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fMRI exploration of the cerebral mechanisms of the perception of pain in others via facial expression

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fMRI exploration of the cerebral mechanisms of the perception of pain in others via facial expression

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Résumé

La douleur ressentie entraine des réactions de différents ordres : physique, neurologique, comportemental. L'expression de la douleur sur un visage constitue une de ces réactions, d'ordre comportemental. Cette expression faciale intègre les éléments caractérisant la douleur ressentie et il est possible de l'analyser en tant qu'observateur extérieur. Les travaux d'imagerie cérébrale étudiant la réaction du cerveau à la perception d'une douleur chez autrui ont mis en lumière un chevauchement entre les régions du cerveau réagissant à une douleur personnellement ressentie et celles réagissant à l'observation d'une expression de douleur chez les autres. Dans la première étude présentée ici, la réaction du cerveau à l'expression de la douleur chez autrui a été analysée en établissant dans quelle mesure l'intensité plus ou moins forte de la douleur exprimée pouvait moduler cette réaction. Les résultats de cette étude indiquent que la perception de la douleur chez autrui ne concerne pas seulement certaines régions du cerveau réagissant à la douleur personnellement ressentie mais aussi des régions habituellement impliquées dans le système des neurones miroirs (MNS; « human mirror neuron system ») ainsi que dans des régions associées à la Théorie de l'esprit ('Theory of Mind', ToM; ou « mentalizing »). En outre, ce travail montre que l'implication relative de ces différentes régions varie selon que la personne évalue la signification affective de l'expression – la magnitude de la douleur – ou qu'elle discrimine les composantes motrices de l'expression – les mouvements faciaux. Une deuxième étude a donc été réalisée, s'appuyant sur un paradigme combinant l'observation et l'exécution pour vérifier et confirmer la « réponse miroir » observée dans la première étude et pour examiner plus en détail les différences apparentes entre la résonance émotionnelle et la résonance motrice. En confirmation de la première étude, il a été établi que ce sont différentes régions du cerveau qui sont impliquées dans les réactions à l'expression de la douleur selon qu'elles relèvent de la résonance émotionnelle ou de la résonance motrice. En somme, ces résultats montrent que la perception de la douleur chez autrui est un processus complexe qui met en jeu un chevauchement entre les régions réagissant à une douleur personnellement ressentie et à une douleur constatée chez autrui, ainsi que les phénomènes de résonance motrice (« mirroring ») et de « mentalizing », processus plus généraux de la cognition sociale.

Mots-clés : imagerie par résonance magnétique fonctionnelle (IRMf), empathie de la douleur, système de neurones miroir humain, mentalisation, cortex cingulaire antérieur, gyrus frontal inférieur, lobule pariétal inférieur

Abstract

The pain experience provokes several responses – physical, neural, behavioral. The facial expression of pain is one such behavioral response: it encodes the subjective experience of pain and, as observers, we can decode it. Neuroimaging studies looking at the brain response to the perception of pain in others have identified overlap between brain areas active for the experience of self-pain, and those active during the observation of pain in others. In the first study described below, the brain response to pain in others was investigated using a paradigm that investigated how the intensity of the perceived pain modulated the brain response. The results of this work indicate that the perception of pain in others involves not only certain brain regions involved in self-pain, but also regions previously implicated in the human mirror neuron system (MNS), as well as areas underlying Theory of Mind (i.e. mentalizing). Further, the relative contribution of these areas depended on whether the subject is evaluating the affective meaning of the expression – the pain magnitude – or if they are discriminating the motor components of the expression – the facial movements. A second study was thus designed, using a combined observation and execution paradigm, to confirm the mirroring response observed in the first study, as well as to further explore the hypothesized difference between emotional and motor mirroring. Similarly to the first study, it was found that different brain regions are responsible for mirroring for emotional, versus motor, content of the observed pain expressions. Taken together, these results reveal the perception of pain in others to be a complex process that involves overlap between self and other affective pain areas, as well as mirroring and mentalizing – more general processes of social cognition.

Keywords: functional magnetic resonance imaging, pain empathy, human mirror neuron system, mentalizing, anterior cingulate cortex, anterior insula, inferior frontal gyrus, inferior parietal lobule

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List of Abbreviations

ACC	anterior cingulate cortex
aINS	anterior insula
aIPS	anterior intraparietal sulcus
AMY	amygdala
CMA	cingulate motor area (monkey)
CMZ	cingulate motor zone (human)
FACS	Facial Action Coding System
IFG	inferior frontal gyrus
INS	insula
IPL	inferior parietal lobule
IPS	intraparietal sulcus
MNS	mirror neuron system
mOFC	medical orbitofrontal cortex
mPFC	medial prefrontal cortex
MT	movement task (in context of Articles 1 and 2)
MTL	mentalizing system
NFR	nociceptive flexion reflex
pACC	posterior anterior cingulate cortex
PFC	prefrontal cortex
pMCC	posterior middle cingulate cortex
PoCG	postcentral gyrus
PrCG	precentral gyrus
pSTG	posterior superior temporal gyrus
pSTS	posterior superior temporal sulcus
PT	pain task (in context of Articles 1 and 2)
TMS	transcranial magnetic stimulation

For my family.

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Chapter 1: Introduction

1.1. A pain story

Imagine the following scenario: You and a friend are on vacation somewhere warm, close to the beach. Being students, you are sharing a room in a cheap motel. Due to a lack of space in the tiny room, your friend has placed her suitcase on the floor in one corner, underneath the television, which is anchored onto a metal frame jutting out from the wall at about head-height. One morning as you are getting dressed, your friend is bent over under the television, rummaging through her suitcase for her bathing suit. Suddenly you hear her cry "Oh!"

You turn quickly to look: she's now standing with her right hand pressed to the top of her head, her gaze fixed on the sharp corner of the metal TV stand. Her eyes are scrunched in a squint, her nose is drawn up and wrinkled, and her teeth are bared in a grimace.

'Oh!" you say, feeling alarmed, "I was afraid that would happen! It must really hurt! Are you okay?"

Your unlucky friend has just experienced a noxious stimulus – a painful bump of the head against a hard, sharp object. Although she does not explicitly state "I have bumped my head on the TV stand and am now experiencing pain", you not only have figured out what physical event took place, but you are also aware of how your friend feels, internally, in response to this event. There are several potential sources of information regarding the event, such as your pre-existing awareness of the threat posed by a sharp object in the room, and perhaps the sound of the bump. However, as a social creature, your main source of information about what has happened to your fellow human, and her reaction, is her behavioral response to it: her vocalization – "oh!", her hand rubbing her head, and last, but definitely not least, her facial expression, which identifies the emotional component of her response as negative and withdrawing. Once you realize what has occurred, you may also have a memory of bumping your own self on a sharp corner and be able to reference this memory for further knowledge of what your friend may be feeling. All of these things contribute to your understanding of her pain.

Now, rewind back to the moment you hear your friend say "Oh!", and consider a different scenario. When you turn to look at her, she's standing with her hand pressed to her head, as before, but this time her face is different: her eyes and mouth are open, but her lips and nose are relaxed rather than drawn up and wrinkled, and her teeth are not showing.

"Oh!" you say, feeling no alarm this time. You look down to see, in her other hand, the sunglasses she was certain she'd lost in the ocean while swimming in the ocean the day before. "You weren't wearing them after all!"

In this case, the emotional content is clearly different, and it is possible to realize this simply via the expression on your friend's face. Even without realizing the exact cause of the expression, the emotional content is clearly not negative or withdrawing, and thus in this second version, the first visual information you receive tells you a different story about what your friend has experienced and is feeling, compared to that of the first scenario.

* * *

The above story is an example of pain communication and pain empathy. There are many ways for one person to transmit to another the message that they are suffering. Verbal cues can be the most obvious – e.g. "I hit my head on that damned TV corner!" Non-verbal cues can be equally so, particularly if the observer witnesses the triggering event and therefore has access to information about the noxious stimuli. However, even if this is not the case – for example, when a doctor examines a crying infant but does not yet know if the problem is an earache or a stomachache – the message can be easily transmitted via vocalizations and physical behaviors.

Regardless of the communication channel, there are two stages of pain communication: encoding and decoding. The sufferer expresses – 'encodes' – their subjective experience of pain through a facial expression and then the observer then interprets – 'decodes' – this expression. Detecting pain in others may on the surface appear to be a simple process, but as one form of social cognition, it has many component steps. It requires perceiving the emotional state of another by reading behavioral cues, such as facial expressions, and interpreting them as pain rather than another emotion, such as surprise, disgust, or anger. It also requires the observer to understand that the pain experience belongs to the other, and not

to the self, and that the other has their own mind with thoughts, beliefs, and feelings that may or may not be shared by the observer. Thus, it is in fact a sophisticated and complex feat of social cognition. As such, it involves multiple brain regions, and evidence suggests it utilizes networks involved in the perception of pain in the self, as well as those involved in theory of mind and emotional mirroring.

Pain empathy is important, as it has many implications: the information that someone feels pain can help the observer avoid a threat, or it can provoke the observer to provide aid. In many situations involving acute pain, however, the observer is not explicitly told of what is happening. In this case, how does the observer know the subject feels pain? Moreover, how is pain detected in those who cannot verbalize what they are feeling, such as infants, older patients with dementia, or patients who are otherwise incapacitated and unable to communicate verbally? Obviously, the perception of pain in others via non-verbal routes can be critical.

1.2. Objectives and general outline

The general objective of this manuscript is to contribute to the understanding of pain communication, specifically the decoding component. In Chapter 1, the introduction will begin with a brief description of the perception of pain in the self and how self-pain leads to, and is encoded by, the facial expression of pain. Next, it will continue into a discussion of pain empathy and the perception of pain in others and provide a background for the original research described in the following two chapters.

Chapter 2 is a published manuscript describing the first neuroimaging study, which examines pain decoding. Specifically, this work investigated how the brain response to the facial expression of pain is modulated by the intensity of the observed pain, and how the brain perceives the affective content of a pain expression, versus the physical movements of the face.

Chapter 3 is a published manuscript describing a second neuroimaging study, which investigated the overlap in brain representations for both observed and executed pain expressions. The design of this second study was intended to both reproduce and extend the findings of the first study.

Chapter 4 is a discussion of the results of the two imaging studies. First, it will summarize the findings from the two studies, and address similarities and differences in their findings. Then it will address the results in the context of the literature on pain empathy. In light of results that implicate both neural systems for pain in the self as well as more general systems involved in social cognition, the discussion will then broaden to include the concepts of motor mirroring and mentalizing, and how the work presented above fits into a more general model of social cognition that incorporates these two components. The general idea of overlapping cognitive processes for both self- and other- experiences – pain, specifically – will be the core theme of this discussion. Next, the discussion will address some limitations of the methods and alternative interpretations of the results. Finally, possible future directions for this work will be explored, as well as the contributions it could offer to the understanding of pathological conditions in which perception of emotion in others is abnormal.

1.3. Pain in the self (execution)

Before discussing how the pain experience is conveyed to, and perceived by another person, it is helpful to take a brief look at the pain experience in the self: what is happening, physiologically, during an acute pain experience? This section will briefly and simply introduce the concept of pain, describe the pathways for the perception of acute self-pain from peripheral nociceptors in the skin to the spinal cord and brain, and give an overview of pain responses and their underlying brain mechanisms, particularly in regard to the facial expression of pain.

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP, 2012). Ideally, pain is an acute experience that warns the sufferer of danger, so that one may distance oneself from the danger, return to a safe position and thus end, or at least reduce, the pain. Anyone who has ever bonked their head on a sharp corner knows how unpleasant, attention-grabbing, and immediate the sensation can be. Acute pain demands and directs attention, more so than any other physical sensation. Prior to bumping her head, your friend was rummaging through her suitcase looking for her swimsuit; when she located it, perhaps for a few seconds she was

aware its slippery texture, but once she had it in hand and began to get to her feet, it is likely she was no longer consciously attending to this aspect of her sensory experience. Furthermore, the mechanoreceptors in her skin responsible for carrying the sensory input generated by the gentle contact with the suit's material adapt to this contact and become less responsive. If she were to hold her hand still, she would quickly become unable to feel the material much at all. The forceful contact of her head to the television corner, however, triggers different types of mechanoreceptors which do not adapt so quickly to continuous stimulation. Likewise, the sensation of this contact demands much more of her attention, and her conscious experience of it persists for a much longer time. Unpleasant as it may be, this fact is quite useful; digging through one's suitcase for prolonged periods of time causes no harm, whereas repeated trauma to the head certainly will.

Pain can be described in terms of two dimensions – sensory and affective. The former refers to the sensory aspects of the pain: when it occurs (right…*now*), where it occurs (the scalp), its quality (sharp, aching), and its intensity (strong). The latter refers to the hedonic qualities of the pain (very unpleasant), the emotional arousal it causes, and its motivational effects on behavior (i.e. attentional orientation and motor facilitation). Together, these create the subjective feeling that this sensation is negative, salient, and requires attention and action. These two dimensions, while closely linked, are nonetheless distinct; this can be observed in subjective reports about both clinical and experimental pain, as well as in experimental protocols where the two dimensions are modulated independently of each other (Horn et al., 2012; Price et al., 1987; Rainville et al., 1999) As will be discussed later in this introduction, this distinction is also reflected in brain activity underlying the pain experience (Danziger et al., 2006; Hofbauer et al., 2001; Kulkarni et al., 2005; Rainville et al., 1997).

Finally, it is important to note that classically described nociceptive pathways do not necessarily provide a direct link between a given noxious stimuli and experienced pain, for several reasons. Noxious stimuli do not always trigger nociceptive pathways and the subjective feeling of pain. Lesions or other interruptions to these pathways do not always disrupt or halt the pain experience. Factors other than the characteristics of stimuli can affect both nociception and the subjective experience of pain; the intensity and type of the noxious stimulus is only one component in the creation of the pain experience: attention (and distraction), expectations, context, individual differences in pain sensitivity, and physiologic

mechanisms also contribute. While a more in-depth discussion of these points is beyond the scope of this manuscript, the important concept they illustrate is that pain is not always the equivalent of nociception, and vice-versa. Ultimately, the subjective experience of pain is comprised of both physiological and psychological elements, all of which are subject to various internal and external factors: a given noxious stimulus could be perceived as less painful when a subject is distracted by a cognitive task or a competing sensory stimulus, or more painful when the subject is primed with a negative emotional cue. The target of this manuscript is one type of visible evidence of the subjective experience of pain: the facial expression of pain. Non-visible evidence of the subjective experience of pain will not be addressed, nor will be objective measures such as activation of the peripheral nervous system (i.e. as detected via conductive skin response or heart rate) or spinal reflexes such as the nociceptive flexion reflex.

1.3.1. Body to brain: pain perception via afferent pathways from periphery to brain

1.3.1.1. Periphery to spinal cord: nociceptors to spinal tracts

There are five different afferent pathways that carry information about noxious stimuli from the tissues of the body to the brain; the primary of these is the spinothalamic tract, which carries most of the information about the location and nature of the pain (intensity, burning versus stinging, etc.), while the other pathways contribute more to the response to pain. The following section will summarize the pathways linking peripheral nociceptors to the thalamus as described by Byrne and colleagues, and Willis and colleagues (Byrne and Dafny, 1999; Willis and Westlund, 1997)

Imagine the impact of a metal corner against the scalp. Even if there is no external breaking of the skin, compression and distortion of the tissue is detected by mechanical nociceptors, first-order sensory neurons specialized to respond to certain types of intense stimuli representing the first step in the afferent pathway for processing noxious stimuli. The bodies of these neurons reside in root ganglions – in this case, the trigeminal ganglion. One

branch of the fibers terminates in free nerve endings in the skin, where they are triggered by physical changes such as pressure and mechanical distortion of the skin by the sharp metal corner, and the other terminates in a synapse in either the chief sensory nucleus in the pons, or the spinal trigeminal nucleus in the medulla.

If the noxious stimulus was to the shoulder instead, the pathway would be slightly different in that the body of the first-order neuron is found in a dorsal root ganglion next to the spinal cord, and its secondary axon fiber terminates in a synapse with a second-order neuron in the dorsal horn of the spinal cord. In both the head and shoulder examples, the axon of the second neuron crosses the anatomical midline and ascends towards the thalamus. In the former case it does so via the ventral trigeminal thalamic pathway, terminating in the ventral posterior medial thalamic nucleus (VPM), and in the latter case, via the lateral spinothalamic tract, ending in the ventral posterior lateral thalamic nucleus (VPL).

1.3.1.2. Pain in the brain: thalamus to cortex

Pain is a multidimensional phenomenon and, as such, its neural representation requires a complex interaction of multiple brain regions rather than a single "pain center." Noxious sensory input from spinal tracts enters the thalamus and propagates through a pain-responsive, though not necessarily pain-specific, network of cortical brain regions, including SI, SII, PFC, ACC, and the INS. These areas have been identified in several ways: in monkeys, viral neural tracing of STT targets in the thalamus and cortex and single-unit recordings provides direct evidence of activation in, and connections between, neurons responsive to noxious stimuli. The results of these studies can then guide human research, which uses methods such as the assessment of abnormalities in pain perception due to lesions, triggering of pain sensations via direct cortical stimulation (less commonly done), and neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron-emission tomography (PET).

