain in a sample of amputees with phantom pain (Fitzgibbon et al., unpublished manuscript).

Giummarra et al. (2008a) have also reported a case of synaesthesia for pain in one upper limb amputee. This patient, MM, reported phantom pain when watching footage on television of amputation, others being injured on their arms, or when stimuli associated with potential pain/amputation (e.g., axe, chainsaw, sharp knife) were near her own arm, or near another's limbs. The final documented case of synaesthesia for pain is CB who

Box 1. This box describes known characteristics of synaesthesia for pain in a sample of amputees with phantom pain (Fitzgibbon et al.).
Known Characteristics of Synaesthesia for Pain in a Sample of Amputees with Phantom Pain
Brought on by viewing others in pain and/or observing pain on the television and in movies.
Brought on both when observed pain matches that of the amputated site and/or any general pain
Brought on regardless of the identity of the observed person in pain, i.e. can be a loved one or a stranger.
The experience is similar to the experiences of phantom pain, for example, described as a short sudden 'electric shock'.
Experienced in the phantom limb and/or stump.

experienced a long and painful labour with obstruction resulting in an emergency caesarean section delivery. Since this distressful event, CB reports the experience of "*shooting pains from the groin that radiate down the legs*" when told of another's traumatic experience (Giummarra and Bradshaw, 2008). Following a second scheduled c-section delivery, CB's synaesthesia for pain has worsened, occurring more frequently, and triggered by lower threshold stimuli (unpublished).

Almost all these cases of pain synaesthesia report intense, traumatic or chronic pain. For example, of eight lower limb amputees, six suffered from traumatic limb loss, and two suffered complications of vascular disease leading to amputation. Only one patient did not experience pain prior to amputation. The rest experienced pain in the limb between 13 h to three years prior to amputation. The commonality of intense, traumatic or chronic pain suggests that pain may be the leading risk factor in the development of this phenomenon. While most amputees experience some pain prior to amputation, the intensity of this pain is one of the strongest predictors of post-amputation phantom pain (Hanley et al., 2007). Our group proposes that pain experiences may cause disinhibition of mechanisms underlying empathy for pain, resulting in synaesthesia for pain. This proposal is supported by studies that have found mirror activity to be involved in the pain matrix (e.g. Ochsner et al., 2008; Singer et al., 2004); however, the specific processes that weaken these inhibitory mechanisms are unclear (Giummarra and Bradshaw, 2008).

Synaesthesia for pain may manifest itself as a motor response to perceived threat. This response to protect the body (flight/fight response) may be linked to the motivational-affective aspect of pain processing. In our mirror box study using the rubber limb paradigm, we found that synaesthetic pain and pain behaviours (e.g. withdrawal) were elicited in six out of eight pain synaesthete lower limb amputees when stimuli presented to the fake or real hand were of high intensity (e.g. vibration) or threatened (e.g. syringe, Giummarra et al., submitted). This suggests that the motor system is involved and acts to protect, avoid, or escape from, perceived threat. This is consistent with the finding that the observation of pain can bring about slower approach movements and faster withdrawal movements using the go/no-go paradigm (Morrison et al., 2007b) and increased activation in the cingulate cortex thought to be involved in the motivational-affective processing of pain (Morrison et al., 2007a). It is also consistent with a study demonstrating that the observation of pain to a hand may not only cause corticospinal inhibition ("freezing") in the corresponding hand, but corticospinal facilitation ("escaping") in the opposite hand (Avenanti et al., 2009).

We suggest that synaesthesia for pain may be modulated by sensitisation to pain and attention to pain cues. Sensitisation to pain occurs following injury through peripheral and central sensitisation. Peripheral sensitisation is an adaptive response causing the site of injury to increase in sensitivity promoting repair. Central sensitisation, comparatively, reduces pain thresholds, increases pain responses and extends pain sensitivity beyond the injured area. This post-trauma hypersensitivity can led to clinical pain conditions such as spontaneous pain (pain without peripheral nociceptive input), allodynia (pain in response to intrinsically non-painful stimuli), and hyperalgesia (increased sensitivity to pain) (Ji et al., 2003). Evidence suggests that the process of central sensitisation can be enhanced and/or maintained through cognition, emotion and attention, e.g. hypervigilance to pain cues (see Zusman, 2002). For example, people who have had more intense pain experiences tend to have lower pain thresholds and focus more on potentially threatening stimuli (Rollman et al., 2004). As such, synaesthesia for pain may be caused by sensitisation to pain and hypervigilance to pain cues resulting in disinhibition of the mirror system involved in empathic processing of pain in another (see Fig. 1. depicting proposed mechanisms involved in the production of synaesthesia for pain).

4. Empathy and mirror systems

Empathy involves an affective response to another person's observed or imagined emotional state, with the implicit knowledge that the self and other are differentiated (e.g. Batson et al., 1997; Eisenberg, 2000; Goldman, 1993; Ickes, 1997). Empathy is therefore a tool by which the experiences, needs and goals of another can be communicated (Carr et al., 2003) allowing the observer to respond appropriately (de Waal, 2008). The importance of this ability is illustrated in neurological conditions where the processing of emotional states is dysfunctional; for example, patients with bilateral amygdala damage who are unable to establish enhanced memory for emotionally loaded stimuli compared with neutral stimuli (Adolphs et al., 1997), and in other conditions where empathy is compromised or dysfunctional including autistic spectrum disorders (ASD: Gillberg, 1992, 1999), psychopathy (Agnew et al., 2007) and sexual offending disorders (Blake and Gannon, 2008).