Primate work has traced direct connections from the thalamus to primary and secondary sensory cortex, the posterior insula and supracallosal regions of the ACC – particularly medial-wall cingulate motor regions, the human equivalent of which are consistently activated in response to pain (Craig, 2003; Dum et al., 2009; Gingold et al., 1991; Kenshalo et al., 1980) – and studies using evoked potentials provide evidence that these

regions are involved in early responses to pain in humans, as well ((Frot et al., 2008), see review (Craig, 2003)). In humans, the best evidence for a direct link between a particular structure and its role in pain would, in theory, come from lesion studies showing reduced or abnormal pain perception associated with cortical damage. For example, one case study showed a patient with unilateral damage to SI and SII resulting in a deficit in the perception of the sensory aspects of noxious heat stimuli (Ploner et al., 1999). However, other studies have failed to find similar impairments in regard to primary sensory cortex (see reviews (Bushnell et al., 1999; Craig, 2003) and, overall, a clear connection between cortical lesions and abnormal pain perception has only been established for the insula. Furthermore, the insula is one of only two regions where direct cortical stimulation has been found to trigger pain sensations, the other being the secondary somatosensory cortex ((Mazzola et al., 2009, 2006), also see review (Garcia-Larrea, 2012)). Nevertheless, as will be explained below, there is a clear pattern of structures consistently activated during pain, and thus the lesion and stimulation data simply provide further evidence that pain is a multidimensional, distributed process.

Most research into the brain mechanisms of pain perception in humans has employed fMRI, which while unable to directly measure neural activity or trace pathways as is possible with more invasive methods, has nonetheless provided strong evidence for a network of regions commonly activated during pain experiences that includes the thalamus, SI, SII, supracallosal ACC (within BAs 24 and 23), insula (posterior and anterior portions), as well as the SMA, PFC, and subcortical regions of the striatum, cerebellum, and periaqueductal grey (Apkarian et al., 2005; Coghill et al., 1994; Duerden and Albanese, 2013; Garcia-Larrea and Peyron, 2013; Peyron et al., 2000). This collection of areas has been commonly referred to as the “pain matrix”, and while none of these regions are specific to pain nor is their activation sufficient for the subjective pain experience, they have nevertheless been the main focus of imaging studies looking at acute pain perception in humans.

Correlations between BOLD activation and reported levels of pain intensity has been described for the SI, SII, INS, and ACC (Apkarian et al., 2005; Coghill et al., 1999; Porro et al., 1998), but these areas do not necessarily show the same stimulus-response function in terms of coding for pain intensity. The SI and SII code for stimulus intensity, responding in a parametric fashion to both innocuous and noxious stimuli, whereas the posterior insula shows

a parametric response for pain intensity, not discriminating between innocuous and low-intensity noxious stimuli (Bornhövd et al., 2002; Büchel et al., 1998; Frot et al., 2007). However, when considering the role of each pain matrix region in the pain experience, it is helpful to consider the two dimensions – sensory/discriminative and affective/motivational – described earlier; none of the studies mentioned above distinguished between the pain intensity (sensory aspect) and pain unpleasantness (affective aspect).

Thalamocortical projections are sometimes described in terms of 'lateral' and 'medial' pain systems, with those from lateral thalamic nuclei to sensory and posterior insular cortices thought to carry primarily sensory information such as location and quality, and those from medial thalamic nuclei to the ACC and the INS to carry more general information, such as arousal, that contributes more to the affective-motivational dimension of pain (Albe-Fessar et al., 1985; Garcia-Larrea and Peyron, 2013; Treede et al., 1999).

Responses of the somatotopically-mapped primary sensory cortex code for stimulus location and intensity (Bornhövd et al., 2002; Bushnell et al., 1999; Kulkarni et al., 2005; Peyron et al., 2000; Porro et al., 1998). Increasing the perceived intensity, versus unpleasantness, of a pain stimulus via hypnotic suggestion increases the magnitude of the response of SI (Hofbauer et al., 2001; Rainville et al., 1997), as does increased attention to the location, versus the unpleasantness, of the stimulus (Kulkarni et al., 2005). Damage to the somatosensory cortex has been observed to selectively disrupt the perception of sensory, but not affective, aspects of noxious heat stimuli (Ploner et al., 1999). Thus, SI and SII are typically described as processing the sensory components of a pain experience.

The involvement of the insula in pain processing has been well established. Years of neuroimaging research in humans have proved that the insula responds to all types of pain, anywhere in the body, in both clinical and experimental conditions (Apkarian et al., 2005; Coghill et al., 1994; Duerden and Albanese, 2013; Price, 2000). The posterior portion receives direct connections from thalamic nuclei (VMpo) that receive STT input from noxious stimuli (Treede et al., 2000, 1999), and the magnitude of its response correlates with self-reports of pain intensity (Bornhövd et al., 2002; Coghill et al., 1999; Frot et al., 2007). It shows somatotopic organization for both painful and non-painful stimuli, and direct electrical stimulation of this area elicits painful sensations (Brooks et al., 2005; Mazzola et al., 2009; Ostrowsky et al., 2002). Post-stroke damage in the opercular-insula region has been associated

with deficits in pain perception coupled with a type of central pain similar to that produced by lesions to the upper spinothalamic tract (Garcia-Larrea et al., 2010). These findings have led to the proposal that the posterior portion of the insula might represent a sort of 'primary cortex for pain' (Garcia-Larrea, 2012). However, looking beyond pain, it is clear that the insula is not performing purely first-order sensory processing. In a broader context, the insula is known to be a sensory association area where information about a wide variety of internally-felt sensations related to homeostasis and physiologic status are integrated into a coherent sense of interoceptive awareness (Craig, 2009, 2002; Critchley et al., 2004). Insula response has been associated with the perception of bodily and visceral sensations such as itch, thirst, air hunger, and stomach distension (Craig, 2009), all of which are examples of sensory stimuli associated with the internal physical state and which are highly salient in that they indicate the need for attention and action. Pain is perhaps one of the clearest examples of such stimuli, and the findings gathered for insula response to a wide range of seemingly disparate conditions – e.g. pain and thirst – illustrate how the insula transforms information about what a noxious stimulus *is* (the sensory aspects) into what it *means* (the affective aspect). In other words, it is helping to answer the global question "How am I?" using information from basic sensory processes that has already answered the questions "How is my body positioned? What sensation do I feel on my scalp?"

This transformation appears to occur in a posterior to anterior progression, as is suggested by the timing of pain response in each subregion (Frot et al., 2014; Pomares et al., 2013). Passing from posterior to anterior, the information is transformed from an initial somatosensory representation to a subsequent subjective feeling; one study comparing processing of stimulus intensity versus reported pain intensity observed that the response of the posterior region encoded the former, while the latter was reflected in the response of the anterior insula (Kong et al., 2006). Functional connectivity work has lent further support to this distinction between a posterior region linked to a network for sensory processing and an anterior one linked to limbic regions and supporting cognitive and affective processing (Cauda et al., 2011; Chang et al., 2013; Deen et al., 2011). These connectivity patterns are consistent with the findings of early tracing studies of primate insular efferent and afferent cortical projections (Mesulam and Mufson, 1982; Mufson and Mesulam, 1982).

It is thus clear that the insula participates in both sensory and affective processing of pain, creating and monitoring a sensory representation of the bodily state, using it to build a subjective feeling state that is then linked to emotional and motivational drives. This last step is postulated to occur in connection with the anterior cingulate cortex; as discussed above, these two regions are nearly always indicated in pain studies as key regions involved in the affective experience of pain, and their responses during pain and other interoceptive sensations are highly coordinated (Craig, 2009).

Along with the anterior insula, the supracallosal portion of the ACC is widely reported in studies on self-pain. Early single-neuron recoding work in cingulotomy patients reported neurons responsive to noxious stimulation (Hutchison et al., 1999), and subsequent neuroimaging work on self-pain further defined pain-related activation of the ACC, in particular the supracallosal, midcingulate area comprising BAs 24 and 32 (Apkarian et al., 2005; Duerden and Albanese, 2013; Shackman et al., 2011; Torta and Cauda, 2011), a region referred to as the posterior ACC (pACC) as well as the anterior middle cingulate cortex (aMCC). Typically, response of this area is associated with the affective/motivational dimension of pain, and more specifically, emotional and motivational drives that affect behavioral and physiological responses such as arousal, attentional orientation, and motor responses.

In a broader context, the ACC is believed to play a key role in the modulation of autonomic arousal, especially in regard to emotion processing, monitoring of action outcomes, and adaptive behavioral control (Paus, 2001; Rushworth et al., 2007; Vogt, 2005), and there is a well-established link between ACC response and affect – particularly negative emotional states (Kober et al., 2008; Shackman et al., 2011; Vogt, 2005). Its response reflects cognitive and motor task difficulty and is correlated with associated markers of stress and arousal (e.g. heart rate variability) (Critchley et al., 2003, 2000; Paus et al., 1998). Likewise during painful stimulation, cingulate response has been correlated with specific markers of autonomic response such as changes in skin conductivity (Dubé et al., 2009; Piché et al., 2010), as well as with affective pain ratings (i.e. unpleasantness) (Rainville et al., 1997). It has also been associated with attentional orientation towards aversive stimuli, including pain (Frot et al., 2008; Peyron et al., 1999; Tölle et al., 1999). Taken together, these findings support the idea

that the ACC contribution to the affective and motivational aspects of pain includes the modulation of autonomic arousal and the orientation of attention.

In addition to emotional and attentional modulation, the ACC participates in motor responses to pain. In monkeys, the medial supracallosal region receives direct nociceptive input from the spinothalamic tract (Dum et al., 2009; Vogt et al., 1987; Vogt and Pandya, 1987), but also has clearly defined motor properties: individual neurons here have been demonstrated as active during motor tasks, and tracing studies have identified projections from this area to premotor and primary motor cortex, as well as to motor neurons in the spinal cord (Dum and Strick, 2005; Picard and Strick, 1996). The human homologue of this 'cingulate motor area' has similarly been found to project to premotor, primary motor, and supplementary motor cortical areas, as well as the spinal cord; to display response profiles implicating involvement in the planning and control of voluntary movement; and to respond to pain (Dum et al., 2009; Picard and Strick, 1996; Shackman et al., 2011).

The combination of pain- and motor-responsiveness in this subregion of the ACC has led to the hypothesis that this region has a motor function in the pain response, such as motor readiness or priming, and/or response inhibition. Indeed, ACC response has been associated with motor withdrawal in response to aversive stimuli (Isomura and Takada, 2004), and studies using go/no-go paradigms have associated increased button-press reaction times as well as inhibition of motor responses with modulations in ACC activity (Morrison et al., 2007a; Rubia et al., 2001). In addition to voluntary motor control, it may also be involved in reflexive motor responses to pain (Frot et al., 2008; Piché et al., 2010).

This motor-related and pain-responsive portion of the ACC/MCC receives direct input from the amygdala (Morecraft et al., 2007; Shackman et al., 2011; Vogt and Pandya, 1987; Vogt, 2005), an area with which a strong functional relationship has also been identified (Kober et al., 2008). The amygdala has a well-defined role in fear conditioning and the linking of stimuli with aversive outcomes (LeDoux, 2003), making it a possible source of information reinforcing the affective value of a painful stimulus. It has thus been proposed that it is the awareness-building function of the insula, in connection with affective- and motor-related functions of the ACC, that creates the subjective emotional state (Craig, 2009, 2002).

In recent years, further work has suggested that the pain matrix may not be specific for pain, but instead might be a more general system for the detection of saliency within sensory

perception (Legrain et al., 2011; Mouraux et al., 2011). Nevertheless, this network is reliably associated with pain experience across different types of noxious stimuli (e.g. heat, cold, mechanical pain), body location, and experimental contexts (Duerden and Albanese, 2013). The pain experience comprises a collection of physiological, emotional, and cognitive factors and, while it is unlikely that the above-described network of brain regions is pain-specific, pain is supported by a common and identifiable brain network.

1.3.2. Brain to body: the response to pain, and pain behaviors

There are several responses to a painful experience: physiological, cognitive, emotional, and behavioral. Returning to the example in the story presented earlier, a hard bump of the head against a sharp metal corner would likely provoke increased physiological arousal, which manifests as changes in heart rate and skin conductivity. The cognitive response includes orientation of attention towards the potential threat, priming the motor system for action, and the production of conscious thoughts about the situation ("Is my head bleeding? Do I need help? How can I avoid bumping my head again in this tiny room?"). The emotional response in this case is the immediate feeling that something negative and unpleasant has occurred.

The behavioral response is the most visible, e.g. a quick jerk of the head away from the corner, vigorous rubbing of the scalp with the hands, movement of the entire body a few steps away while keeping the head ducked low in order to avoid additional contact. This illustrates one of two general functions that can be ascribed to pain behaviors: withdrawal from noxious stimuli and protection of the body from further damage. Another behavioral response in this example is the display of a facial expression of pain to the second person, illustrating the second general function of pain behaviors – communication to others, either to warn of a potential threat or to solicit help (Williams, 2002).

Part of the behavioral response is automatic and reflexive and does not necessarily require cortical involvement. Spinal motor responses allow 'flinching before feeling' – the reflexive withdrawal of a body part away from the noxious stimulus, via neural circuits connecting peripheral nerves, the spinal cord, and skeletal muscles. However, more complex motor responses such as head rubbing or facial expression require cortical-level processing

(Morecraft et al., 2004; Müri, 2016). The subsequent sections will focus on the facial expression of pain as a behavioral response, as it is intended for the purpose of pain communication.

1.3.3. Encoding pain in the face

There are many behavioral responses that can convey the sufferer's experience of pain: verbalizations (e.g. crying out), body movements (e.g. flinching away from a sharp corner, rubbing a sore head), and postures (e.g. hunching or guarding). The facial expression of pain can occur with or without these other behaviors. It is nonspecific in that it does not in itself offer information about the cause of the pain nor the body part affected, but it is universal in that the same core expression has been consistently observed across a range of different types of acute pain in experimental or clinical settings, as well as in chronic pain patients (LeResche et al., 1992; Prkachin, 1992). There is not, for example, one expression for head bumps and another, completely different, expression for low back pain. Likewise, observers can easily differentiate between this fundamental expression and those of other negative emotions such as anger, sadness, disgust, and fear (Boucher, 1969; Simon et al., 2008).

Any emotional expression can be described by its component facial movements and the muscles involved in effecting those movements. The most commonly used tool for the qualification of expressions, including pain, is the Facial Action Coding System (FACS) created by Ekman (Ekman and Friesen, 1978). Using this tool, a trained evaluator determines which facial muscle groups, called 'Action Units' (AUs), are engaged throughout an expression, and the amplitude of the movement of those groups. The prototypical pain face involves four core elements, the primary of which is a lowered, crinkled brow (AU 4, the corrugator muscle) and tightened and/or lowered eyelids (AUs 6 and 7, orbicularis oculi). This is accompanied by raising of the cheeks (also AUs 6, 7), nose wrinkling with a raised upper lip (AU 9 and 10, levator labii), and closing of the eye (AU 43). To quantify the facial response during pain, points are given for each core AU, representing intensity, duration, and frequency, to comprise a final score (Craig et al., 2011; Prkachin and Craig, 1995). This coding system is considered the gold standard for the assessment of pain expressions both in

experimental settings as well as in clinical applications, particularly those in which the subjects are unable to give clear self-reports about their pain.

The 'core' pain expression is an innate behavioral response. It is observed in newborns (Craig et al., 1994; Grunau and Craig, 1987) and blind subjects (Kunz et al., 2012a), and, as with other facial expressions of emotion, does not change with age (Kunz et al., 2008b; Williams, 2002). It also does not differ significantly between males and females (Kunz et al., 2006). However, encoding different intensities of pain is most likely learned through observation and can be modified by various intrinsic and extrinsic factors (Craig et al., 2011; Kunz et al., 2011). Intrinsic factors that can effect pain displays include the severity and nature of the pain (for example, a head bump versus childbirth) and concurrent emotional states (Craig et al., 2011). Individual differences in pain expressiveness exist as well, with some subjects showing greater facial reactivity to painful stimuli over a range of stimulus intensities. These differences may be due in part to variations in pain sensitivity, with higher pain expressiveness correlated with greater sensitivity to pain (Kunz et al., 2008a). Expressiveness during a particular pain experience can also be influenced by extrinsic factors such as the sociocultural context, in which display rules create a broad sense of what people should or should not show, and situation-specific cues, where aspects of the immediate context guide displays of pain (Hadjistavropoulos et al., 2011; Williams, 2002).

Nevertheless, at the individual level, pain expression correlates with self-reports of pain ratings (Kunz et al., 2004), encodes both the intensity of pain and its unpleasantness (Kunz et al., 2012b), and can be distinguished from other concurrent emotions (Williams, 2002). One study even found that observers were able to determine stimulus intensity based on the facial responses (Patrick et al., 1986). Thus, while there is variation in how individuals encode pain, pain expression is nonetheless a good reflection of the subjective pain experience; for this reason it is a valid way to assess pain and a relevant target for research on how we perceive pain in others.

As discussed above in regard to pain behaviors in general, the facial expression of pain may be considered as having two functions: first, a physical response for self-protective withdrawal, with the goal of reducing exposure to the noxious stimuli; and second, a socio-behavioral response, with the goal of communicating the pain experience to others.

1.4. Perception of pain in others (observation)

Pain communication is important for two reasons: it can help the sufferer solicit help from others, and it can provide others with information about an aversive stimulus and warn them of potential harm. Prkachin and Craig present a model that structures nonverbal pain communication as a three-step process, described as A -> B -> C., wherein given an episode of pain, A represents the internal state of the pain sufferer, B represents the encoding of this internal state via a specific set of expressive features, and C represents the decoding performed by the observer ((Prkachin and Craig, 1995)). Once the pain message is encoded and broadcast by the sufferer, it must then be observed and decoded by the observer. The previous sections have discussed the first steps – A, the internal state (self-pain, sensory and affective dimensions), and B, encoding (the facial expression of pain); the material presented in the following sections, as well as in the work described in the following two chapters, will be concerned with the third step, C – decoding the pain experience.

1.4.1. Pain empathy in the brain

An ever-growing body of imaging research has provided evidence that the decoding aspect of pain communication – pain empathy – shares a neural basis with the experience of pain in the self (see review (Lamm et al., 2011)). This work has used a variety of stimuli to investigate the perception of pain in others, such as cues that a loved one is in pain (Singer et al., 2004), still images or videos of body parts in painful situations (X Gu and Han, 2007; Jackson et al., 2005; Morrison and Downing, 2007), or even descriptive narratives (Bruneau et al., 2012b; Xiaosi Gu and Han, 2007)).

The first functional imaging study looking at pain empathy observed brain activation in subjects as they viewed cues indicating that either they or a loved one would receive a painful stimulus to the hand (Singer et al., 2004). The results found overlapping activation only in the regions supporting the affective dimension of self-pain – the supracallosal ACC and the anterior INS – and not those underlying the sensory dimension of pain – S1, SII, and the posterior INS (Singer et al., 2004). As described above, the anterior INS is involved in both interoception and pain in the self; thus it is in this region, where a feeling state is represented

subjectively and in terms of its saliency, where an overlap with observed pain occurs (Singer et al., 2004). Similarly, the anterior insula has also been found to show overlapping responses for observation and experience of other affective states, such as disgust and gustatory pleasure (Jabbi et al., 2008, 2007; Wicker et al., 2003), suggesting a role for the insula in empathy for affective states in general, not just for pain.

Later work employed images and videos of body parts in painful situations, with similar results showing overlap for observed versus experienced pain in the anterior insula and the ACC (Jackson et al., 2005; Morrison et al., 2004). It is in this body of work where the role of the ACC in observed pain was more closely examined. For example, Morrison and colleagues compared ACC response to that of SI, for both noxious and innocuous felt and seen pain conditions, finding that the former responded only to the noxious stimuli in both conditions, while the latter responded to felt stimuli only, whether or not they were painful. They concluded that these results suggest that the same idea of a functional dissociation of sensory and affective/motivational aspects of self-pain applies to observed pain, and that the ACC plays a role in organizing behavioral responses, most likely via modulation of motor regions (Morrison et al., 2004). Following this reasoning, the authors presented additional work showing that viewing pain in others facilitates motor responses to self-pain, and that this behavioral effect is reflected in the ACC response (Morrison et al., 2007a, 2007b). Later work has further shown that viewing images of body parts in painful situations lowers the threshold for reflexive spinal responses to self-pain (Vachon-Presseau et al., 2011).

Taken together, these results support the hypotheses that, as in the case of pain in self, the role of the ACC in the perception of pain in others is to create motivational drives influencing behavior (specifically, motor responses), whereas the anterior INS is involved in representing physical saliency.

In all of the above studies, however, the source of the pain is known to the observer; either it is witnessed outright, as in the videos and pictures of limbs receiving painful stimuli, or it is known but not seen, as in the cue-based paradigms. More importantly, neither type of protocol provides information about the subjective response to the pain stimuli, such as withdrawal responses or facial expressions of pain. As in the opening pain story, there are many real-world examples of pain communication in which the observer may only see the pain response, not the actual event causing the pain. In fact, it can even be said that these

protocols are not examining pain communication at all, as there is no pain message to be decoded. Thus, an important subsequent question concerns what happens when an observer does witness pain-related behavior – specifically, the facial expression of pain. While there has been extensive work looking at the brain response to facial expressions of emotion (e.g. (Fusar-Poli et al., 2009; Sabatinelli et al., 2011)), prior to the preparation of the first study presented in this manuscript only three published works had specifically looked at the response to pain expressions (Botvinick et al., 2005; Saarela et al., 2007; Simon et al., 2006).

1.4.2. Faces as the channel: decoding pain from the face

In most protocols, the type of noxious stimuli and the affected body part is known – a needlestick to the finger, an arm dunked in ice water, an electrical shock to the foot, or the manipulation of an injured shoulder are some examples. However, pain communication does not require the observer to witness the injury or to be given a narrative describing it; as in the introductory story, an observer can receive the message that an injury has occurred simply by viewing the facial expression of the other.

Perceiving the emotional content of a facial expression is a complex feat of social cognition that involves several steps: basic visual perception, recognition of a configuration of visual features as a meaningful whole object classified as a 'face' (face detection), and lastly, recognition of the emotional message being conveyed by this face.

1.4.2.1. Perception of faces

In terms of visual perception, faces represent a class of complex visual stimuli that enjoy a special status in the human visual system and are processed separately from other types of objects. Newborn infants orient preferentially toward face-like configurations despite the immaturity of their visual cortex, and the widely accepted view is that an innate bias for faces shapes the developing visual system to create a specialized system for face processing (Johnson et al., 2015; Tsao and Livingstone, 2008). The dissociation between face and object processing is evident from behavioral studies, for example in protocols showing disrupted recognition of inverted faces but not of inverted objects (Kemp et al., 1990)), and the particular robustness of face recognition to various types of visual distortion (Tsao and

Livingstone, 2008). This distinction can also be seen in observations of patients with the disorder known as prosopagnosia, who show deficits in recognizing familiar faces without similar deficits for non-face objects (Kress and Daum, 2003; McNeil and Warrington, 1993).

Furthermore, this difference is also reflected in the brain response, with certain regions showing clear preference for faces and face-like stimuli. Following early processing in the primary visual cortex, face processing begins with recognition of the face-like configuration of features in the fusiform gyrus of the occipitotemporal cortex, an extrastriate region dubbed the fusiform face area (FFA) (Allison et al., 1994; Kanwisher et al., 1997; Sergent et al., 1992), as well as in the occipital face area (OFA), a portion of the inferior occipital gyrus (Grill-Spector et al., 2004; Johnson et al., 2015; Tsao and Livingstone, 2008). Whereas these two regions are associated with initial face detection and recognition, which involve processing invariant features and their configurations, a third region – the posterior superior temporal sulcus (pSTS) – is recruited for the processing of dynamic features such as gaze direction and movement of facial features (Allison et al., 2000; Haxby et al., 2000, 2002; Phillips et al., 1997). Together, these three regions comprise the core system for cortical face detection and recognition.

1.4.2.2. Perception of emotional expression

While face identification depends on occipitotemporal pathways, and the perception of facial emotion recruits a wider network of regions, evidence suggests these are not distinct, separate processes, but rather interactive mechanisms, with even early face processing showing sensitivity to emotional content, most likely via fast subcortical pathways and top-down modulation of the fusiform by the amygdala (Vuilleumier et al., 2004).

Facial expression recognition, however, is a multi-level, multi-process task preceded by face detection and dissociated from face identification (recognition of gender, age, or identity); this distinction is reflected in the timing and location of brain responses, with recognition of emotional expression occurring subsequent to the initial face detection associated with the earliest brain responses, although evidence suggests that emotional content can then modulate the fusiform response via feedback from subcortical pathways involving the amygdala (Geday et al., 2003; Vuilleumier, 2007; Vuilleumier and Driver, 2007). Looking

again at the case of prosopagnosia, it has been observed that patients often retain the ability to recognize facial expression despite deficits in facial recognition (Humphreys et al., 2007; Palermo et al., 2011).

There does not seem to be one dedicated neural circuit for the perception of all emotional expressions; rather, much differentiation has been observed for different emotions (Fusar-Poli et al., 2009; Hennenlotter and Schroeder, 2006). Processing facial affect has been linked with increased activation in numerous brain regions, including prefrontal, temporal, parietal, visual, limbic, and subcortical areas (Fusar-Poli et al., 2009; Vuilleumier, 2007). Despite a large body of research on the subject, there is still not a consistent picture of any of the basic emotions most frequently studied – anger, fear, disgust, happiness, sadness and surprise – although some patterns have emerged. For example, fear expressions are strongly linked with amygdala response, in line with the amygdala's known role in fear conditioning and aversive learning, whereas disgust faces activate the anterior insula but not the amygdala (Hennenlotter and Schroeder, 2006; Phillips et al., 1998). This insula response overlaps with that for other aversive stimuli such as unpleasant tastes and smells (Jabbi et al., 2008; Wicker et al., 2003), providing an example of an interoceptive emotion showing recruitment of the same regions for both self- and other- experience.

1.4.2.3. Perception of pain expressions

Although there is generally a wide body of work looking at the brain mechanisms for the perception of facial expressions, less attention has been given specifically to pain expressions. As of the time the study reported in Chapter 2 of this manuscript was designed and carried out, only three earlier studies had looked specifically at brain response during the perception of pain in others via facial expression.

In the first study, subjects viewed short video clips showing facial expressions produced by shoulder injury patients undergoing physiotherapy assessment exams; clips showed both painful and neutral expressions (Botvinick et al., 2005). In alternate blocks, subjects were given painful and non-painful thermal stimulations. Brain response to painful versus non-painful thermal stimulation was compared to the response for pain expressions versus neutral expressions. Overlap for felt pain and observed pain expressions was observed

in the ACC and the anterior insula, consistent with previous studies on the perception of pain in others. Consistent with the broader body of work on the perception of emotional expression in general, activation was also observed in the amygdala and the OFC.

The second study, also using video clips, compared expressions of pain to those of anger, as well as neutral expressions (Simon et al., 2006). In this protocol, subjects performed a gender discrimination task while viewing the stimuli; this task was intended to result in implicit processing of the pain content of the expressions, as subjects' attention was at least partially directed away from the pain content of the faces. Here, the most significant results were found when comparing brain response to pain as shown by male models, versus female models. Face-processing regions of the FFA and STS, as well as the amygdala, responded more strongly to pain expressions, versus angry or neutral expressions. This is consistent with a subcortical pathway for emotional modulation of face processing via the amygdala, discussed above. Compared to anger, pain expressions also provoked greater response in the vmPFC, the anterior insula, and SII/posterior insula. However, all of these effects were seen only in response to male models and, additionally, there were no results reported in the supracallosal portion of the ACC identified in other studies on pain empathy. The authors hypothesized that these results reflected gender differences in the perceived social role of pain expression, with male pain faces representing greater potential threat, and that this perception of threat may prevent or reduce processes of pain empathy. However, it could also be that engagement of self-pain regions during pain empathy requires attention to the pain content of the face. Testing this possibility would require a protocol using two task conditions to manipulate subject attention.

Another important question is how the brain may code for the intensity of an observed pain expression. As described earlier, the intensity of self-pain modulates the response of the INS and ACC, and pain expressions are a reliable indicator of the subjective experience of pain. It is possible that information about the intensity of observed pain is decoded via the same mechanisms that encode pain in the self. Indeed, the response of the ACC has been shown to code for perceived intensity of other pain when viewing images of body parts in painful situations (Jackson et al., 2005). Thus, the third study looking at brain response to pain faces attempted to answer the question of pain intensity coding (Saarela et al., 2007). Here, subjects viewed photos of 'provoked' versus 'chronic' pain expressions displayed by chronic

pain patients, in addition to neutral expressions displayed by healthy volunteers. Following the scanning session, subjects rated the intensity of pain displayed in each image, and a correlation was found between these ratings and the response of the ACC and the aINS during the viewing of the stimuli. However, as with the first study, task instructions during scanning were simply to attend to the images; subjects were not specifically instructed to judge how much pain was displayed.

Taken together, the evidence from these studies suggests that the perception of pain faces, like that of other cues relating to pain in others, does recruit brain regions involved in self-pain. However, some questions remain. In particular, the influence of attentional and task demands on the recruitment of these areas is an important factor; in the studies described above, subjects were either instructed simply to attend to the visual stimuli (Botvinick et al., 2005; Saarela et al., 2007), or they performed a non-pain-related task (i.e. gender discrimination) (Simon et al., 2006). In the latter case, this can be considered implicit processing of the affective content of the expressions, as subjects were instructed to attend to another aspect of the stimuli. Observing an emotional expression, as has been discussed above, involves both the perception of a complex, dynamic object, as well as perception of the meaning of that object. In using only one task, or only passive viewing, these earlier works do not address the potential difference in coding for the dynamic visual attributes of an expression versus its affective content. In other words, is recruitment of brain regions involved in the processing of self-pain linked to explicit attention to the pain content of an expression? Further, how is the response of these areas during explicit processing of pain modulated by the perceived pain intensity? These questions were therefore the motivation for the first study, described in Chapter 2.

1.5. Hypotheses for studies in this work

The objective of this work is to contribute to the understanding of pain communication, specifically the decoding component. The specific hypotheses of the two studies were closely linked and comprised two main themes – overlap with self-pain areas, and engagement of regions involved in motor mirroring and in mentalizing.

In Study 1, we hypothesized that the explicit evaluation of pain expressions would recruit brain regions involved in the processing self-pain and that a subset of these regions would also show a parametric effect in response to the perceived pain intensity. Further, we hypothesized that evaluation of the meaning of the expressions would reveal greater responses in midline cortical regions involved in thinking about the mental states of others, whereas evaluation of the movement shown in the expressions would result in greater responses in motor regions identified in action observation and motor mirroring.

In Study 2, our hypotheses were similar to, and expanded on, those of Study 1. Once again, we expected that evaluation of the emotional content of a pain expression would recruit brain regions involved in the processing self-pain, and that attending to the meaning of the expressions would more strongly engage the frontal portions of the action observation/mirroring network, whereas attending to the movement in the expressions would more strongly engage parietal regions of this network. While the first study included only observational conditions, the experimental protocol of Study 1 added an execution condition to allow greater confidence in the identification of 'mirroring' processes.

Chapter 2: Articles

Article 1: Brain responses to facial expressions of pain: emotional or motor mirroring?

Title: Brain responses to facial expressions of pain: Emotional or motor mirroring?

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Authors' contributions: LB, PLJ and PR contributed to the conception and design of the study; LB acquired and analyzed the data; LB, PLJ and PR contributed to the analysis design and interpretation; LB drafted the manuscript. All authors contributed important intellectual content and approved the final version.

ABSTRACT

The communication of pain requires the perception of pain-related signals and the extraction of their meaning and magnitude to infer the state of the expresser. Here, BOLD responses were measured in healthy volunteers while they evaluated the amount of pain expressed (pain task) or discriminated movements (movement task) in 1-second video clips displaying facial expressions of various levels of pain. Regression analysis using subjects' ratings of pain confirmed the parametric response of several regions previously involved in the coding of self-pain, including the anterior cingulate cortex (ACC) and anterior insula (aINS), as well as areas implicated in action observation, and motor mirroring, such as the inferior frontal gyrus (IFG) and inferior parietal lobule (IPL). Furthermore, the pain task produced stronger activation in the ventral IFG, as well as in areas of the medial prefrontal cortex (mPFC) associated with social cognition and emotional mirroring, whereas stronger activation during the movement task predominated in the IPL. These results suggest that perception of the pain of another via facial expression recruits limbic regions involved in the coding of self-pain, prefrontal areas underlying social and emotional cognition (i.e. 'mentalizing'), and premotor and parietal areas involved in motor mirroring.

Keywords: functional magnetic resonance imaging, anterior cingulate cortex, anterior insula, human mirror neuron system, empathy

Abbreviations:

ACC = anterior cingulate cortex
aINS = anterior insula
IFG = inferior frontal gyrus
INS = insula
IPL = inferior parietal lobule
MNS = mirror neuron system
mPFC = medial prefrontal cortex
PCG = post central gyrus
SFG = superior frontal gyrus

STG = superior temporal gyrus

INTRODUCTION

Pain behavior is vital to pain communication: how we move our bodies and our faces in response to a noxious stimulus provides observers with key information about our experience/inner state. Current neuroimaging techniques have allowed us to begin to investigate neural processes involved in the perception of pain in others. It has been demonstrated that certain brain regions previously identified as involved in processing the affective dimension of pain in the self, namely, the posterior (supracallosal) part of the anterior cingulate cortex (ACC; BA 24) and the anterior insula (aINS) (Apkarian et al., 2005) are also engaged when individuals view cues indicating that a loved one is receiving a painful stimulus (Singer et al., 2004), images of limbs receiving noxious stimuli (Jackson et al., 2005; Lamm et al., 2007b; Morrison et al., 2004) or images and/or videos of people in painful situations (Ochsner et al., 2008).

As the facial expression of pain is the most prominent non-verbal pain behavior, it has an enormous impact on the social communication of pain (Hadjistavropoulos and Craig, 2002). The few studies that have looked at brain responses to the observation of facial expressions of pain have also found engagement of brain regions underlying self-pain, even in the absence of information about the nature of the painful stimulus (Botvinick et al., 2005; Saarela et al., 2007). These findings have been discussed in the context of "shared representations" theories of empathy, which assert that empathic processes, from emotional contagion to cognitive empathy, begin with a mapping of the perceived emotional state of the expresser on a representation of the corresponding state in the observer [e.g. (Keysers and Gazzola, 2009; Preston and de Waal, 2002)]. When pain states are communicated through facial expression, the neurobiological substrate of this shared representation may involve the human "mirror neuron" system (MNS) (Fadiga et al., 1995; Grafton et al., 1996; Iacoboni et al., 1999; Rizzolatti et al., 1996), perhaps via interactions with brain areas involved in emotions (Iacoboni, 2009). However, empathy could potentially occur without the involvement of the classic (motor) MNS [e.g. (Chakrabarti et al., 2006)] and mirroring processes may be common across several brain areas beyond the motor system (Keysers and Gazzola, 2009).