There are two primary theories, predating the discovery of mirror neurons, of the cognitive underpinnings of empathy: "theory theory" and "simulation theory". Both were originally developed to explain theory of mind, that is, the ability to attribute the mental states of oneself and another and to differentiate between the two (Frith and Frith, 1999; Vollm et al., 2006). Empathy is characterised as different to other forms of social cognition (like theory of mind) due to its focus on emotion: that is empathy involves understanding the emotional state of another (Vollm et al., 2006). Applied to empathy, the "theory theory" suggests that we make inferences about the mental states of other people through developing theories (Gopnik and Meltzoff, 1997). For example, if a person falls off their bike, we can infer, through prior knowledge that accidents hurt, that they are injured and therefore in pain. Alternatively, "simulation theory" suggests that we obtain information about another person's emotional state by internally simulating the other's situation (Goldman, 1989). For example, understanding another's pain by consciously simulating what it would feel like to fall off a bike and be injured. This process-driven theory requires a person to already understand a state to simulate it (Goldman, 1989). In an adapted model of simulation theory, simulation is not a conscious choice but a fundamental ability to perceiving another as a person at all (Gordon, 1995). Therefore, we perceive the emotional state of another person through *automatic* internal simulation of their experience (Gazzaniga, 2008; Goldman and Sripada, 2005).

We propose that it is empathy operating through an automatic internal simulation of another person's emotional state that is of most interest in synaesthesia for pain. To empathise with another, however, requires more than the simulation of the other's

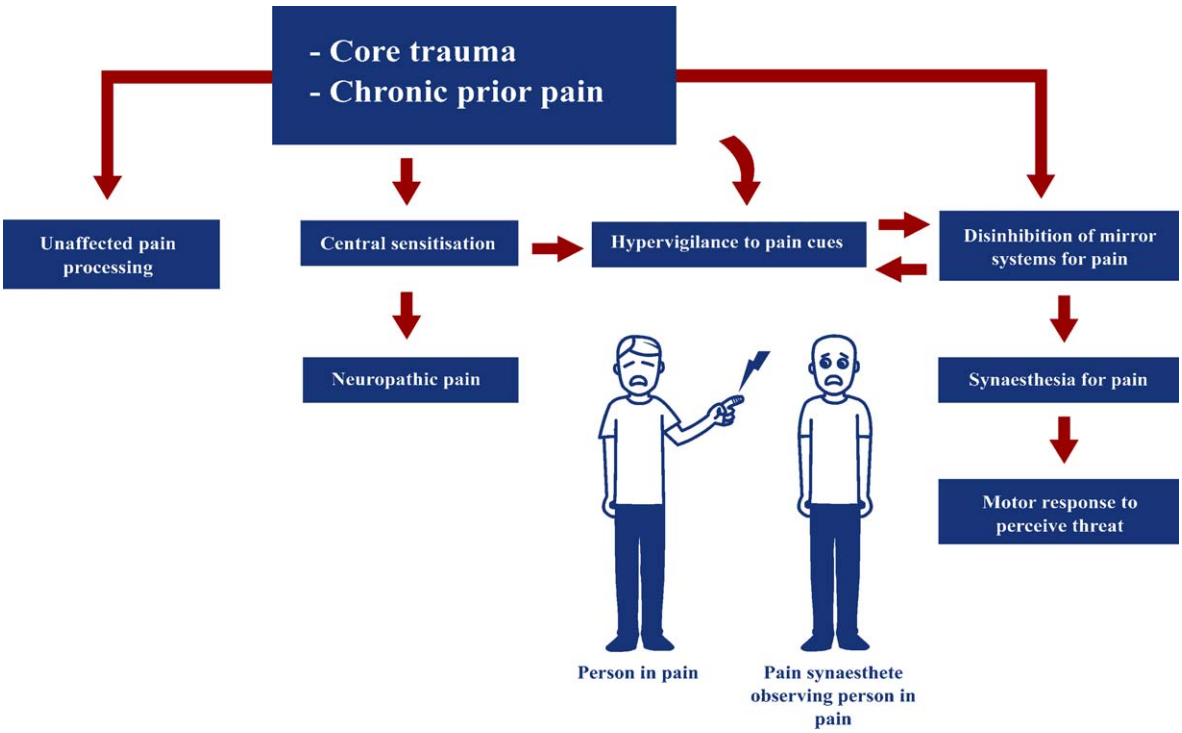

Fig. 1. Figure depicting proposed mechanisms involved in the production of synaesthesia for pain.

emotional state resulting in the affective experience of that state. In addition, empathy requires the ability to take the perspective of another person without confusing it with one's own perspective, as well as to maintain regulatory mechanisms that preserve boundaries between one's own and another's emotional state (Decety and Jackson, 2004, 2006). Without self–other distinction and the regulation of emotions, an affective response to another person's emotional state could be aversive causing distress or excessive emotional stimulation in the observer: this is particularly important in the context of modern life where we may experience the emotional states of others *en masse* (Decety and Lamm, 2006)! However, in synaesthesia for pain, there is no self–other distinction in the observation of pain in another person.

Automatic and unconscious simulation of another person's state may be facilitated by similar mechanisms found in the macaque brain (Gallese and Goldman, 1998). Almost two decades ago Rizzolatti et al. (1988) discovered mirror neurons (MNs); neurons that are active during both the observation and execution of goal-directed actions; in the inferior frontal gyrus (region F5) and the inferior parietal lobule of the macaque brain. These findings suggested that monkeys are capable of internally resonating their own representation of an action with an observed action. Brain-imaging research suggests that similar processes may also occur in the human brain. That is, the human inferior frontal cortex and inferior parietal lobe (classical mirror neuron areas) are also active when a person observes and when executes an action (Iacoboni et al., 1999; Rizzolatti et al., 1996). However, it is important to note that some authors argue there is little evidence to support the existence of mirror neurons in humans (see Hickok, 2009). Further, while it may be possible that overlapping brain activity (human mirror neuron system; MNS) includes mirror neurons (Gazzola and Keysers, 2009; Morrison and Downing, 2007), current investigatory techniques are unable to determine single cell activity.

In our paper, we will refer to research demonstrating human brain MNS-like behaviour as 'mirror system' activity. Mirror system activity describes the activation of commonly recruited brain areas when a person observes an action, or experiences an emotion or sensation and when a person executes the same action, or personally experiences the same emotion or sensation (Saarela et al., 2007). Further, mirror system activity in the human brain extends beyond the classical visuomotor mirror neuron areas found in monkeys (Molenberghs et al., 2009). For example, mirror systems have been suggested in emotion (Carr et al., 2003; Grosbras and Paus, 2006; Krolak-Salmon et al., 2003; Ruby and Decety, 2004; Wicker et al., 2003). More recently, evidence has emerged to suggest that mirror systems may even be involved in processing the sensation of touch (Avikainen et al., 2002; Blakemore et al., 2005; Keysers et al., 2004) and pain in others (e.g. Avenanti et al., 2005, 2006; Botvinick et al., 2005; Minio-Paluello et al., 2006; Morrison et al., 2004; Ochsner et al., 2008; Saarela et al., 2007; Singer, 2006; Singer et al., 2004).

Support of mirror system involvement in empathy has been found clinically in autistic spectrum disorders where social impairments are considered a primary deficit (Dapretto et al., 2006; Oberman et al., 2005; Théoret et al., 2005). Two studies have found that mirror system activity in response to hand movements is reduced in individuals with ASD compared with healthy controls (Oberman et al., 2005; Théoret et al., 2005). Oberman et al. (2005) found that while the mu wave, oscillations over the sensorimotor cortex, is suppressed in both real and observed action conditions in typically developing individuals, the mu wave is not suppressed in observed action in individuals with ASD. Using transcranial magnetic stimulation (TMS), Théoret et al. (2005) found that the excitability of the primary motor cortex in ASD individuals was significantly lower when observing action compared with healthy controls. In an fMRI study, Dapretto et al. (2006) found that unlike healthy controls, the observation and imitation of emotional expression failed to activate the inferior frontal gyrus in children with ASD. Moreover, the severity of social symptoms of children with ASD was strongly negatively correlated with activation in this area. Further support for the involvement of mirror systems and empathy has been found in psychopathy (Fecteau et al., 2008). Using TMS, Fecteau et al. (2008) investigated whether psychopathic

personality traits were related to mirror system function. Across all subjects, watching a needle penetrate a hand caused a reduction in TMS-induced motor-evoked potentials. However, this reduction showed a negative correlation with high scores on the cold-heartedness subscale of the Psychopathic Personality Inventory. This finding supports a relationship between psychopathy and motor empathy. It remains unclear whether psychopathy is related to other forms of empathy including empathy for pain.

5. Empathy for pain

The ability to identify pain in another is of clear evolutionary and adaptive value. Only once a potentially painful situation is determined, can the observer either escape from the situation (flight) or assist in helping behaviours (fight) to aid the person in pain (Saarela et al., 2007; Williams, 2002). Despite the importance of this ability, the potential neural mechanisms involved in empathy for pain have only recently begun to emerge. Recent research suggests that areas of the pain matrix activated in response to self-pain are similarly activated when observing potentially painful situations (e.g. Jackson et al., 2006a, 2005), when viewing pain-related facial expressions (Botvinick et al., 2005; Saarela et al., 2007), when signaling that another person is to be administered a painful stimulus (Singer et al., 2004) and when being presented with pain-associated words (Gu and Han, 2007b). However, it is not currently clear whether empathy for pain involves both the affective and sensory components of the pain matrix that are involved in processing self-pain. Nor is it clear that mirror systems are the only neural systems involved in this specific form of empathic processing.

Early fMRI investigations of mirror systems and empathy for pain suggested that only the emotional aspects of pain processing are shared between the self and the other. Singer et al. (2004) used fMRI to compare a participant's neural activity when a painful stimulus was administered to the participant and when they were told their partner was being administered the same painful stimulus. They found that self-pain caused increased activation across the entire pain matrix, yet other-pain activated only affective areas of the pain matrix, specifically the bilateral AI and the rostral ACC. In addition, participants who scored higher on empathy measures showed increased activation within these areas when thinking about their partner in pain. At the same time, Morrison et al. (2004) used fMRI to investigate hemodynamic response in the ACC compared to the SI in response to a pin-prick to the self (tactile stimulation) and when observing this same stimulation in another person (visual stimulation). In accord with earlier findings, it was found that the ACC was activated for both self-pain and other-pain while the SI was only activated in response to self-pain.

Jackson et al. (2005) detected ACC activation using fMRI in response to the observation of other-pain without the application of any noxious stimuli. In this study, participants observed a series of still images depicting hands and feet in everyday situations that were either pain-related or non-pain-related, and were asked to rate the level of pain associated with the image; for example, a hand near a door versus a hand caught in a door. Observation of painful experiences in others significantly activated the ACC, the AI, the cerebellum, and the thalamus bilaterally. Moreover, a cluster of activation in the right ACC showed a linear relationship to pain intensity ratings. In a later study using a similar design, they investigated the neural representation of taking the perspective of the self versus that of another in pain (Jackson et al., 2006a). They found that taking either perspective activated common areas of the pain matrix. However, whereas taking the perspective of the self generated the greatest and most widespread activation in this neural network including the ACC, insula proper, thalamus, and S2, taking the perspective of the other activated areas only associated with the affective processing of pain. Moreover, taking the perspective of the self generated higher subjective pain ratings and faster response times, demonstrating that different processes are involved in processing self- and other-pain.

Because of the importance of facial expression in social communication (see Williams, 2002), Botvinick et al. (2005) used fMRI to investigate the neural responses to viewing facial expressions of pain. Participants were asked to view video footage of facial expressions depicting moderate pain or no-pain. Participants were also administered painful and non-painful thermal stimulation in order to determine neural activation in response to a person's own pain. A region of interest (ROI) analysis was conducted in the dorsal ACC and bilateral insula, and found that these areas were more strongly activated in response to the experience of pain (thermal stimulation) compared to no-pain. Moreover, these areas were also significantly more activated in response to viewing facial expression of pain in others compared to no-pain.