It should be noted that the basic processing of facial expression of emotions may not be sufficient to activate the MNS system reliably and this system is generally not included as a part of the basic brain network underlying the perception of emotional faces [(see review by (Vuilleumier and Pourtois, 2007)]. However, several recent studies have reported overlapping engagement of areas of this network during the observation/evaluation and execution of facial expressions of emotion, specifically the inferior frontal gyrus (IFG) (Carr et al., 2003; Enticott et al., 2008; Hennenlotter et al., 2005; Leslie et al., 2004; van der Gaag et al., 2007) and the inferior parietal lobule (IPL) (Montgomery and Haxby, 2008). Furthermore, the response of an adjacent and more dorsal part of the IFG to the passive viewing of facial expressions of basic emotions has been associated with individual scores on an empathy questionnaire (Chakrabarti et al., 2006). In the specific case of pain expressions, one study found that subjective ratings of acute versus chronic pain expressions correlated with activation in the left inferior parietal lobule (IPL) (Saarela et al., 2007), one area posited as part of the human MNS (Iacoboni, 2005).

The facial expressions of pain and emotions have at least two dimensions: dynamic facial movements, and an affective meaning. As these two components are strongly linked, it is not clear if brain activation evoked by the viewing of pain expressions is driven by the amount of pain expressed (the affective dimension), the magnitude of the movement of facial features (the motor dimension), or both. Therefore, studies of brain responses during the perception of pain expressions must consider and attempt to separate these two dimensions.

In order to differentiate between the observer's responses reflecting the affective meaning conveyed by the expressions and the perception of facial movements coding for the expressions, we used two tasks intended to manipulate the attention allocated to those separate dimensions of the facial expressions. The first was a pain evaluation task in which subjects reported the amount of pain expressed (i.e. attentional focus on meaning), and the second was a movement discrimination task in which subjects compared the movement in the upper versus lower regions of the face (i.e. attentional focus on movements). This is, to our knowledge, the first study looking at pain facial expressions that has not only used an explicit, online evaluation task, but that has also contrasted it with a control task condition.

We hypothesized that the explicit processing of the meaning of facial expressions of pain would engage cortical areas also involved in the experience of pain in the self, and that

activity in a subset of these areas would correlate with the amount of pain perceived. Moreover, we expected that brain activation in response to the facial expression of pain would differ depending on task demands and attentional focus. Specifically, we expected that explicitly attending to and evaluating pain in others would activate midline prefrontal areas believed to be involved in social cognition and, specifically, "mentalizing" – that is, thinking about the emotional states of others (Amodio and Frith, 2006; Frith and Frith, 2006), whereas attending to and evaluating movement would lead to greater activation in areas believed to code for motor aspects of observed action, such as the premotor cortex (BA 6) (Morin and Grezes, 2008), as well as the ventral IFG and IPL (Iacoboni, 2005, 2009; Kilner et al., 2009).

MATERIALS AND METHODS

Subjects

Subjects were 18 healthy, right-handed volunteers (9 women) between 18 and 25 years of age, with no history of neurological or psychiatric disorder. Data from one participant were discarded due to excessive movement during scanning. Subjects were informed as to the purpose and procedures of the study, and written consent was obtained prior to the experiment. The study was approved by the research ethics committee of the Institut universitaire de gériatrie de Montréal.

Stimuli

The stimuli used in this study were one-second video clips of facial expressions of pain, taken from a larger collection of such stimuli previously created and validated in the laboratory, for which eight actors (4 female) were videotaped while producing facial expressions of pain at three different levels – mild, moderate, and strong (Simon et al., 2008). Each 1-second video clip was extracted from the raw video footage using the peak of the expression as the end point, and then converted to black and white. Neutral/no pain expressions were taken from video segments that featured only non-emotionally-suggestive movements such as eye-blinks and incidental mouth movements. The stimuli then underwent a two-step validation process in order to ensure the specificity of the expressions for pain,

versus other negative emotions. In the first stage, 288 unique clips (211 pain, 33 neutral, 44 other negative emotions – anger, disgust, fear, and sadness) were evaluated for their emotional specificity by thirty-three naïve subjects, who rated each clip for emotional content and intensity. Of these clips, 104 were identified as showing primarily pain, with little or no contamination by the other negative emotions. The objective of the second stage of validation was to ensure that the 104 clips identified in the first stage depicted a range of pain intensities. Here, twenty subjects rated the amount of pain shown in each clip using a visual analog scale (VAS). The result of this stage yielded a set of 96 clips depicting four levels of pain: neutral/no pain (pain 0), mild pain (pain 1), moderate pain (pain 2), and strong pain (pain 3) (8 actors [4 female] x 4 levels x 3 versions per actor/actress).

Experimental Procedure

Prior to entering the scanner, subjects were instructed on how to perform the two experimental tasks, and completed a brief training session with ten additional stimuli not used in the actual experiment. For the first task – pain evaluation ("pain task", or "PT") – subjects were instructed to rate the amount of pain expressed on a continuous VAS ranging from "no pain" (left end of the scale) to "the worst pain imaginable" (right end). For the second task – movement discrimination ("movement task", or "MT") – subjects were instructed to compare the amount of movement in the upper versus lower regions of the face, and indicate where the greatest amount of movement occurred, using a continuous VAS that ranged from "eyes" to "mouth." Trial structure is shown in Figure 1. At the beginning of each trial, a one-second cue screen indicated which task – "pain" or "movement" – to perform on the upcoming clip. Next, the clip was presented, immediately followed by a five-second response window displaying the corresponding VAS for that task. In both task conditions, subjects reported their answers by pressing two buttons on a response box to position a slider bar on the onscreen VAS. The initial position of the slider at the start of each response window was randomized. At the end of each rating period, the position of the sliding bar on the VAS was recorded and linearly converted to a number between 0 and 100. These numbers – the subjective pain ratings – were normalized within each run using a z-transformation.

Stimuli presentation and the recording of subject responses were done using the E-Prime 1.2 presentation package (Psychology Software Tools, Inc). An LCD Projector

(EPSON, EMP-8300 XGA) was used to project the visual stimuli onto a screen inside the scanning chamber that subjects could view via a mirror positioned over the head coil. Subjects entered their responses using the index and middle finger keys of a five-key response box that was strapped comfortably to their right hand and wrist.

Each of the 96 stimuli was shown twice, once per task, for a total of 192 trials, which were arranged in 6 series of 32 trials each, and presented in 6 functional runs (one series per run). Trials were separated by a pseudo-randomized inter-trial-interval (ITI) of 4, 6, or 8 seconds. Within each of the 6 series, the order of stimuli was pseudo-randomized according to pain level, actor gender and identity, and task, and the order in which the series were presented was reversed for half of the subjects. Each run lasted 8.5 minutes. The entire scanning session comprised the 6 functional runs, lasting 8.5 minutes each, and an anatomical run of 9 minutes.

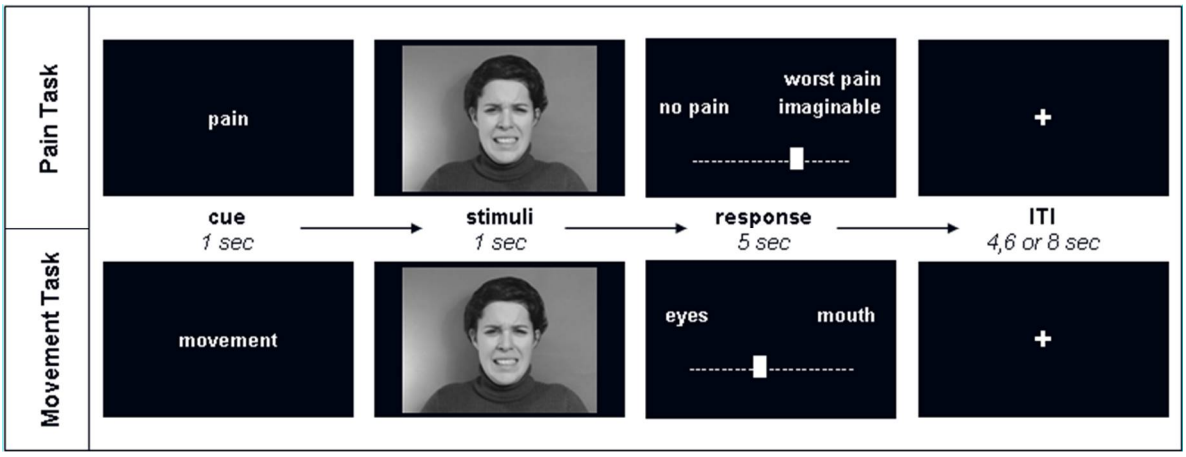

Figure 1. Trial structure for pain evaluation and movement discrimination tasks.
A cue at the beginning of each trial indicates which task to perform on the upcoming video clip. Immediately following each clip is response window where subjects use a visual analog scale (VAS) to either rate pain or compare movement. Each trial ends with a fixation screen (ITI; inter-trial-interval) of variable duration. Note: Text in response window boxes is enlarged for legibility and is not to scale.

Magnetic Resonance Imaging (MRI): equipment, data acquisition and analysis

Imaging was performed on a 3.0 Tesla whole-body scanner (Siemens TRIO), using an 8-channel head coil, at the Centre de recherche de l'Institut universitaire de gériatrie de

Montréal (CRIUGM) in Montréal, QC, Canada. Blood oxygenation level-dependent (BOLD) signal was acquired using a standard T2*-weighted gradient-echo EPI sequence (TR = 3 sec; TE = 30 msec; FOV = 220 mm; flip angle = 90°; 64 x 64 mosaic matrix; 180 volumes; 40 interleaved, axial slices per whole-brain volume at 3.4 mm thickness; in-plane resolution of 3.4 x 3.4 mm for isotropic voxels). Structural images were acquired using a high-resolution, T1-weighted MPRAGE sequence (TR= 2.3 ms; TE= 2.99 ms; flip angle= 9°; FOV= 256 mm; matrix = 256 x 256; 1 x 1 x 1.2 mm voxels; 160 slices per whole-brain volume).

Processing of imaging data began with online inspection after each run for poor contrast, field inhomogeneity, major artifacts, or subject movement great enough to compromise the effectiveness of online motion correction. All runs for one male subject were discarded due to excessive movement. All subsequent data preprocessing and analysis was done using BrainVoyager QX (Version 1.10; Brain Innovation; Maastricht, Netherlands). Offline preprocessing of functional images included slice-time correction, motion correction and realignment, co-registration of each subject's functional and anatomical volumes, spatial normalization (Talairach), and smoothing (8 mm FWHM Gaussian kernel), and temporal smoothing with a high-pass filter to remove low-frequency noise.

Statistical analysis of imaging data was performed using a general linear model (GLM) based on a canonical haemodynamic response function (HRF), which was used to model the expected BOLD signal change for each cue and visual stimulus event. A GLM was created for each individual run/subject that included the following predictors: two cue events defined by task ("pain" and "movement") and the stimuli events defined by pain level, task, and actor gender. Single-subject GLMs were then combined in group-level random-effect analyses. Although actor gender was included in the model, no significant effects were seen for this predictor and so male and female stimuli were combined in all of the analyses described below.

In total, seven analyses are reported that looked at various contrasts, as summarized in Table 1. To identify cortical areas responsive to pain expressions, we performed a contrast between all pain expressions and the neutral expressions in the PT (Contrast A), as well as the same subtraction contrast for the MT (Contrast B). A conjunction analysis on all pain expressions, versus neutral, was used to identify regions that showed main effects of pain across both tasks (Contrast C).

Cortical areas involved in the precise parametric encoding of the perceived amount of pain in the expressions were further examined in a regression analysis using the ratings provided by subjects for each stimulus in the PT. A new predictor was added to the design matrix and given a value for each trial based on the corresponding (normalized) pain rating. These values were used to weight each stimulus event of the PT trials in the GLM by modulating the amplitude of the predicted HRF. A conjunction analysis (Contrast D) was performed in order to identify areas that both demonstrated a stimulus-evoked response during the PT (unweighted predictor), and coded for the amount of pain (weighted predictor).

Differences between tasks in stimulus-related responses were obtained by contrasting responses to all stimuli in one task versus the other (Contrasts E and F). Task effects were also examined using only the pain expressions, or only the neutral expressions. To look for a possible interaction between task and pain expression, task effects were compared for strong pain versus neutral expressions (Contrast G).

In general, for all contrasts, a directed search was first conducted on a group of a priori defined areas, including the anterior cingulate cortex, insula, medial prefrontal cortex, and medial temporal structures including the amygdala. This was followed by a global search over the rest of the brain. A statistical threshold of $p < 0.05$ (corrected) and a $t > 4.01$ was used in the directed search based on an estimated volume of 250 mm3, and a $p < 0.001$ (uncorrected) and a $t > 4.7$ was used in the whole-brain global search. Additional peaks found at $p < 0.005$ ($t > 3.25$) were reported to protect against Type II error.

Table 1. Models used in the analysis of imaging data in this study.
The main models discussed are A, D, E, and F. Note: pain 0 = neutral; pain 1 = mild pain; pain 2 = moderate pain; pain 3 = strong pain.

Model	Description	Formula
A	Effect of pain expression in pain task (PT).	$pain(1,2,3)_{PT} – pain0_{PT}$
B	Effect of pain expression in movement task (MT).	$pain(1,2,3)_{MT} – pain0_{MT}$
C	Effect of pain expression across both tasks (conjunction).	$[pain(1,2,3)_{PT} – pain0_{PT}] \cap [pain(1,2,3)_{MT} – pain0_{MT}$
D	Effect of amount of perceived pain on stimulus-evoked responses in PT.	$(pain0,1,2,3)_{PT} \cap [pain0,1,2,3 * pain\ ratings]_{PT}$
E	Task effect on stimulus-evoked responses: PT minus MT.	$[pain(0,1,2,3)]_{PT} – [pain(0,1,2,3)]_{MT}$
F	Task effect on stimulus-evoked responses: MT minus PT.	$[pain(0,1,2,3)]_{MT} – [pain(0,1,2,3)]_{PT}$
G	Interaction between amount of pain expressed and task	$[pain(3)_{PT} – pain(3)_{MT}] – [pain(0)_{PT} – pain(0)_{MT}]$

RESULTS

Behavioral Results

In the PT trials, subject ratings for the amount of pain expressed (0-100) matched the pre-defined levels – neutral/no pain (pain 0; mean ± SD = 1.68 ± 3.48), mild (pain 1; 22.25 + 10.17), moderate (pain 2; 46.41 + 13.98), and strong (pain 3; 70.01 + 13.08), showing that subjects not only differentiated significantly between the levels ($F(3,51) = 463.81$; $p < 0.001$), but that they also perceived the intended pain level of the stimuli. There was no effect of the gender of the subjects or of the actors on pain ratings.

Imaging Results

Effects of Pain Expression

A contrast was performed between pain and neutral faces in the PT to find areas where activation showed a significant effect for pain expression during the evaluation of pain (Contrast A; see Table 2 and Figure 2). Peaks of activation associated with pain expression were found bilaterally in the posterior ACC and in a cluster overlapping the IFG and the aINS. Additional peaks were noted bilaterally in the superior frontal (posterior part; premotor) and pre-central gyri, the left frontal gyrus, bilateral post-central gyrus (primary sensory), right STG, and bilateral IPL and precuneus. Visual areas where significant peaks appeared included the bilateral occipitotemporal junction, middle occipital gyrus, and left lingual gyrus. Subcortical areas of activation included the bilateral thalamus and midbrain/pons, the right lateral globus pallidus and putamen, and the right cerebellum.

The same contrast performed for the MT (Contrast B) produced few results (see Supplementary Table S1). A single significant peak was found at the border between the right posterior cingulate and adjacent white matter (tal: 21, -19, 37; $t = 4.03$; $p < 0.001$) and subthreshold activation was found in occipital and occipitotemporal visual areas. The conjunction of pain faces versus neutral across both tasks (Contrast C) also produced few significant results other than bilateral activation of occipital and occipitotemporal visual areas, and bilateral posterior middle temporal gyrus (see Supplementary Table S2). Subthreshold activation was also found in some of the frontal areas identified in Contrast A.

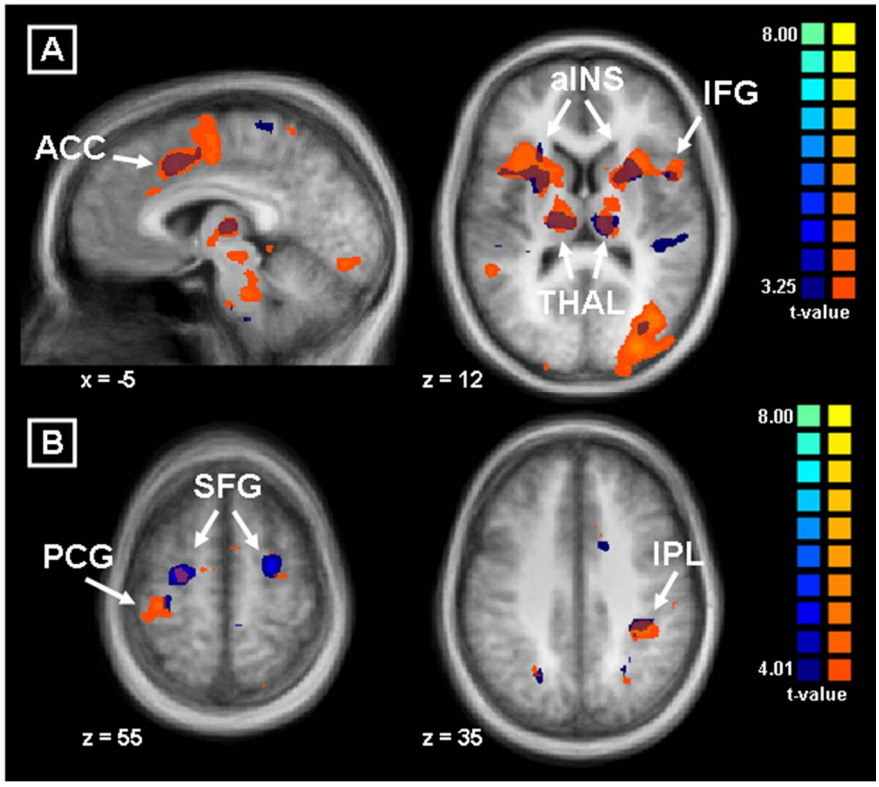

Figure 2. Effects of pain expression (Contrast A; blue) and amount of pain perceived (Contrast D; orange).
A: Overlapping clusters for the contrast of pain minus neutral and for the pain ratings regression analysis in the supracallosal ACC, anterior INS, and thalamus (lowered threshold is for better visualization of anterior INS activation clusters; $p < 0.005$, uncorrected). B: Overlapping clusters in the PCG, SFG, and IPL ($p < 0.001$, uncorrected). See Table 2 for coordinates and t-values of peaks.