Godinho et al. (2006) used somatosensory event-related potentials (SEPs) to investigate the effect of emotional modulation on pain intensity processing. To do so, participants were administered a direct painful stimulus and were simultaneously presented with pictures that were either pertaining to the body or not, and were either pleasant or unpleasant. They found that behavioural reports of pain intensity to the self were increased by the presentation of a picture depicting pain in another. In contrast, unpleasant pictures not depicting pain in another did not demonstrate this effect. SEP data showed that early latency responses were not affected by the emotional content of viewed images, while late latency responses demonstrated an accentuated response that was correlated with subjective ratings located in the right prefrontal, right temporo-occipital junction, and right temporal pole. Interestingly, they found no modulation in sensory areas, supporting prior findings that sensory processing does not modulate empathy for pain.

Collectively, these studies suggest that while there are mirrored neural representations in the experience and observation of pain, these may be restricted to affective understanding and not operational in sensory aspects of pain processing. This notion is not consistent with mirror system theory, which would predict activation of somatosensory areas, as seen in processing self-pain. In accord with this prediction (mirror systems), recent research using TMS, electroencephalography (EEG) and magnetoencephalography (MEG) suggests that empathy for pain may also involve the mirroring of the sensory qualities of pain (e.g. Avenanti et al., 2005, 2006; Bufalari et al., 2007; Cheng et al., 2008). This discrepancy is important in the context of understanding synaesthesia for pain as it could be argued that synaesthesia for pain is caused by heightened sensory processing during empathy for pain.

Avenanti et al. (2005) were the first to suggest that the sensory component of pain is mirrored during empathy for pain. Using TMS, while recording motor-evoked potentials (MEPs), patterns of corticospinal sensorimotor activation were observed in participants as they watched a needle pierce another's hand. Corticospinal patterns were studied because corticospinal excitability affecting upper limb muscles becomes inhibited in response to the application of a painful stimulus to one's own hand. Avenanti et al. found that the observation of a muscle being pricked evoked a reduction in MEP amplitude in the observer's hand, suggesting that the motor response to observing a needle pierce another person's hand is similar to when pain is experienced in oneself. Further, this response was found to be specific enough to distinguish between the pain intensity and location of the stimulus. For example, the application of a cotton bud to the observed hand did not cause a reduction in excitability nor did a needle piercing a foot. Moreover, subjective reports of the sensory qualities of observed pain were

correlated with the reduction in amplitude changes (inhibition) and not with emotional, state or trait empathy measures.

Because sensory activation had not previously been seen in empathy for pain literature, Singer and Frith (2005) suggested that sensorimotor responses may be caused by participant's attitudes to observed pain. That is, changes in sensorimotor activity may be caused by asking participants to *attend* to and rate pain experience in another. Subsequently, Avenanti et al. (2006) again used TMS to examine whether instruction-based (e.g. passive versus active) features influenced sensorimotor responses. Participants were asked to either passively observe the stimuli or to take a first person perspective to the experience of that pain. The authors were able to demonstrate the same pattern of sensorimotor inhibition seen in their earlier study regardless of the attitudes (1st person versus 3rd person) of the participants. A second experiment was conducted to investigate whether stimulus-based features (e.g. the intensity of the pain) influenced sensorimotor responses. Participants observed either needles pin-pricking or penetrating (i.e., 'flesh and bone') a body part. Sensorimotor inhibition was not found when participants observed pin-pricking needles, but was present when needles penetrated the skin, and this effect was correlated with pain intensity (i.e. sensory) ratings but not with pain unpleasantness (i.e. affective) ratings: the higher the pain intensity ratings, the larger the MEP inhibition. Further investigation by this group suggests that consciously determining the location and intensity of the observed pain caused a greater inhibition when the left hemisphere was stimulated (Minio-Paluello et al., 2006). This suggests that the left hemisphere may play a greater role than the right in processing the sensory features of pain.

These TMS studies demonstrate reduced corticospinal activity in response to observing "flesh and bone" pain images that correlate with subjective reports of sensory aspects of pain (pain intensity), but not with the affective qualities of pain (image unpleasantness). These results suggest that empathy for pain elicits mirroring processes that go beyond evaluating another's emotional state by mapping sensory features of the observed pain, such as intensity and location. These TMS findings are, however, unable to elucidate the neural locus of mirrored sensory representations in pain empathy. Two studies using EEG and MEG, respectively, have been more fruitful in determining mirrored sensory activation. First, Bufalari et al. (2007) examined the role of S1, using EEG to measure SEPs, while participants observed an actor's hand being administered painful and non-painful (tactile) stimuli. They found that the amplitude of activity in the S1, reflected in the P45 component, was significantly heightened in the painful conditions and positively correlated with subjective reports of the level of intensity of the pain the actor must have experienced (but not with unpleasantness). This amplitude was significantly reduced and negatively correlated with pain intensity ratings in the non-painful conditions, revealing that processing painful and non-painful stimuli modulates activity in the P45, implicating involvement of the primary sensory cortex in empathy for pain. These findings suggest that SI is not just involved in processing somatic sensation in oneself but in another as well, and therefore support the role of a sensory mirror system processing of aspects of pain. Further, using MEG, Cheng et al. (2008) found stronger somatosensory cortex activation (measured by suppressed somatosensory oscillations) when subjects watched pictures of painful situations compared to non-painful situations. Moreover, this accentuated suppression correlated with the perspective taking subscale of the interpersonal reaction index. These findings, consistent with previous TMS/EEG investigations, demonstrate sensory processing in empathy for pain; however, such somatosensory involvement in empathy for pain may not activate strongly enough to reach significance thresholds for fMRI.

Together these findings provide the first demonstration that a sensorimotor component specific to the observed pain experience is present in empathy for pain. Widespread activation of the pain matrix, including sensory regions, suggests that noxious input is not necessary to activate sensory areas of the pain matrix. Other studies have also identified activity in both affective and sensory areas of the pain matrix in the absence of direct painful stimulation; for example, when amputees were asked to imagine their phantom limb in a painful position (Willoch et al., 2000), when participants were asked to imagine pain to themselves (Ogino et al., 2007) and when people process pain-associated words (Gu and Han, 2007b).