Table 2. Effects of pain expression.
(A) Effects of pain expression: peak values for areas of significant BOLD response change identified by analysis of pain minus neutral in the pain task trials. (B) Effects of amount of pain perceived: peak values for areas of significant BOLD response change identified by conjunction analysis of weighted and unweighted pain task trials. Note: Identification and labeling of brain regions. Coordinates for activation peaks are given in Talairach Space according to the Talairach atlas incorporated into the BrainVoyager QX software package. Brodmann area (BA) labels identified using the original Talairach atlas (Talairach and Tournoux, 1988) and the online application for the Talairach Daemon (TD) database (Lancaster et al., 2000). $P < 0.001$ (uncorrected) unless otherwise indicated. *$P < 0.002$; peaks in the insular cortex are from overlapping clusters in the two contrasts (A and D).

			(A) Pain Expression				(B) Amount of Pain Perceived			
Anatomical location	**Hemisphere**	**BA**	**x**	**y**	**z**	**t-value**	**x**	**y**	**z**	**t-value**
FRONTAL LOBE										
superior frontal gyrus	R	6	12	-13	70	5.43	-	-	-	-
	R	6	24	-7	55	5.13	30	-10	46	4.61
	L	6	-21	-10	49	5.51	-21	-7	49	5.25
inferior frontal gyrus (frontal operculum)	R	44	-	-	-	-	48	5	19	4.86
inferior frontal gyrus (pars orbitalis)	L	11/47	-48	26	-11	5.19	-	-	-	-
anterior cingulate cortex	R	24/32	15	5	46	5.48	-	-	-	-
(supracallosal)	R	24	9	11	31	4.78	9	11	43	4.51
	L	24/32	-6	11	43	4.55	-9	8	43	5.28
pre-central gyrus	R	4	39	-7	25	5.58	-	-	-	-
	L	4	-12	-28	61	5.32	-	-	-	-
	L	4	-	-	-	-	-36	-25	61	5.12
INSULAR LOBE										
inferior frontal gyrus / anterior insula	R		42	8	16	4.36	-	-	-	-
	L		-47	11	5	3.80*	-	-	-	-
anterior insula	R		-	-	-	-	33	8	4	4.98
	L						-33	20	10	4.56
PARIETAL LOBE										
central sulcus / postcentral gyrus	R	3/4	9	-37	61	5.17	-	-	-	-
	L	1/2/3	-9	-34	61	5.29	-	-	-	-
postcentral gyrus/parietal operculum	R	1/2/3	54	-19	28	4.84	-	-	-	-
postcentral gyrus (S1)	L	3	-30	-31	52	4.45	-37	-29	58	4.66
superior parietal lobe	L	7	-	-	-	-	-18	-61	40	5.17
precuneus	R	7	12	-67	40	5.44	-	-	-	-
	L	7	-12	-67	43	4.58	-	-	-	-
intraparietal sulcus	R	7/40	24	-58	40	4.77	-	-	-	-
	L	7?	-21	-61	31	5.03	-	-	-	-
inferior parietal lobule	R	40	33	-34	37	4.73	33	-34	37	5.39
	R	40	27	-64	28	4.76	-	-	-	-
TEMPORAL LOBE										
anterior/posterior transverse temporal gyrus/STG	R	41/42	51	-25	7	5.24	-	-	-	-
occipitotemporal junction	R	37	39	-61	1	5.21	39	-67	6	6.20
	R	37	-	-	-	-	45	-61	-5	7.08
	L	37	-42	-64	1	5.12	-42	-64	1	4.91
OCCIPITAL LOBE										
superior occipital gyrus	R	19	-	-	-	-	30	-67	28	5.34
middle occipital gyrus	R	18/19	27	-85	7	4.91	27	-85	1	5.80
	L	18/19	-21	-82	1	5.74	-24	-88	-2	5.27

lingual gyrus	R	18	18	-82	-8	4.28	-	-	-	-
fusiform gyrus	R	19	-	-	-	-	9	-70	-11	5.12
SUBCORTICAL										
thalamus	R	-	9	-19	10	5.58	6	-19	7	4.65
	L		-15	-16	10	4.56	-12	-16	10	4.82
lateral globus pallidus	R	-	18	-1	-2	5.71	-	-	-	-
putamen	R	-	24	8	10	4.71	-	-	-	-
	R		15	8	7	5.05	15	8	7	4.29
	L		-	-	-	-	-27	-1	-5	4.96
cerebellum	R	-	15	-40	-38	4.13	-	-	-	-
	R		-	-	-	-	24	-52	-20	4.70
	L		-	-	-	-	-33	-40	-20	4.78
midbrain / pons	R	-	6	-22	-35	4.45	9	-22	-35	5.00
	L		-9	-22	-38	4.46	-	-	-	-
mesencephalon/pons	L	-	-	-	-	-	-9	-22	-8	4.42

Main Effects of Perceived Pain

Areas where activation showed a significant effect for the amount of pain perceived were revealed in the conjunction analysis combining all stimuli events in the PT with the corresponding regressor value based on the subjective pain ratings for each trial (Contrast D; see Table 2 and Figure 2). Peaks of activation were found bilaterally in the supracallosal ACC and aINS. Additional peaks were noted bilaterally in the superior frontal gyrus (premotor), the right ventral IFG, the left pre- and post-central gyri and superior and inferior parietal lobules, and bilaterally in the occipitotemporal junction. Visual areas where peaks appeared included bilateral middle occipital gyrus and right fusiform gyrus. Subcortical areas of activation included the left putamen, and bilateral thalamus, midbrain/pons, and cerebellum.

Main Effects of Tasks

We contrasted all stimuli events in the PT versus all stimuli events in the MT to find areas where activation showed a significant task effect (Contrast E; see Table 3 and Figure 3). Positive peaks associated with the pain evaluation task were found in bilateral/midline SFG (anterior part), anterior medial frontal gyrus, and subgenual ACC. Additional peaks were noted in the left anterior IFG, and posterior and anterior regions of the left STG. Visual areas where peaks appeared included bilateral middle occipital gyrus and left lingual gyrus.

Regions showing stronger activation in the MT versus the PT (Contrast F; see Table 3 and Figure 3) were identified in bilateral superior frontal gyrus (posterior part) and precentral gyrus, and in three regions of the left middle frontal gyrus. Additional peaks were noted

bilaterally in the IPL, the left intraparietal sulcus, the left precuneus, and the occipito-temporal junction.

Similar patterns of activation were found when contrasting the two tasks using only the pain expressions, or only the neutral expressions. A direct contrast of task effects for strong pain, versus task effects for neutral, did not produce any significant results (Contrast G), consistent with the main effects of task across stimuli.

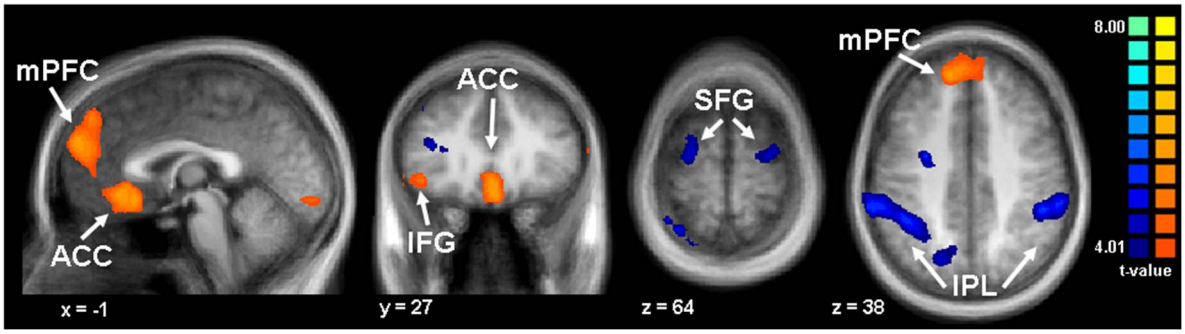

Figure 3. Effects of task.
For the pain task, (Contrast E; orange) clusters of activation were observed bilaterally in the mPFC and ACC, and in the left ventral IFG. For the movement task (Contrast F; blue), clusters were observed bilaterally in the posterior SFG (premotor region) and the IPL ($p < 0.001$, uncorrected). See Table 3 for coordinates and t-values of peaks.

Table 3. Main effects of task: peak values for areas of significant BOLD response change during viewing of the facial expression stimuli in the pain evaluation task condition (A), versus the movement discrimination task condition (B).
Note: See note in Table 2 regarding identification and labeling of brain regions.

Anatomical location	Hemisphere	BA	x	y	z	t-value
(A) PAIN TASK > MOVEMENT TASK						
FRONTAL LOBE						
medial frontal gyrus	R	8	1	50	43	5.28
	R	9	6	49	18	4.93
	L	8	-9	47	43	6.34
	L	9	-3	56	31	6.40
	L	9	-4	50	15	5.01
inferior frontal gyrus	L	45/47	-42	29	-2	5.30
	L	47	-42	20	-14	5.09
anterior cingulate cortex (subgenual)	R	24/32	3	23	-8	6.75
	M/Bilat	24/32	0	32	-5	6.46
TEMPORAL LOBE						
superior temporal gyrus (temporal pole)	L	38	-45	14	-23	5.16
superior temporal gyrus (posterior)	L	20	-51	-31	1	4.18
middle temporal gyrus (temporal pole)	L	38	-45	17	-32	4.97
OCCIPITAL LOBE						
middle occipital gyrus	R	18	30	-88	1	5.93
	L	17/18	-15	-91	1	6.51
lingual gyrus	L	17	-12	-91	-5	8.62
	L	18	-15	-72	-5	5.12
	L	18	-17	-85	-11	9.86
(B) MOVEMENT TASK > PAIN TASK						
FRONTAL LOBE						
superior frontal gyrus (posterior)	R	6	27	-10	64	4.70
	L	6	-21	10	61	4.99
	L	6	-21	-13	52	5.09
medial frontal cortex	L	6	-12	2	52	4.28
paracentral sulcus	L	6	-24	-13	46	5.34
	L	6	-27	4	37	6.44
middle frontal gyrus (in inferior frontal sulcus)	L	46	-36	26	19	5.33
middle frontal gyrus	L	8	-45	23	43	4.43
	L	46	-42	44	28	6.05
	L	9/10	-39	48	27	5.08
	L	46	-45	41	10	4.46
PARIETAL LOBE						
superior parietal lobule (precuneus)	L	7	-15	-67	49	4.89
	L	7	-18	-70	37	5.05
	L	7	-9	-70	52	5.07
superior/inferior parietal lobule (intraparietal sulcus)	L	40	-30	-46	34	5.67
inferior parietal lobule	R	40	45	-37	40	6.11
	L	40	-54	-40	49	6.13
TEMPORAL LOBE						
occipitotemporal junction	L	19	-48	-58	-8	4.52

DISCUSSION

The results of the present study support, strengthen, and go beyond earlier work in several important ways. For the first time, we looked at the evaluation of pain in others in a paradigm combining dynamic pain expressions (rather than static images), several well-controlled discrete levels of pain including a neutral expression, and a target task involving the online rating of pain perceived in each stimulus (as opposed to passive viewing and post-scan stimuli evaluation). Most importantly, we contrasted the brain responses to facial expressions during a pain assessment task to the brain responses produced by a control task involving discrimination of facial movements and performed on the same stimuli. As in previous studies, we found that regions of the ACC and aINS are activated in response to pain in others [e.g. (Botvinick et al., 2005; Jackson et al., 2005; Lamm et al., 2007a; Lamm et al., 2007b; Saarela et al., 2007; Singer et al., 2004)]. Moreover, the magnitude of the brain response was related to the amount of pain perceived, both in the supracallosal ACC and the aINS, as well as in premotor, motor, and parietal areas. BOLD activation specifically related to pain evaluation, as opposed to movement discrimination, was found in medial PFC areas, including the perigenual ACC, and in the ventral IFG. In contrast, activation during the movement discrimination task was found predominantly in areas previously associated with motor imitation, action observation, and visuospatial processing/visual attention, such as the superior and inferior parietal lobules, and premotor regions of the superior frontal gyrus. Interestingly, task effects were observed in the ventral IFG (pain > movement), and premotor and parietal association areas (movement > pain), all of which are recently posited to be part of a human mirror neuron system (MNS) [(Iacoboni, 2005) however, see a different view on the functional role of the IFG in (Morin and Grezes, 2008)]. This network, in turn, may be a key component of the mechanism of shared representations proposed to underlie empathy and other social cognitive functions (Iacoboni, 2009). For the first time, we show a dissociation of the ventral IFG, which appears to be more engaged in extraction of the meaning of the facial expression (pain evaluation task), and premotor and parietal regions, which appear to be more involved in the extraction of the physical aspects of movement (movement discrimination task).

Coding for Perceived Pain

In keeping with the findings of other studies looking at the perception of facial expressions of pain (Botvinick et al., 2005; Saarela et al., 2007), we found that the explicit evaluation of pain, versus neutral expressions, was associated with increased activation bilaterally in the supracallosal ACC and aINS. These areas have also been identified in other protocols examining the perception of pain in others using videos of people receiving injuries (Ochsner et al., 2008) and still images of hands and feet in painful conditions (Jackson et al., 2005). Moreover, these areas have also been implicated in the observation and recognition of other emotional expressions, such as disgust (Jabbi et al., 2008; Jabbi et al., 2007; Wicker et al., 2003), fear (Morris et al., 1998), anger and sadness (Blair et al., 1999), and pleasure/happiness (Jabbi et al., 2008; Jabbi et al., 2007). Most importantly, and in confirmation of the expectations of this study, these areas showed evidence of coding for the amount of pain perceived, as the BOLD signal changes showed a parametric correlation with the pain ratings provided by the subjects. The ACC peaks found here match those of Jackson and colleagues regarding brain activation and pain ratings for images of hands and feet in painful conditions (Jackson et al., 2005). The parametric effects previously reported between subjects in that earlier study are confirmed here within subjects and across stimuli.

The supracallosal ACC peaks (Contrasts A & D) observed here lie very near to those found in previous studies looking at correlations between subjective ratings for self-pain and BOLD signal increases (Christmann et al., 2007; Coghill et al., 2003). Although a direct comparison cannot be made here, as there was no self-pain condition in this protocol, the ACC peak locations are somewhat more anterior to those typically seen for self-pain, a distinction that has been previously described (Jackson et al., 2006b; Morrison and Downing, 2007) and which suggests that ACC regions for self-experienced vs. observed pain may be closely adjacent, but not necessarily overlapping completely [(see review (Jackson et al., 2006b)]. Consistent with a role of the posterior supracallosal ACC in motor preparation for both self-pain and observed pain, ACC involvement could reflect a form of motor mirroring (Morrison et al., 2007) and/or the engagement of an alarm or warning system, which not only responds to potential threats, but also codes for their magnitude. Engagement of the insula may represent a complementary part of this warning system that puts the potential threat in the context of a negative internal state (Craig, 2002).

We also find that activation in bilateral premotor areas and the right IPL correlates with perceived pain, and with the observation of pain vs. neutral faces in the PT condition. Overall, however, involvement of these areas appears to be related more to perception of the motor aspects of the pain faces, as the contrast of tasks revealed stronger bilateral involvement in the movement task. Interestingly, analyses of pain expression and pain ratings further showed increases in BOLD signal within the IPL and the ventral IFG, areas suggested to be part of the human 'mirror neuron' system (Iacoboni, 2005), and in the STG, an area implicated in the perception of biological motion (Allison et al., 2000). The task-effect analysis shows a distinction between these areas; the IFG and STG are more active in the pain task, whereas the IPL and premotor areas are more active in the movement task. This fits well with the model described by Iacoboni and colleagues, in which the frontal lobe MNS areas are thought to code for intentions of observed actions, whereas parietal areas code for their motor aspects (Iacoboni, 2005).