6. Methodological influences on empathy for pain mirror systems

Models of empathy for pain involving mirror systems suggest that empathy for pain may not be an entirely automatic process that occurs in response to passive observation (de Vignemont and Singer, 2006). This may mean that inconsistent findings in pain matrix activation during empathy for pain may be due to methodological factors such as inconsistent instructions and stimuli between studies (Avenanti et al., 2006; Minio-Paluello et al., 2006). Possible differences include passive versus active observation, description of the stimuli, pain intensity of the stimuli, intensitionality of the pain stimuli, experience, perspective taking, and attention.

For example, instructions to imagine the sensory experience of observed pain may bring about a sensory representation of pain otherwise not seen in passive observation (Singer and Frith, 2005). Even the description of pain may influence empathy for pain processing as observed in touch in an fMRI study. McCabe et al. (2008) applied cream to participants' own forearms or to an observed forearm and described the cream as either 'rich moisturising cream' or 'basic cream'. This simple descriptive manipulation modulated participant's subjective reports of the pleasantness and richness of the perceived/observed touch, and fMRI activation within touch regions. It is also possible that observed pain stimuli must be particularly intense to bring about a sensorimotor response (Avenanti et al., 2006). This is consistent with the two TMS studies by Avenanti et al. (2005, 2006) reporting sensory activation in response to the presentation of deep needle penetrations, and with the fMRI study by Saarela et al. (2007) that found that pain intensity observed on the face of a conspecific is reflected in the strength of neural response. Activity in the pain matrix is most likely modulated by subjective ratings of the sensory qualities of observed pain. Intentionality of the observed pain may also affect mirror systems involved in empathy for pain. For example, in the mirror system for touch, activation of SI was dependent on the intentionality of the observed touch, unlike SII that was independent of the intentionality of the observed touch (Ebisch et al., 2008).

Prior experience also affects empathy for pain processing as demonstrated by Cheng et al. (2007) in a study investigating the perception of pain and the effect of expertise (acupuncturists) versus controls. In this study, inexperienced control participants demonstrated widespread activation of both affective and sensory areas of the pain matrix while observing a body being pricked by a needle. These areas included the anterior insula, anterior medial cingulate cortex, supplementary motor area, the somatosensory cortex and the periaqueductal gray. These regions were not activated in the expert group and their ratings of intensity and unpleasantness were significantly lower than in controls.

Lamm et al. have recently demonstrated that perspective taking may have an influence on empathy. Using fMRI, Lamm et al. (2007) presented participants with pictures depicting pain-related facial

expression following medical treatment. Participants were asked to either imagine how the person must feel or to imagine how they would feel in the situation and were either told that the medical treatment had or had not been successful. Both manipulations affected participant's behavioural responses and caused changes in fMRI activation. For example, empathic concern was higher when participants took the perspective of the other while personal distress was higher when participants took the perspective of the self. Further, different subregions of the left and right parietal cortex were active dependent on whether the perspective of the self or other was taken. Lamm et al. (2008) then recorded facial electromyographic (EMG) and electrocardiographic (ECG) activity to measure the psychophysiological effects of perspective taking during empathy for pain. To do this, participants were presented with videos of people having painful sonar treatment. Consistent with their earlier study, participants were asked to imagine how the person must feel or to imagine how they would feel in the situation. They found that activity of *M. orbicularis oculi* was modulated by perspective taking with matching facial expression only when imagining how they would feel if in the observed situation. Further, they found this was positively correlated with emotional contagion and perspective taking scores. In the most recent fMRI study by Lamm et al. (2009), the authors investigated the brain activation of participants asked to empathise with another person dissimilar to themselves. To do this, they compared responses to two groups of targets receiving a painful or non-painful stimulus. In the 'similar' group, the target responded to each stimulus as the participant would (pain to an injection versus no-pain to a touch from a Q-tip), while in the 'dissimilar' group, the target responded differently to the participants (pain to touch from a Q-tip but no-pain to an injection). In both conditions, participants' elicited activation in expected empathy for pain areas, such as bilateral ACC and insula. However, when the participants observed a painful stimulus to which the target responded neutrally, activation was seen in the dorsomedial prefrontal cortex and the right inferior frontal gyrus, regions that are involved in self–other distinction and cognitive control, respectively.

Attention also modulates empathy for pain. In two studies by Fan and Han (2008) and Gu and Han (2007a), participants observed photos or cartoons of hands in painful and neutral scenarios and were asked to rate pain intensity or to count the number of hands in the picture. By asking participants to respond to the pictures in two different ways, the authors were able to modulate task demands: while the former task required participants to attend to pain, the latter required their attention to be drawn away from it. Using fMRI, Gu and Han (2007a) found that pain intensity ratings of painful pictures produced increased activation in ACC/paracingulate and the right frontal gyrus. This pattern of activity was not seen when participants were asked to count the number of hands in the picture, suggesting that empathy for pain is influenced by attention to pain cues. They also found that stimuli of different levels of realism produced differential patterns of cortical activity: the bilateral inferior frontal cortex and the right insula/putamen were activated for pictures, and the left parietal cortex, the postcentral gyrus, and the occipitotemporal cortex were activated for cartoons. In addition, ACC activation was weaker in response to cartoons than to pictures. Using event-related potentials to provide information on the temporal dynamics of empathy for pain, Fan and Han (2008) found that differential activity between painful and neutral stimuli involved an early response around 140 ms over the frontal lobe, and a late response after 380 ms over central-parietal regions. While the early response was modulated by contextual reality, the late response was affected by top-down processes (e.g. attention). Moreover, the early ERP response was correlated with subjective reports of the pain intensity thought to have been experienced by the model, and the level of unpleasantness that was felt by observing the stimuli. These results suggest that short-latency (early) ERP responses are associated with automatic, bottom-up emotional sharing processes, whereas long-latency (late) ERP responses are associated with controlled, top-down processes related to cognitive evaluation.

7. Self- and other-pain are just different?

While methodological differences may have caused discrepancies in previous findings, it is also possible that the differences observed indicate that self-pain and other-pain are unique experiences that require the recruitment of unique regions. This would be consistent with the notion that one must differentiate between self- and other-processing, otherwise empathic response and personal distress would become confused (Decety and Grezes, 2006). Jackson et al. (2006a) propose that differences in activation sites are due to the self versus other distinction. The crucial factor in the differences in mirrored activation of pain therefore depends on who is actually experiencing the pain. This is most clearly demonstrated in the ACC and IC where evidence suggests a caudal-rostral organisation of activation, with more activity in caudal regions for perception of self-pain, while there is more activity in rostral regions for perception of other-pain.

The self–other distinction may be explained through an affective-sensory continuum (Jackson et al., 2006b) that highlights different processes for perceiving pain in oneself or in others, and how self- or other-pain is mapped in the mirror systems for empathy for pain (Ochsner et al., 2008). For example, perceiving self-pain includes sensory information such as location and intensity. As this sensory input is not provided when perceiving pain in others, observed perceptual or social cues such as facial expressions may be more important. Using fMRI, Ochsner et al. (2008) compared brain activity during the application of noxious stimulus (heat), to participants with activation during observation of video footage of other people being injured. Consistent with previous research, common areas of activation included the ACC and AI. Unique areas of activation in the self-pain condition included the anterior insula and mid-insula, whereas unique areas found in other-pain included frontal, premotor, parietal and amygdala regions. These regions are associated with interoception and nociception, and in emotional learning and processing social cues, respectively. Further, trait anxiety was correlated with activity in the rostral lateral prefrontal cortex in other-pain but not self-pain. These results suggest that there are both common and unique areas of activation in processing pain in the self and in others, but the main difference is the "purpose" for which these areas are recruited: the translation of the experience of pain (Ochsner et al., 2008).

8. Future directions of empathy for pain research

Overall, it is apparent that there are differences in processing self- and other-pain. To reconcile these issues, new methodologies and technologies should be explored. For example, neuro-imaging data should be investigated at the individual level. While research in this area may accurately report mirror system activity, it may also be the result of averaging together what are actually two distinct responses to observation and execution. To illustrate, fMRI data is almost always analysed at the group level after each subject's data has been smoothed. This may pool together activation that may in fact be distinct and not present at the individual level (Gazzola and Keysers, 2009; Morrison and Downing, 2007). Morrison and Downing (2007) addressed this issue in their key paper investigating to what degree cingulate areas involved in processing self- and other-pain share the same

neural basis. Participants underwent fMRI as they experienced self-pain (a mildly painful prick is applied to the finger) and as they observed a video of a model being applied a prick to the finger (other-pain). The authors found that group-averaged data showed overlapping activation in selected ROI in the cingulate and clear activation peaks for self- and other-pain. However, at an individual level, not all subjects demonstrated overlapping activation. Further, in individuals who did show an overlap between self- and other-pain, the location was between self and other peak pain responses. These results suggest that the finding of overlapping neural systems in group-averaged data does not necessitate that these areas overlap in individual subjects.

Using fMRI, Gazzola and Keysers (2009) investigated if similar findings were present for mirrored representations of actions. The authors measured brain activity of participants as they observed movies of hand actions and then executed similar actions. Comparative to Morrison and Downing (2007) findings, Gazzola and Keysers (2009) found that in individual data, overlapping neural activity was reliably seen in both observed and executed conditions. Regardless, the authors' urge future research to investigate group data at the individual level, in addition to the group level when investigating mirror systems.

It has also been suggested that interaction effects between activated regions of the brain should be examined in order to determine if key areas differentially respond to self-pain versus other-pain; that is, if an area is modulated by the target (self/other) of the pain (Ochsner et al., 2008). For example, Singer et al. (2004) found that self-/other-pain differentially activated the somatosensory cortices and the left lateral occipital cortex, respectively. Another methodology that could be explored is functional connectivity analysis, which rather than just demonstrating average activity like fMRI, would instead detect patterns of communication within the brain. The first functional connectivity analysis of empathy for pain was able to determine that the ACC and AI are part of distinct functional networks (Zaki et al., 2007).

It is also important to explore factors other than mirror systems that may be involved in empathy for pain. For example, how pain perception in oneself is affected by one's own empathic state towards another. In a recent study, a thermal stimulus was applied to participants while they watched video footage of a neutral cityscape video (Loggia et al., 2008). Participants were then presented with either a video of an actor telling a sad story that elicited a high-empathic response, or a story whereby the participant had low empathy for the actor. Participants received thermal stimuli again while they watched footage of painful/non-painful thermal stimuli being applied to the actor. They found that participants who were presented with footage of the actor for whom they had a high-empathic response reported a higher intensity and unpleasantness of the stimulus compared with the low empathy condition. It is therefore not only the observation of pain in another but empathy for another that modulates the perception of pain: the more you empathise with another, the larger the increase in pain sensitivity.

Empathy may be influenced by contextual factors such as familiarity or similarity to the observed person in pain. This has been seen in non-human animal studies where showing pain in a non-conspecific has no effect upon a chimpanzee (Mirksy et al., 1958), in rodents where emotional contagion is stronger between cagemates than strangers (Langford et al., 2006), and in monkeys where an empathic response is modulated by familiarity with the monkey in pain (Masserman et al., 1964). This is consistent with evolutionary theories that predict that empathy would be biased towards those with whom one is familiar or with whom one has a positive relationship (de Waal, 2008). Gender differences have also been found in empathy for pain (Han et al., 2008; Yang et al., 2009). In a re-analysis of the first ERP study in this area, females, but not males, were found to demonstrate early activity that correlated with subjective ratings of other-pain and self-unpleasantness and an enhanced long-latency response (Han et al., 2008). An investigation into EEG mu-suppression patterns in empathy for pain found that although both genders exhibited sensorimotor activity, females showed stronger mu-suppression to painful stimuli, and this was correlated with behavioural measures (Yang et al., 2009).