Task effects: emotional versus motor mirroring

To investigate how task demands affect the processing of facial expressions of pain, we measured brain response to pain expressions under two task conditions: the evaluation of pain, and the evaluation of facial movement. As the same stimuli were used for both tasks, differences in brain activity revealed differences in the specific processing requirements of each task. For pain faces versus neutral in the pain task (Contrast A), we observed a pattern of activation that included areas previously implicated in the perception of pain in the self, as well as areas identified as potential locations for the human MNS. However, relative involvement of the latter showed a strong effect of task. We found that evaluation of the emotional content (i.e. magnitude of pain perceived) of the pain expressions, versus movement evaluation, elicited increased activation in bilateral medial and superior PFC (BA 9/10), the subgenual ACC (BA 24/32), and the posterior STG, areas theorized to underlie "mentalizing" – that is, thinking about the mental and emotional states of others (Amodio and Frith, 2006; Frith and Frith, 2006; Frith and Frith, 2003). We can consider the pain task as conscious, deliberate mentalizing: thinking about the amount of pain someone else is expressing. The fact that increased activation of these areas is seen in the task contrast, but not in a contrast of pain versus neutral, and that it is also seen in a task contrast of only neutral expressions, suggests

they underlie a general process of emotional evaluation rather than a specific response to a particular emotional state (e.g. pain). The mPFC activation is compatible with that found in a previous study by Jackson and colleagues (Jackson et al., 2006a) when they contrasted the task of assessing pain in an individual with that of attributing damage to an artificial limb (no mentalizing). The current results expand the idea that midline PFC structures are crucial for mentalizing and perspective taking during the perception/evaluation of emotional states, including those associated with pain and conveyed by facial expression.

We also found increased activation in the left inferior frontal gyrus/ventrolateral PFC (putative BA 45/47) during the pain vs. movement task, which also appeared in the contrasts examining areas coding for the amount of pain. Repeatedly, this area has been implicated in the human MNS, responding to both observed and imitated non-emotional actions of the hands (Buccino et al., 2001; Iacoboni et al., 1999; Kilner et al., 2009), and the face (Leslie et al., 2004; van der Gaag et al., 2007), as well as to facial expressions of emotion (Carr et al., 2003; Schulte-Ruther et al., 2007; van der Gaag et al., 2007). This dual response, for pain task and amount of pain, is consistent with a role in the extraction of emotional meaning from the perceived facial movements.

As described earlier, peaks in the ventral IFG found for the pain task were also identified in the contrast of pain minus neutral (in the pain task), and correlated with the amount of pain perceived. However, the other MNS areas identified in those initial contrasts, the superior and inferior parietal lobules, are significantly more active during the MT. While other studies on the observation of facial expressions of pain, as well as other emotions, have observed activations in ventral IFG and the IPL, here these areas have been dissociated by task effects, based on whether the subject is attending to the emotional or motor aspects of the expression. It may be that while both areas are involved in the human MNS, the ventral IFG region underlies understanding of the meaning of an expression, whereas the IPL is more directly related to movement discrimination. In this way, the "motor" mirroring may support the judgment of emotional intensity, without being specifically related to pain or emotion. This type of dissociation of mirror areas – i.e. IFG vs. parietal areas – has been demonstrated in a study looking at static pictures of hands in painful vs. non-painful conditions that also used a control task (counting fingers) in opposition to rating pain (Gu and Han, 2007). In this

study, the IFG was more active when subjects rated pain, while parietal areas were more active when subjects counted fingers.

Thus, the IPL and SPL appear to be critical to the perception of movement and spatial features of facial expression, rather than emotional content, and may then be involved primarily in the response to the motor, rather than the emotional, dimension of the face stimuli. That bilateral premotor areas show more activation during the movement task supports this idea; these areas have identified in other studies looking specifically at mirroring for facial expression and other facial movements (Carr et al., 2003; Enticott et al., 2008; Leslie et al., 2004; van der Gaag et al., 2007). The combined activation of the parietal lobule with premotor areas appears to reflect primarily the processing of facial movements, as shown by the task contrast. This movement-related response may nevertheless contribute relevant information about the amount of pain perceived, as demonstrated by the significant response observed in the parametric analysis of pain in the pain task.

Finally, robust task-related effects were also observed in primary visual cortices (bilateral middle and inferior occipital gyri; BA 18/19), during the PT versus the MT, and most likely reflect top-down modulation of sensory processing by emotional stimuli. Previous studies have shown amplified processing of emotional versus neutral stimuli in visual and auditory sensory areas (Grandjean et al., 2005; Schupp et al., 2003; Vuilleumier and Driver, 2007). The present results further demonstrate that the response of visual areas to identical facial stimuli is enhanced when the task requires in-depth processing, beyond basic analysis of dynamic properties of facial movements, in order to extract the meaning of the expression.

Potential limitations

The absence of a self-pain or self-expression condition may be considered potential limitations of this study. In regards to the former, many previous studies have shown involvement of these regions of the ACC and aINS for self-pain (the two relevant areas discussed here in terms of shared representations for self- and other-pain), including several with protocols using a combination of self- and other-pain conditions. These earlier studies have shown, if not overlap, at least an adjacency of regions responding to self- and other- pain in BA 24/32 and the aINS (Jackson et al., 2006b). Furthermore, the goal of the present study was not to find direct, voxel-specific overlap of self and other pain processing, but rather to

show how recruitment of these areas is determined by task demands, and is modulated by the amount of pain perceived. Finally, we of course cannot state that activation in areas previously implicated in MNS involve specific populations of mirror neurons; the activation clusters are simply located in the relevant regions.

The absence of a pain expression execution condition is perhaps more problematic, as paradigms investigating mirror neuron activity do usually include both observation and execution conditions. While the inclusion of a self-expression condition would have provided a more direct test of motor mirroring, the specific objective of the present study was to compare two aspects of observation, emotional versus motor, rather than to compare observation and execution. However, future studies could expand the results presented here by including an execution condition, and thus more specifically addressing overlap between regions involved in both the observation and production of pain expressions.

Finally, although only pain expressions were presented in this study, activation during the pain-task condition included several areas previously implicated in the perception of facial expressions of emotion. While we cannot generalize or extend our findings to other emotions, it would be difficult to support an argument that they are specific to pain. Brain response to expressions of pain versus expressions of other negative emotions has not been well investigated, but some preliminary results suggest there is some overlap (Chen et al., 2006). However, one benefit to looking at pain, versus other emotions, is that the neural basis for the experience of self-pain has been extensively studied and a well-recognized "pain matrix" has been identified (Apkarian et al., 2005).

CONCLUSION

In conclusion, we first confirmed earlier findings that implicate the ACC and INS in the perception and evaluation of pain in others. Second, we found that the explicit evaluation of pain expression engages areas considered to be important for general, high-level social cognition – specifically, thinking about what others are feeling. Third, and most significantly, we find that areas recently posited to be part of a human mirror neuron system are differently engaged, depending on the specific task requirements. Some authors have referred to the

activity of anterior INS and posterior ACC during both observation and experience of pain and other emotions as “emotional mirroring”; the present study extends this idea by demonstrating a dissociation between emotional and motor mirroring when observers process the meaning of the facial expression of pain, versus when they process the facial movements conveying this meaning.

Notes

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SUPPLEMENTARY TABLES

Table S1. Effects of pain expression in the movement task (Contrast B).
Peak values for areas of significant BOLD response change identified by analysis of pain faces minus neutral faces in the movement task condition. Note: Coordinates for activation peaks are given in Talairach Space according to the Talairach atlas incorporated into the BrainVoyager QX software package. Brodmann area (BA) labels identified using the original Talairach atlas (Talairach and Tournoux, 1988) and the online application for the Talairach Daemon (TD) database (Lancaster et al., 2000). $P < 0.001$ (uncorrected) unless otherwise indicated. *$P < 0.005$ (uncorrected).

Anatomical location	Hemisphere	BA	x	y	z	t-value
FRONTAL LOBE						
posterior cingulate	R	24	21	-19	37	4.03
TEMPORAL LOBE						
inferior temporal gyrus (posterior part) / occipitotemporal junction	R	19	45	-55	-2	3.74*
occipitotemporal cortex	R	20	39	-37	-20	3.31*
OCCIPITAL LOBE						
lingual gyrus	R	17	21	-85	1	4.00*
	L	18	-15	-91	-11	3.90*
SUBCORTICAL						
thalamus	M/Bilat		0	-10	-2	3.39*

Table S2. Conjunction analysis of pain and movement tasks. (Contrast C).
Peak values for areas of significant BOLD response change during pain versus neutral expressions in both tasks. Note: See note in Table S1 regarding identification and labeling of brain regions. *P < 0.005 (uncorrected).

Anatomical location	Hemisphere	BA	x	y	z	t-value
FRONTAL LOBE						
superior frontal gyrus	*L*	*6*	*-21*	*-10*	*49*	*3.45**
medial frontal gyrus	*L*	*6*	*-6*	*2*	*49*	*3.54**
PARIETAL LOBE						
parietal lobe / supramarginal gyrus	R	40	36	-37	28	4.23
TEMPORAL LOBE						
superior temporal gyrus	R	41	45	-31	7	4.35
middle temporal gyrus	R	37	36	-58	4	4.22
	L	37	-39	-58	4	4.24
OCCIPITAL LOBE						
middle occipital gyrus	R	17	24	-82	1	4.96
inferior occipital gyrus	L	17	-18	-91	-8	4.40
SUBCORTICAL						
globus pallidus	R		21	-4	-2	3.58*
	L		-18	2	-2	3.30*
cerebellum	R		33	-55	-23	4.18

REFERENCES

Allison, T., Puce, A., McCarthy, G., 2000. Social perception from visual cues: role of the STS region. Trends Cogn Sci 4, 267-278.

Amodio, D.M., Frith, C.D., 2006. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci 7, 268-277.

Apkarian, A.V., Bushnell, M.C., Treede, R.D., Zubieta, J.K., 2005. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 9, 463-484.

Blair, R.J., Morris, J.S., Frith, C.D., Perrett, D.I., Dolan, R.J., 1999. Dissociable neural responses to facial expressions of sadness and anger. Brain 122 (Pt 5), 883-893.

Botvinick, M., Jha, A.P., Bylsma, L.M., Fabian, S.A., Solomon, P.E., Prkachin, K.M., 2005. Viewing facial expressions of pain engages cortical areas involved in the direct experience of pain. Neuroimage 25, 312-319.

Buccino, G., Binkofski, F., Fink, G.R., Fadiga, L., Fogassi, L., Gallese, V., Seitz, R.J., Zilles, K., Rizzolatti, G., Freund, H.J., 2001. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. Eur J Neurosci 13, 400-404.

Carr, L., Iacoboni, M., Dubeau, M.C., Mazziotta, J.C., Lenzi, G.L., 2003. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proc Natl Acad Sci U S A 100, 5497-5502.

Chakrabarti, B., Bullmore, E., Baron-Cohen, S., 2006. Empathizing with basic emotions: common and discrete neural substrates. Soc Neurosci 1, 364-384.

Chen, J.-I., Simon, D., Duncan, G., Rainville, P., 2006. Brain responses to facial expressions of pain and negative emotions., Poster session presented at: 35th Annual Meeting of the Society for Neuroscience. Society for Neuroscience, Washington.

Christmann, C., Koeppe, C., Braus, D.F., Ruf, M., Flor, H., 2007. A simultaneous EEG-fMRI study of painful electric stimulation. Neuroimage 34, 1428-1437.

Coghill, R.C., McHaffie, J.G., Yen, Y.F., 2003. Neural correlates of interindividual differences in the subjective experience of pain. Proc Natl Acad Sci U S A 100, 8538-8542.

Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 3, 655-666.

Enticott, P.G., Johnston, P.J., Herring, S.E., Hoy, K.E., Fitzgerald, P.B., 2008. Mirror neuron activation is associated with facial emotion processing. Neuropsychologia 46, 2851-2854.

Fadiga, L., Fogassi, L., Pavesi, G., Rizzolatti, G., 1995. Motor facilitation during action observation: a magnetic stimulation study. J Neurophysiol 73, 2608-2611.

Frith, C.D., Frith, U., 2006. The neural basis of mentalizing. Neuron 50, 531-534.

Frith, U., Frith, C.D., 2003. Development and neurophysiology of mentalizing. Philos Trans R Soc Lond B Biol Sci 358, 459-473.

Grafton, S.T., Arbib, M.A., Fadiga, L., Rizzolatti, G., 1996. Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. Exp Brain Res 112, 103-111.

Grandjean, D., Sander, D., Pourtois, G., Schwartz, S., Seghier, M.L., Scherer, K.R., Vuilleumier, P., 2005. The voices of wrath: brain responses to angry prosody in meaningless speech. Nat Neurosci 8, 145-146.

Gu, X., Han, S., 2007. Attention and reality constraints on the neural processes of empathy for pain. Neuroimage 36, 256-267.

Hadjistavropoulos, T., Craig, K.D., 2002. A theoretical framework for understanding self-report and observational measures of pain: a communications model. Behav Res Ther 40, 551-570.

Hennenlotter, A., Schroeder, U., Erhard, P., Castrop, F., Haslinger, B., Stoecker, D., Lange, K.W., Ceballos-Baumann, A.O., 2005. A common neural basis for receptive and expressive communication of pleasant facial affect. Neuroimage 26, 581-591.

Iacoboni, M., 2005. Neural mechanisms of imitation. Curr Opin Neurobiol 15, 632-637.

Iacoboni, M., 2009. Imitation, empathy, and mirror neurons. Annu Rev Psychol 60, 653-670.

Iacoboni, M., Woods, R.P., Brass, M., Bekkering, H., Mazziotta, J.C., Rizzolatti, G., 1999. Cortical mechanisms of human imitation. Science 286, 2526-2528.

Jabbi, M., Bastiaansen, J., Keysers, C., 2008. A common anterior insula representation of disgust observation, experience and imagination shows divergent functional connectivity pathways. PLoS One 3, e2939.

Jabbi, M., Swart, M., Keysers, C., 2007. Empathy for positive and negative emotions in the gustatory cortex. Neuroimage 34, 1744-1753.

Jackson, P.L., Brunet, E., Meltzoff, A.N., Decety, J., 2006a. Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. Neuropsychologia 44, 752-761.

Jackson, P.L., Meltzoff, A.N., Decety, J., 2005. How do we perceive the pain of others? A window into the neural processes involved in empathy. Neuroimage 24, 771-779.

Jackson, P.L., Rainville, P., Decety, J., 2006b. To what extent do we share the pain of others? Insight from the neural bases of pain empathy. Pain 125, 5-9.

Keysers, C., Gazzola, V., 2009. Expanding the mirror: vicarious activity for actions, emotions, and sensations. Curr Opin Neurobiol 19, 666-671.

Kilner, J.M., Neal, A., Weiskopf, N., Friston, K.J., Frith, C.D., 2009. Evidence of mirror neurons in human inferior frontal gyrus. J Neurosci 29, 10153-10159.

Lamm, C., Batson, C.D., Decety, J., 2007a. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. J Cogn Neurosci 19, 42-58.

Lamm, C., Nusbaum, H.C., Meltzoff, A.N., Decety, J., 2007b. What are you feeling? Using functional magnetic resonance imaging to assess the modulation of sensory and affective responses during empathy for pain. PLoS One 2, e1292.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, et al. (2000) Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 10: 120-131.

Leslie, K.R., Johnson-Frey, S.H., Grafton, S.T., 2004. Functional imaging of face and hand imitation: towards a motor theory of empathy. Neuroimage 21, 601-607.

Montgomery, K.J., Haxby, J.V., 2008. Mirror neuron system differentially activated by facial expressions and social hand gestures: a functional magnetic resonance imaging study. J Cogn Neurosci 20, 1866-1877.

Morin, O., Grezes, J., 2008. What is "mirror" in the premotor cortex? A review. Neurophysiol Clin 38, 189-195.

Morris, J.S., Friston, K.J., Buchel, C., Frith, C.D., Young, A.W., Calder, A.J., Dolan, R.J., 1998. A neuromodulatory role for the human amygdala in processing emotional facial expressions. Brain 121 (Pt 1), 47-57.

Morrison, I., Downing, P.E., 2007. Organization of felt and seen pain responses in anterior cingulate cortex. Neuroimage 37, 642-651.

Morrison, I., Lloyd, D., di Pellegrino, G., Roberts, N., 2004. Vicarious responses to pain in anterior cingulate cortex: is empathy a multisensory issue? Cogn Affect Behav Neurosci 4, 270-278.

Morrison, I., Peelen, M.V., Downing, P.E., 2007. The sight of others' pain modulates motor processing in human cingulate cortex. Cereb Cortex 17, 2214-2222.

Ochsner, K.N., Zaki, J., Hanelin, J., Ludlow, D.H., Knierim, K., Ramachandran, T., Glover, G.H., Mackey, S.C., 2008. Your pain or mine? Common and distinct neural systems supporting the perception of pain in self and other. Soc Cogn Affect Neurosci 3, 144-160.

Preston, S.D., de Waal, F.B., 2002. Empathy: Its ultimate and proximate bases. Behav Brain Sci 25, 1-20; discussion 20-71.

Rizzolatti, G., Fadiga, L., Matelli, M., Bettinardi, V., Paulesu, E., Perani, D., Fazio, F., 1996. Localization of grasp representations in humans by PET: 1. Observation versus execution. Exp Brain Res 111, 246-252.

Saarela, M.V., Hlushchuk, Y., Williams, A.C., Schurmann, M., Kalso, E., Hari, R., 2007. The compassionate brain: humans detect intensity of pain from another's face. Cereb Cortex 17, 230-237.

Schulte-Ruther, M., Markowitsch, H.J., Fink, G.R., Piefke, M., 2007. Mirror neuron and theory of mind mechanisms involved in face-to-face interactions: a functional magnetic resonance imaging approach to empathy. J Cogn Neurosci 19, 1354-1372.

Schupp, H.T., Junghofer, M., Weike, A.I., Hamm, A.O., 2003. Emotional facilitation of sensory processing in the visual cortex. Psychol Sci 14, 7-13.