Clinical populations may be vital to reconcile discrepancies between pain representations in self versus other. One potentially important population may be patients with congenital insensitivity to pain (CIP) who, despite having a lack of pain experience, do not demonstrate impaired empathy when observing pain in others (Danziger et al., 2006). In a recent event-related fMRI study, Danziger et al. (2009) found that while patients with CIP have never experienced pain, when observing body parts in painful situations or pain-related facial expressions, normal activation is seen in known areas involved in empathy for pain: the mid-cingulate cortex and anterior insula. The authors also found that, unlike controls, empathy trait scores in participants with CIP correlated with activation in anterior and posterior midline structures. These structures may therefore be necessary for emotional perspective taking and for understanding feeling in another person, even in the absence of any experience of self-pain. Another clinical population that may reconcile discrepancies are patients with alexithymia, a disorder in which patients have difficulty recognizing and expressing their emotions. Research on empathy for pain in this clinical population has shown decreased pain judgments, empathy scores and atypical neural activation compared to controls (Moriguchi et al., 2007). Finally, investigation into empathy for pain in pain synaesthetes may further our understanding of the mechanisms underlying empathy for pain.

9. Phantom limbs and mirror systems

We propose a framework in which synaesthesia for pain may be produced post-trauma in amputees. To date, the highest recorded number of pain synaesthetes has been found in amputees who experience phantom pain (see Giummarra and Bradshaw, 2008). Traditionally, synaesthesia for pain in amputees has been grouped as an emotional trigger, a widely accepted trigger of phantom pain (see Flor, 2002; Giummarra et al., 2007; Katz, 1992). Examples of emotional triggers of phantom pain include talking about the phantom, tiredness or being "run down", loud noises, fright, surprise, "strong emotions", stress, anger, depression, and frustration (Giummarra and Bradshaw, 2008; Giummarra et al., 2006). Examples where synaesthesia for pain has been considered an emotional trigger of phantom pain include Hill et al. (1996), who reported a patient whose phantom pain was "emotionally triggered" by the observation of a leg injury on a television show. Another example is that by Wilkins et al. (2004) who reported a similar case of phantom pain triggered by watching a horror movie. While these examples of synaesthesia for pain have been categorised as being emotional triggers, we suggest this is unlikely. Emotional triggers of phantom pain, such as stress, cause increased cardiovascular activity (e.g. heart rate, systolic blood pressure: Angrilli and Koster, 2000) and although emotional distress may trigger mirror systems disinhibition, emotional distress would be unlikely to produce synaesthesia for pain for two reasons: first, synaesthesia for pain is generated by observed or imagined pain in another and, second, synaesthesia for pain results in activation of the action system producing pain behaviours such as startle or vocalization (Melzack and Wall, 1965).

Phantom pain itself is considered to be related to peripheral and central changes (Flor, 2008). As discussed, earlier pain experiences can cause changes in the central nervous system that may then affect later pain experiences; for example, through central

sensitisation (for a review, see Coderre et al., 1993; Melzack et al., 2001). As such, in amputees, pre-amputation pain is a risk factor for phantom pain post-amputation (Jensen et al., 1985). Hanley et al. (2007) found that the intensity of pre-amputation pain predicted the intensity of phantom pain up to two years post-amputation. Comparatively, the intensity of acute phantom pain immediately following amputation predicted chronic phantom pain up to one year post-amputation. These findings suggest that the intensity of pre-amputation pain and persistent acute pain immediately following amputation may make amputees susceptible to long-term pain (Hanley et al., 2007).

Phantom pain may also manifest as a result of the development of somatosensory pain memories from pain in the limb prior to amputation (Flor, 2008). Katz and Melzack (1990) and Giummarra et al. (unpublished manuscript) have reported the incidence and nature of somatosensory pain memories in amputees; however, Flor (2008) proposes that phantom pain may be more closely related to the presence of implicit memories of past pain. While pain immediately before the loss of a limb may be strong enough to influence phantom pain in amputees (Hill et al., 1996; Nikolajsen et al., 1997) and to cause the development of post-traumatic stress disorder (Schreiber and Galai-Gat, 1993), we do not propose that synaesthesia for pain results from the observation of pain in another person triggering a pain memory in the observer. Although synaesthesia for pain could be interpreted as the recall of a somatosensory memory in response to the visual cue of another in pain, it is likely that mirror system dysfunction affects residual neural representations of the intact body.

Brugger et al. (2000) proposed that mirror systems may be involved in the perception of phantom limbs when they described the case of AZ, a congenital amputee who experienced vivid phantoms of all four missing limbs. Clearly, phantom perception in this case did not result from remembering one's body parts, or comparing between body parts. They proposed that the ability to match perception with action, paired with the ongoing observation of others using their limbs, could even, in the absence of limbs, activate the neural architecture involved in that limb's innate representation, thereby triggering the experience that the limb is present. This proposal has since been supported by the identification of motor cortex activity in the paralysed limb of participants with brachial plexus avulsion, in response to visual images of a virtual hand creating the sensation of movement in the limb (Giraux and Sirigu, 2003).

Brugger et al. (2000) proposal does not go against reorganisation of sensorimotor systems which is thought to occur following amputation (Flor et al., 1995; Ramachandran et al., 1992). Using EMG, Reilly et al. (2006) found distinct activity in stump muscles in response to making specific phantom movements in upper limb amputees. Using TMS to simultaneously investigate the cortical representation of phantom movement and muscle activity in the stump, Mercier et al. (2006) found that stimulating the M1 region corresponding to the hand in upper limb amputees created the sensation of movement in the missing hand, as well as muscle activity in the stump. Together these results suggest that the missing limb continues to be represented in its original location of the cortex, together with the extended representation of stump muscles (Reilly and Sirigu, 2008). These findings support the suggestion that reorganisation following limb loss may only affect muscle maps per se, and not motor command maps. While the former are involved in limb movement by establishing muscle synergies, the latter produce actual motor commands (Reilly and Sirigu, 2008). The preservation of motor command maps is also evident in the rapid restoration of the hand's neural representation and motor use following hand transplant (Giraux et al., 2001).