Simon, D., Craig, K.D., Gosselin, F., Belin, P., Rainville, P., 2008. Recognition and discrimination of prototypical dynamic expressions of pain and emotions. Pain 135, 55-64.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not sensory components of pain. Science 303, 1157-1162.

Talairach, J., Tournoux, P., 1988. Co-planar stereotaxic atlas of the human brain : 3-dimensional proportional system : an approach to cerebral imaging. G. Thieme: Thieme Medical Publishers, Stuttgart; New York.

van der Gaag, C., Minderaa, R.B., Keysers, C., 2007. Facial expressions: what the mirror neuron system can and cannot tell us. Soc Neurosci 2, 179-222.

Vuilleumier, P., Driver, J., 2007. Modulation of visual processing by attention and emotion: windows on causal interactions between human brain regions. Philos Trans R Soc Lond B Biol Sci 362, 837-855.

Vuilleumier, P., Pourtois, G., 2007. Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. Neuropsychologia 45, 174-194.

Wicker, B., Keysers, C., Plailly, J., Royet, J.P., Gallese, V., Rizzolatti, G., 2003. Both of us disgusted in my insula: the common neural basis of seeing and feeling disgust. Neuron 40, 655-664.

Article 2: Mirroring pain in the brain: emotional expression versus motor imitation.

Title: Mirroring pain in the brain: emotional expression versus motor imitation.

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ABSTRACT

Perception of pain in others via facial expressions has been shown to involve brain areas responsive to self-pain, biological motion, as well as both performed and observed motor actions. Here, we investigated the involvement of these different regions during emotional and motor mirroring of pain expressions using a two-task paradigm, and including both observation and execution of the expressions. BOLD responses were measured as subjects watched video clips showing different intensities of pain expression and, after a variable delay, either expressed the amount of pain they perceived in the clips (pain task), or imitated the facial movements (movement task). In the pain task condition, pain coding involved overlapping activation across observation and execution in the anterior cingulate cortex, supplementary motor area, inferior frontal gyrus/anterior insula, and the inferior parietal lobule, and a pain-related increase (pain vs. neutral) in the anterior cingulate cortex/supplementary motor area, the right inferior frontal gyrus, and the postcentral gyrus. The 'mirroring' response was stronger in the inferior frontal gyrus and middle temporal gyrus/superior temporal sulcus during the pain task, and stronger in the inferior parietal lobule in the movement task. These results strongly suggest that while motor mirroring may contribute to the perception of pain expressions in others, interpreting these expressions in terms of pain content draws more heavily on networks involved in the perception of affective meaning.

INTRODUCTION

How do we perceive the pain that others experience? There are many channels through which the emotional and sensory state of another person can be communicated to an observer. Vocalizations – such as "ouch!", and gestures – such as a hand flinching away from a hot stove, are cues which can indicate that someone has experienced a painful stimulus. Another important cue, particularly in situations where the painful stimulus is internal or occurs out of sight of the observer, is facial expression.

In an earlier fMRI study looking at brain response to video clips of facial expressions of pain [1], we found that observation of dynamic facial expressions of pain elicited activation in the anterior cingulate cortex (ACC) and the anterior insula (aINS), two areas associated with the processing of the affective aspects of the pain experience in the self [2], as well as with the perception of pain in others [3,4,5,6,7,8,9].

However, we also noted activation of the inferior parietal lobule (IPL) and the inferior frontal gyrus (IFG); two regions theorized to comprise, along with the superior temporal sulcus (STS), a "core circuit" of the putative 'human mirror neuron system' (MNS), thought to contribute to the internal representation of observed actions and related socially-relevant phenomena [10]. It has been further suggested that it is the interaction of this core system with other networks for motor, sensory, and affective functions that supports various processes of social cognition, such as imitation, action understanding, language, and even emotion recognition and empathy [11]. Previous work looking at this system in humans has demonstrated activation of the IFG and/or IPL during both observation and execution, and/or imitation, of actions such as grasping or reaching for objects with the hands [12,13,14,15,16], facial movements such as chewing or biting [12], and even facial expressions of emotion [15,17,18,19,20]. Our earlier findings suggest that this mirror-type activity may also be involved in the perception of pain in others, via an internal motor simulation of a facial expression [1].

One question that has arisen in regards to motor mirroring is which areas might code for goals, intentions, or meaning of actions. In the context of an action such as grasping an object, evidence suggests that both the IFG and the IPL may be sensitive not only to these types of goals, but also the intention toward them [21,22]. However, these are transitive

actions; goal-directed movements that involve the manipulation of external objects. Facial expressions of emotion are intransitive – while they may be produced in response to an external object, they indicate an internal state of the responder. This raises a fundamental question about the role of MNS regions in the coding of what an expression indicates – i.e. its emotional meaning – in addition to coding simply its motor aspects.

In our earlier work [1], not only did we observe these areas of the MNS to be recruited in the perception of facial expressions of pain, but their relative involvement in the process depended on whether subjects were explicitly attending to and evaluating the amount of pain they observed, or if they were performing a control task involving the discrimination of facial movements. More specifically, when subjects focused on estimating the amount of pain expressed in the videos, the IFG demonstrated stronger activity, whereas activity in the IPL was stronger when subjects focused on the movement of the facial features. Thus, these results revealed a dissociation between frontal and parietal regions possibly involved in processing emotional content of the meaning of the expression as opposed to mirroring facial movements, respectively.

However, making the claim of mirroring activity requires an experimental protocol that involves both the observation and the execution of a particular action. To this end, we designed a new protocol that included both observation and execution of pain faces. Subjects viewed a series of 1-second facial expressions of pain, and performed one of two tasks: express, using their own face, the amount of pain they perceived in the video clip (pain task), or imitate the facial movements (movement task). Importantly, we included a variable time-interval between the observation and execution events (i.e. delayed execution) in order to better separate the two functions.

In addition to replicating the previous results, the first main objective of the current study was to investigate overlapping activation in the IFG and the IPL for both observation and execution of pain expressions, and whether this activation would be stronger in response to pain expressions, versus neutral expressions. Our second main objective was to investigate the role of the IFG and IPL in the extraction of the meaning of the pain expressions. To this aim, we manipulated task demands, predicting a stronger response in the IFG when subjects focused on the affective meaning of the pain expression (pain expression task condition), and

a stronger response in the IPL when subjects focused on the facial movements (movement imitation task condition).

METHODS

Subjects

Participants were 23 healthy volunteers (13 women; 18-33 years old). Subjects were informed as to the purpose and procedures of the study, and written consent was obtained prior to the experiment.

Ethics statement

The study was approved by the research ethics committee of the Centre de recherche de l'Institut universitaire de gériatrie de Montréal (CRIUGM) in Montréal, Canada.

Stimuli

The stimuli used in this study were one-second video clips of facial expressions of pain, previously chosen and validated for our earlier study [1], and taken from a larger collection of facial expression stimuli created and validated in our laboratory [23]. The stimuli set comprised 96 clips portraying four levels of pain: neutral (pain 0), mild (pain 1), moderate (pain 2), and strong (pain 3), as produced by 8 actors and actresses, with 3 versions of each pain level per actor/actress.

Experimental procedure

Prior to entering the scanner, subjects were instructed how to perform the two experimental tasks, and completed a brief practice session with ten additional stimuli not used in the actual experiment. For the pain expression task (pain task, PT) – subjects were instructed to express the amount of pain shown in the clip, using their own face ("use your own face to express the amount of pain that you see"). This was intended to induce stronger activation of a mental representation of the affective meaning of the facial expression and the involvement of a self-referential framework during production of the corresponding

expression. For the movement imitation task (movement task, MT), subjects were instructed to imitate the facial movements shown in the clip, using their own face ("use your own face to imitate the facial movements yourself"). This was intended to emphasize the visuo-motor mapping of the expression. Although both tasks possibly involve automatic visuo-motor mapping as well as the automatic activation of mental representation of the meaning of the expression, the contrast between these tasks was expected to reveal brain regions more closely related to one process or the other.

Trial structure is shown in Figure 1. At the beginning of each trial, a one-second cue screen indicated which task – "pain" or "movement" – to perform on the upcoming clip. Next, the clip was presented (observation phase), immediately followed by a variable length pause of 3, 4, or 5 seconds, during which the screen displayed the cue word for the current task ("pain" or "movement") below a dash symbol. This pause was followed by the response window of 3 seconds, during which the dash symbol was replaced by a circle, signaling the subject to begin their facial response (execution phase). Each trial ended with an ITI (inter-trial-interval) of 3, 4, or 5 seconds, during which subjects viewed a screen marked with a fixation cross.

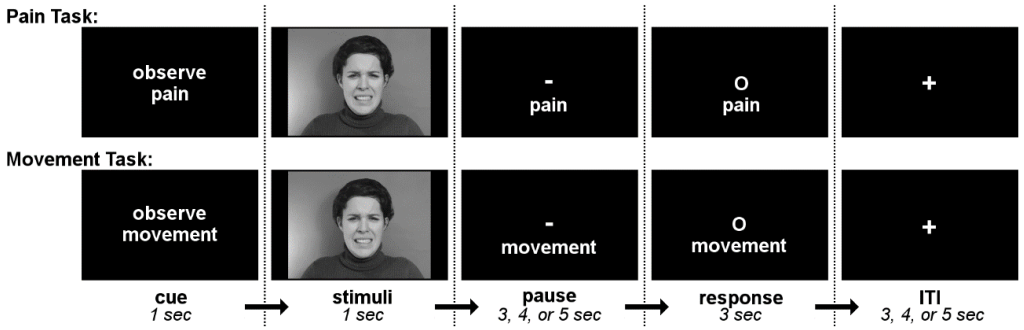

Figure 1. Trial structure for pain expression and movement imitation tasks.
At the beginning of each trial, a one-second cue screen indicated which task – "pain" or "movement" – to perform on the upcoming clip. Next, the clip was presented (observation phase), immediately followed by a variable length pause of 3, 4, or 5 seconds, during which the screen displayed the cue word for the current task ("pain" or "movement") below a dash symbol. This pause was followed by the response window of 3 seconds, during which the dash symbol was replaced by a circle, signaling the subject to begin their facial response (execution phase). Each trial ended with an ITI (inter-trial-interval) of variable duration, during which subjects viewed a screen marked with a fixation cross.

Each clip was shown twice, once per task, for a total of 192 trials, presented in 6 functional runs of 32 trials each. Within each run, the order of stimuli was pseudo-randomized according to pain level, actor gender and identity, and task, and the order in which the runs were presented was reversed for half of the subjects. The complete scanning session consisted of the 6 functional runs (8 minutes each) and an anatomical run (9:50 minutes).

After completing the imaging session, subjects exited the scanner and were brought into a separate room where they completed a rating session. The subjects were re-shown the clips using a laptop computer, and asked to rate each clip for the intensity of pain expressed, using a VAS from "no pain" to "worst pain imaginable." To do this, subjects used the computer keyboard to position an on-screen slider bar on the VAS and to enter their response; the initial position of the slider at the start of each response window was randomized and the final position was recorded and linearly converted to a number between 0 and 100. The 92 clips were presented in a single block and their order within the block was randomized by the presentation software.

Stimuli presentation and the recording of subject responses during both the scanning and post-scanning test sessions were done using the E-Prime 1.2 presentation package

(Psychology Software Tools, Inc.). An LCD Projector (EPSON, EMP-8300 XGA) was used to project the visual stimuli onto a screen inside the scanning chamber that subjects could view via a mirror positioned over the head coil.

Behavioral responses: Facial Action Coding System

Subjects' faces were videotaped during functional runs using an MR-compatible camera (MRC Systems, Heidelberg, Germany) mounted onto the headcoil. The camera captured the face of the subject as it was reflected by a mirror attached above the headcoil, and was positioned so as not to obstruct the visual field of the subject (as described in [24]). The onset of each response window was marked by an audio cue incorporated into the E-Prime presentation program that was recorded in the video but was not audible to the participant; this cue was used to identify the beginning of each 3-second response window for subsequent facial analysis.

Offline analysis of subjects' facial displays during the response windows (execution phase) was done using the Facial Action Coding System (FACS; Ekman & Friesen 1987; see [25]), a finely-grained anatomically-based system that is considered the gold standard when decoding facial expressions and which involves the evaluation of the movement of different muscle groups – "Action Units" (AUs) – of the face. This analysis was used to verify that the responses matched the different pain intensities shown in the clips, to test for potential task differences, and to assess the similarity between the expressions produced by the subjects and those shown in the target clips. Facial movements produced in the 3-second response window were analyzed in each subject, and for both tasks, for a subset of two actors (one female, one male, randomly chosen) and including the four pain levels. FACS analysis was performed by two coders who were blind to the experimental conditions and trained by a certified FACS coder, using a software program designed for the analysis of observational data (Observer Video-Pro 9; Noldus Information Technology, NL). For the next stage of analysis, we selected the Action Units (AUs) that occurred in at least 5% of the coded segments and were more frequent during pain expressions, vs. neutral; this method is consistent with that used in previous studies (e.g. [26,27]). The frequency and intensity values of the selected AUs (AUs 4, 6, 7, 9, 10, 16, 25, 26, 43) were then combined into mean composite scores of pain-relevant facial responses [27]. The effects of task, and the pain intensity represented in the target clips

on facial responses, were tested by entering these composite scores into a within-subject analysis of variance involving the factors type of task (pain vs. movement) and pain intensity (level 1-4). Furthermore, we assessed the similarity between the facial display produced by the subject and the expression shown in the target clips. This accuracy index was calculated by dividing the number of AUs that were shown by both the subject and the actor by the number of AUs that were shown in total, by both. Accuracy values were calculated separately for each pain intensity level and for each task, and were analyzed using analysis of variance (with two within-subject factors: type of task and pain intensity). This index was intended to verify that subjects produced more similar expressions in the movement imitation task than the pain expression task, consistent with the instructions of the movement task, which emphasized accuracy of imitation, vs. the instructions of the pain task, which emphasized transposition of the meaning of the expression onto a self-referential framework.

Magnetic Resonance Imaging (MRI) equipment, data acquisition and analysis

Imaging was performed on a 3.0 Tesla whole-body scanner (Siemens TRIO), using an 8-channel headcoil at the Centre de recherche de l'Institut universitaire de gériatrie de Montréal (CRIUGM) in Montréal, QC, Canada. Blood oxygenation level-dependent (BOLD) signal was acquired using a standard T2*-weighted gradient-echo EPI sequence (TR = 3 sec; TE = 30 msec; FOV = 220 mm; flip angle = 90°; 64 x 64 mosaic matrix; 160 volumes; 40 interleaved, ascending, axial slices per whole-brain volume at 3.4 mm thickness; in-plane resolution of 3.44 x 3.44 x 3.4 mm nearly isotropic voxels). Structural images were acquired using a high-resolution, T1-weighted MPRAGE sequence (TR= 2.3 ms; TE= 2.91 ms; flip angle= 9°; FOV= 256 mm; matrix = 256 x 256; 1 x 1 x 1.2 mm voxels; 160 slices per whole-brain volume).

Processing of imaging data began with online inspection after each run for poor contrast, field inhomogeneity, major artifacts, or subject movement great enough to compromise the effectiveness of online motion correction. All subsequent data preprocessing and analysis was done using BrainVoyager QX (Version 2.2.1; Brain Innovation; Maastricht, Netherlands). Offline preprocessing of functional images included slice-time correction, motion correction and realignment, co-registration of each subject's functional and anatomical

volumes, spatial normalization (Talairach), spatial smoothing (8 mm FWHM Gaussian kernel), and high-pass temporal smoothing.

Statistical analysis of imaging data was performed using a general linear model (GLM) based on a canonical haemodynamic response function (HRF), which was used to model the expected BOLD signal change for each visual stimulus event and task response window. A GLM was created for each individual run/subject that included the following predictors: stimuli events defined by pain level (pain 0, 1, 2, and 3) and task (PT and MT); and response windows, also defined by pain level and task (i.e. 8 regressors of interest). Single-subject GLMs were then combined in group-level random-effect analyses.

In total, nine main analysis models are reported (Table 1). As the current study was designed to expand on an earlier work, the first four models were taken directly from our earlier study, to confirm the reliability of our previous findings in a separate group of subjects using the same stimuli and a similar methodology. To this end, the first two contrasts (Pain:Obs(PT) and Pain:Obs(MT)) were used to identify cortical areas responsive to observation of pain expressions (stimuli events); these involved a weighted contrast between all observed pain expressions and all observed neutral expressions in the PT (Pain:Obs(PT)), as well as the same subtraction contrast for the MT (Pain:Obs(MT)). Further, task differences in the stimulus-related responses were obtained by contrasting brain responses to all stimuli in one task versus the other (PT – MT (Obs) and MT – PT (Obs)).

Our main analyses involved conjunction analyses investigating the overlapping effects of observation and execution of pain faces in the different conditions (conjunction of random effects). To this end, a first model looked at the observation and execution of facial expressions in the pain task, across all pain intensity levels (Obs∩Exec(PT)). The second model examined pain-related responses (weighted contrast of pain vs. neutral expression) that were common to the observation and execution (i.e. conjunction of stimulus and response phases of the task) in the pain task (Obs∩Exec(Pain;PT)), and in the movement task (Obs∩Exec(Pain;MT)). The third, and final, set of models looked for task effects (pain vs. movement) found in both observation and execution (PT – MT (Obs∩Exec) and MT – PT (Obs∩Exec)).

Although this article focuses on the main effects of pain and task across the observation and execution phases, a supplementary analysis was also performed to examine

the interaction of pain and task during observation (models 1 vs. 2 from Table 1). A supplementary conjunction analysis of observation and execution was also performed for this interaction (models 6 vs. 7). These additional results are reported in Table S4.