The persistence of motor command maps is crucial to the hypothesis of mirror system involvement in phantom limbs. While sensory input or proprioceptive feedback may shape the brain's representation of the body as early as in utero, evidence suggests that it is strengthened early in life through bodily experience and visual input (Price, 2006). Observation of others in action may modulate the mirror system thereby providing a mechanism by which congenital amputees experience phantom limbs (Brugger et al., 2000; Price, 2006), and a potential mechanism for the perception of phantom limbs in acquired limb loss (Giummarra et al., 2007). The maintenance of a phantom limb through mirror system activity may be advantageous for the process of empathy, as it provides a mechanism in which the actions of others can be understood. Current research, such as that investigating MNS for touch, suggests that self-body representations in cortical regions may also allow reference for the perception of other bodies. Indeed, when investigating visuo-tactile neurons in monkey parietal cortex, Ishida et al. (2009) found that own and other body parts are represented similarly. In pain synaesthetes, mirror system activity may be disinhibited causing a person to experience pain in their phantom limb when they observe pain in another. Prior trauma may be the mediating factor of this disinhibition causing sensitisation to pain and hypervigilance to pain cues (Giummarra et al., 2008b).

Ramachandran and Rogers-Ramachandran (2008) examined the activation of the sensory mirror system in an amputee when observing touch in another and investigated why this does not result in an actual sensation of touch, as seen in synaesthesia for touch (see Blakemore et al., 2005). The authors proposed that either (a) the observation of touch alone does not activate sensory mirror neurons past the threshold necessary for conscious experience, or (b) although sensory mirror neurons for touch are activated in the observation of touch, a "null signal" is sent to indicate that the observer is not actually being touched, inhibiting its full activation. Using the mirror box paradigm, the amputees experienced touch in their phantom hand in response to observation of touch in a volunteer's intact hand. This perception was interpreted as reflecting the activation of the mirror system for touch, but without sensory input to modulate the experience. This would support the hypothesis of the occurrence of a null signal preventing the sensation of touch through the inhibition of the mirror system when we observe touch in another person. This evidence suggests that in the absence of tactile sensation to provide a null signal for touch, a person is able to experience the sensation of touch through observation alone. However, as hypothesis (a) was not tested, the real mechanism behind mirror system dysfunction in amputees remains unclear.

Similar mechanisms may be involved in synaesthesia for pain. Whether or not the mirror system for pain is disinhibited or affected by the absence of a vetoing system is unknown. However, as we report two other clinical cases, the hyperalgesic man (Bradshaw and Mattingley, 2001) and a woman who experienced a traumatic childbirth (Giummarra and Bradshaw, 2008), of synaesthesia for pain in non-amputees, we suggest vetoing is not always the mechanism involved. We propose that mirror systems are involved in the direct mapping of the experience of others onto the site of neuropathy, or the phantom limb, and urge future research to consider the interplay between vision and sensation, particularly in patient populations.

10. Future research for synaesthesia for pain

Synaesthesia for pain is a new condition about which little is known. Empathy for pain mechanisms, while inconclusive in non-patient populations, may be at play, together with mirror system disinhibition in producing the experience of synaesthesia for pain. Future research should investigate potential mechanisms behind synaesthesia for pain, which appears to be an abnormal experience

of empathy for pain. A greater understanding of empathy may contribute towards therapeutic interventions in clinical populations where empathy or mirror systems do not function normally, as has been suggested in ASDs (Dapretto et al., 2006; Oberman et al., 2005) and in psychopathy (Agnew et al., 2007; Fecteau et al., 2008).

It is unclear how frequent synaesthesia for pain is in amputees, and whether this differs between groups, for example, sudden trauma amputees versus amputees who experienced chronic pain before amputation. Further, the question of how frequent synaesthesia for pain is in other trauma populations, such as traumatic childbirth or third-degree burns victims, is also unclear at present. Other qualitative information relevant to synaesthesia for pain includes details about the experience such as whether the pain observed needs to be specific to the location of past personal injury to cause synaesthesia for pain; whether the identity of the person in pain modulates the experience; whether people who report this experience also demonstrate other forms of synaesthesia; and finally whether there is a relationship between synaesthesia for pain and post-traumatic stress disorder.

A further point of interest is the role of mirror systems in pain synaesthetes. Investigation should be undertaken to clarify whether the pain matrix is activated in pain synaesthetes whilst experiencing pain synaesthesia; if both the affective and sensory areas of the pain matrix are activated in synaesthesia for pain; and if this cortical activation pattern is different to that operating in non-pain synaesthetes. However, as it is not yet understood whether mirror systems alone are sufficient for empathy to take place (Ochsner et al., 2008), and given that there may be additional processes that occur following mirrored representations that allow for an understanding of more complex social cognition (Beer and Ochsner, 2006; Decety and Jackson, 2004; Singer, 2006), factors that modulate the synaesthetic experience of pain, such as similarity or familiarity to the person observed in pain, need to be determined.

Another potential line of investigation is the examination of which factors may predispose people to synaesthesia for pain. Contributing factors may include behavioural traits such as empathy and anxiety. Identifying risk factors may assist in early identification of trauma patients who are at risk of developing synaesthesia for pain. Finally, potentially therapeutic measures such as rTMS should be investigated to determine their efficacy in relieving the experience, and thereby increasing the quality of life for those that experience synaesthesia for pain.

11. Conclusions

To date, research into the complex processes involved in processing pain observed in another person has generated conflicting results. We have presented an abnormal form of empathy for pain, synaesthesia for pain, where people experience "real" pain when they observe or imagine pain in another. We have proposed that the most likely explanation for this experience is a disinhibition of mirror system function, which may underlie normal empathy for pain processing that has come about through prior pain experience. We emphasise that mirror system function alone may not be able to fully explain empathy or synaesthesia for pain. Through investigation of such "abnormal" cases as synaesthesia for pain a greater understanding of empathy for pain, or more broadly empathy, may be obtained.

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