For all contrasts, a directed search was first conducted on a set of a priori areas, based on our previous work using a very similar methodology (Budell et al., 2010), including the ACC, INS, mPFC, IFG, and IPL leading to a total estimated search volume 250 mm3. The statistical threshold was adjusted to $p < 0.05$ (corrected) and $t > 4.01$, based on random field theory [28]. Additional peaks found at $p < 0.005$ ($t > 3.25$) were reported to protect against Type II error in the case of a priori areas. This was followed by a global search over the rest of the brain, using $p < 0.001$ (uncorrected) and $t > 4.7$.

Table 1. Contrast models used in the analysis of imaging data in this study.
Contrasts 1-4 replicate the analyses conducted in our previous study using a similar methodology [1]. Contrasts 5-9 test for overlap in brain activation across the observation and execution phases (conjunction) for all expressions in the pain task (5), for pain-related effects (pain vs. neutral) in the pain (6) and movement task (7), and for task effects (8: PT>MT; 9: MT>PT). Note: pain 0 = neutral; pain 1 = mild pain; pain 2 = moderate pain; pain 3 = strong pain; PT – pain task; MT = movement task; Obs = observation (clip); Exec = execution (response).

Model #	Contrast name	Contrast description	Formula
1	**Pain:Obs(PT)**	Effect of pain expression in pain task, (PT), during stimuli event.	clip: $pain(1,2,3)_{PT} - pain0_{PT}$
2	**Pain:Obs(MT)**	Effect of pain expression in movement task (MT), during stimuli event.	clip: $pain(1,2,3)_{MT} - pain0_{MT}$
3	**PT – MT (Obs)**	Task effect on stimulus-evoked responses: PT minus MT, during stimuli event.	clip: $[pain(0,1,2,3)]_{PT} - [pain(0,1,2,3)]_{MT}$
4	**MT – PT (Obs)**	Task effect on stimulus-evoked responses: MT minus PT, during stimuli event.	clip: $[pain(0,1,2,3)]_{MT} - [pain(0,1,2,3)]_{PT}$
5	**Obs∩Exec(PT)**	Overlap for observation and execution of facial expressions in pain task (PT) (conjunction)	clip ∩ response: $[pain(0,1,2,3)]_{PT}$
6	**Obs∩Exec(Pain;PT)**	Effect of pain expression (vs. neutral) in pain task, (PT), across both stimuli and response events (conjunction).	clip ∩ response: $pain(1,2,3)_{PT} - pain0_{PT}$
7	**Obs∩Exec(Pain;MT)**	Effect of pain expression (vs. neutral) in movement task (MT), across both stimuli and response events (conjunction).	clip ∩ response: $pain(1,2,3)_{MT} - pain0_{MT}$
8	**PT – MT (Obs∩Exec)**	Task effect on stimulus-evoked responses: PT minus MT, across both stimuli and response events (pain expressions only, no neutral) (conjunction)	clip ∩ response: $[pain(1,2,3)]_{PT} - [pain(1,2,3)]_{MT}$
9	**MT – PT (Obs∩Exec)**	Task effect on stimulus-evoked responses: MT minus PT, across both stimuli and response events (pain expressions only, no neutral) (conjunction)	clip ∩ response: $[pain(1,2,3)]_{MT} - [pain(1,2,3)]_{PT}$

RESULTS

Behavioral results

Facial displays produced by participants, and assessed using the FACS, were compared across pain intensity levels and tasks. First, the overall amount of facial action produced during responses was comparable across the two task conditions (main effect of task: $F(1,21) = 1.33$; $p > 0.05$). However, the amount of pain expressed increased significantly across pain levels (main effect of pain intensity: $F(3,63)=120.02$; $p < 0.001$). This effect of pain intensity was not significantly different between tasks (interaction: $F(3,63)=2.62$; $p > 0.05$), confirming that the participants' responses adequately coded pain intensity in both tasks (Figure 2). In addition, the accuracy index, which assessed the similarity between the expressions produced by the participants and those of the actors, confirmed that facial responses were more similar to the target expression in the movement imitation task condition than the pain coding task condition (MT – 76.1 % accuracy; PT – 69.6 % accuracy; main effect of task: $F(1,21) = 13.3$; $p = 0.002$; see Figure 2).

Analysis of the post-scan rating trials demonstrated that subject ratings for the amount of pain expressed (0-100; converted from VAS) matched the pre-defined levels: neutral/no pain (pain 0; mean ± SD = 15 ± 1.5), mild (pain 1; 23.5 ± 7.1), moderate (pain 2; 48.0 ± 9.2), and strong (pain 3; 72.1 ± 9.7). These results demonstrated that subjects not only differentiated significantly between the levels ($F(2,35) = 838.5$; $p < 0.001$), but they also perceived the intended pain level of the stimuli.

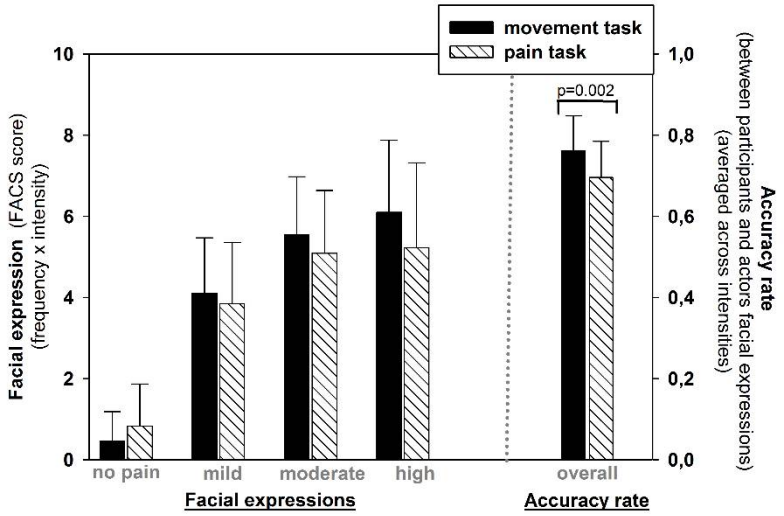

Figure 2. Results of FACS analysis of facial expressions.
(A) Facial response, by intensity level, during subject responses. Results of FACS analysis of facial expressions shown by participants for different pain intensity levels, during response phase of both movement task and pain task conditions. ANOVA confirmed a main effect of pain levels ($p < 0.001$) but no significant effect of, or interaction with, task ($p > 0.05$). (B) Facial response accuracy. Facial responses displayed by the participants were more similar to those in the target expressions in the movement task condition, vs the pain task condition ($p = 0.002$).

Imaging Results

Observation of pain expressions: replication of effects of pain and task

Four initial contrasts were performed to confirm the reliability of the results from our previous study that formed the bases for the hypotheses of this study. The first two looked at observation of pain vs. neutral expressions in the pain task (pain-related response; Pain:Obs(PT)) and in the movement task (Pain:Obs(MT)), and the third and fourth contrasts were performed to compare activation during the observation of pain expressions in the pain task vs. movement task (PT – MT (Obs)and MT – PT (Obs)). Pain-related responses in the PT (Pain:Obs(PT)) confirmed the previous findings showing robust activation in ACC and aINS, which was not observed in the MT (Pain:Obs(MT)) (see Tables S1 and S2). Task-related contrasts confirmed that the PT (PT – MT (Obs)) produced stronger activation in the midline medial frontal gyrus and the ACC, and in the left IFG, while the MT (MT – PT (Obs)) produced stronger activation bilaterally in the IPL (see Table S3). The supplementary analysis of the interaction between pain and task, during observation, confirmed robust effects in

several areas activated by pain expressions in the pain task (e.g. supracallosal ACC and IFG) and in the movement task (e.g. IPL) (see Table S4).

Observation and execution of pain expression

The first main objective of this study was to test if areas activated during the observation of pain expressions are also activated during the execution of pain expressions. A conjunction analysis was performed for the stimuli and response events, across all expression levels in the PT condition (contrast Obs∩Exec(PT); Table 2 and Figure 3). Peaks of activation were found in a large midline cluster extending bilaterally, from the medial/superior frontal gyri to the supracallosal ACC (cingulate motor area; [29,30,31,32], bilaterally in the pre- and post-central gyri, and in large clusters including the posterior IFG (premotor, putative BA 44) and the aINS in both hemispheres. Additional peaks were noted bilaterally in the posterior part of the superior frontal gyrus (premotor), the precentral gyrus (PrCG; primary motor; putative face area), the right superior temporal gyrus (STG), and bilaterally in the IPL and intraparietal sulcus (IPS). Occipital areas where significant peaks appeared included the bilateral cuneus, occipito-temporal junction, and lingual gyrus. Subcortical activation included the bilateral thalamus, globus pallidus and putamen, and cerebellum. Although this was not a main goal of this study, the corresponding analysis performed on data acquired in the MT showed similar effects, indicating that this overlap between observation and execution was clearly not specific to the PT (not shown). However, there were very clear task differences in the magnitude of responses in several areas, as described below (see Effects of task in observation and execution).

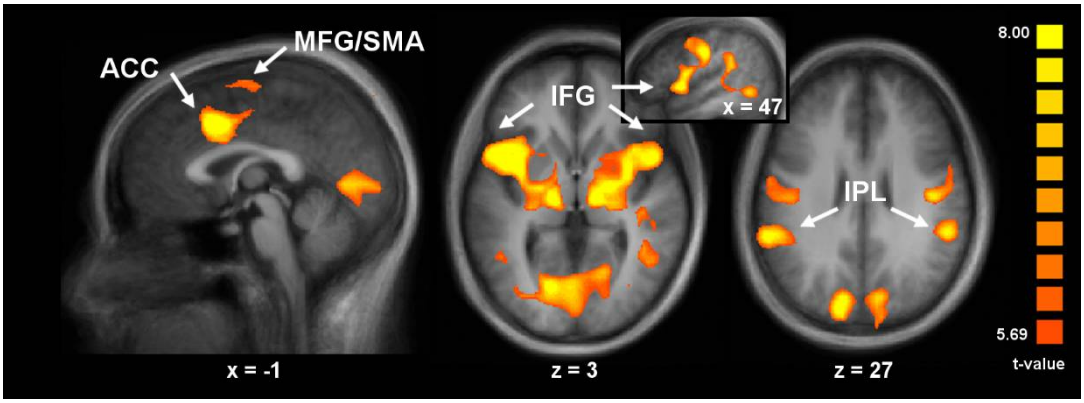

Figure 3. Areas commonly activated during observation and execution phases of the pain task (Obs∩Exec(PT)).
Significant clusters are shown in the mACC, the SMA, IFG/aINS, and IPL ($p < 0.001$, uncorrected). Inset figure shows rostral-caudal extent of activation in the right IFG. See Table 2 for coordinates and peak t-values.

Table 2. Effects of observation and execution of facial expressions in the pain expression task (including pain and neutral conditions).
Peak values for areas of significant BOLD response change identified by conjunction analysis of stimuli presentation (clip) and task performance (response) (Obs∩Exec(PT)).
Note regarding identification and labeling of brain regions: coordinates for activation peaks are given in Talairach Space according to the Talairach atlas incorporated into the BrainVoyager QX software package. Brodmann area (BA) labels identified using the original Talairach atlas [64] and the online application for the Talairach Daemon (TD) database [65]. $P < 0.001$ (uncorrected) unless otherwise indicated.

Anatomical location	Hemisphere	BA	x	y	z	t-value
FRONTAL LOBE						
medial/superior frontal gyrus	R	6	5	-8	66	7.19
	R	6	5	1	63	6.69
anterior cingulate cortex (*posterior/supracallosal*)	MID	24	2	-3	42	6.72
	MID	24	-1	10	39	11.58
middle frontal gyrus	L	6	-49	4	42	7.32
precentral gyrus (*extending into postcentral*)	R	6/4	50	-11	36	8.83
	R	6/4	44	-17	33	8.97
	L	6/4	-43	-17	36	8.29
	L	6/4	-58	-5	15	8.28
inferior frontal gyrus (posterior)	R	44	47	7	3	9.17
	L	44	-49	10	6	11.14
INSULAR LOBE						
middle insula	R	13	29	1	9	9.94
	L	13	-37	1	6	10.08
anterior insula	R	13	47	7	3	9.17
PARIETAL LOBE						
inferior parietal lobule / intraparietal sulcus	R	40	32	-44	36	7.13
	L	40	-40	-50	36	7.43
	R	40	53	-38	24	8.77
	L	40	-58	-41	27	8.64
TEMPORAL LOBE						
middle temporal gyrus (posterior)	R	37	44	-53	0	7.81
	L	37	-43	-53	6	6.65
superior temporal gyrus (posterior)	R	22/42	50	-32	6	6.21
OCCIPITAL LOBE						
cuneus	R	19	8	-77	24	7.93
	L	19	-13	-80	30	9.06
lingual gyrus	R	17	17	-62	3	7.49
	MID/L	18	-4	-71	3	7.85
	L	18	-16	-71	3	8.62
SUBCORTICAL						
globus pallidus	R	–	17	-8	12	9.74
	L	–	-16	-5	15	8.97
putamen	R	–	20	-11	3	9.39
thalamus	R	–	11	-17	9	10.62
	L	–	-13	-17	9	10.41
cerebellum	R	–	32	-56	-21	10.13
	R	–	5	-71	-36	5.54
	L	–	-31	-59	-18	8.74
	L	–	-10	-68	-39	5.62

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Observation and execution of pain versus neutral expressions

A complementary question related to our first objective was to investigate how pain content affected the mirroring response. To this end, we wanted to verify if pain-related responses (pain vs. neutral) during the observation of pain expressions are also activated during the execution of pain expression. A conjunction analysis was performed on stimuli and response events, after contrasting pain expressions minus neutral expressions in the PT (i.e. pain-related effect common to the observation and execution phases of the PT; contrast Obs∩Exec(Pain;PT); Table 3 and Figure 4). Peaks of activation were found in a large midline cluster extending bilaterally from the superior frontal gyrus to the supracallosal ACC; bilaterally in pre- and post-central gyri, and in a cluster including the left posterior IFG (premotor, putative BA 44) and the aINS (similar, sub-threshold activation was also observed in the right IFG/aINS; see Table 3). Additional peaks were noted bilaterally in the supramarginal gyri of the IPL. Occipital areas where significant peaks appeared included the bilateral cuneus and lingual gyrus. Subcortical areas of activation included bilateral thalamus, globus pallidus and putamen, and cerebellum. The same conjunction analysis of pain-related responses across observation and execution phases of the MT (contrast Obs∩Exec(Pain;MT); Table 3) revealed significant effects only in the face area of the central region, as well as in the parietal operculum, lingual gyrus and thalamus.

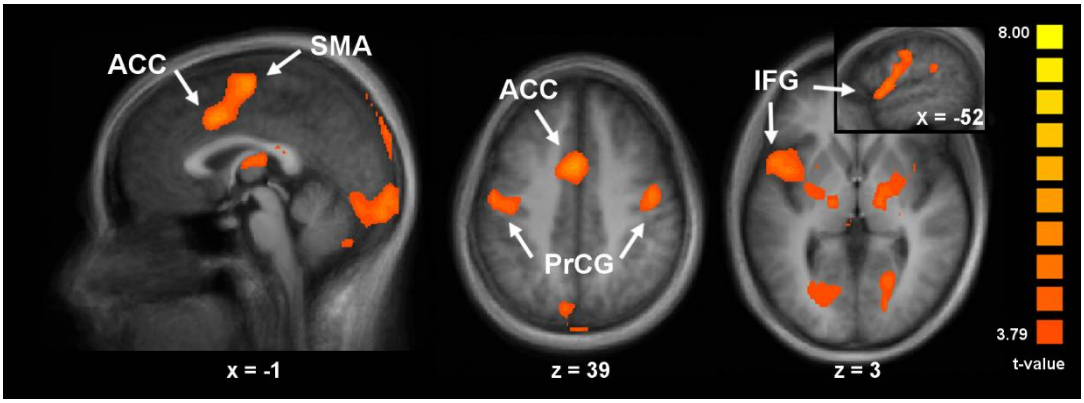

Figure 4. Effects of pain during both observation and execution of pain expressions (Obs∩Exec(Pain;PT)).
A conjunction analysis of pain expressions, minus neutral expressions, during clip and response events, in the pain task condition revealed clusters in the ACC, SMA, the bilateral PrCG, and the left IFG/aINS ($p < 0.001$, uncorrected). Inset figure shows rostral-caudal extent of activation in the left IFG. See Table 3 for coordinates and t-values of peaks.

Table 3. Effects of observation and execution of pain expressions (pain vs neutral).
Peak values for areas of significant BOLD response change identified by conjunction analysis of pain minus neutral during both stimuli presentation (clip/observation) and task performance (response/execution), in the (A) pain expression task condition (Obs∩Exec(Pain;PT)) and (B) movement imitation task condition (Obs∩Exec(Pain;MT)).See note in Table 2 regarding identification and labeling of brain regions. *p < 0.002.

Anatomical location	Hemisphere	BA	x	y	z	t-value
(A) PAIN EXPRESSION TASK						
FRONTAL LOBE						
medial/superior frontal gyrus	MID	6	-1	-11	60	5. 08
anterior cingulate cortex (supracallosal)	MID	32	-4	7	39	5.85
precentral gyrus	R	6/4	44	-8	39	4.99
	L	6/4	-46	-17	36	5.13
	L	4/6	-49	-5	18	5.07
	L	4	-46	1	12	5.36
inferior frontal gyrus (posterior)	R	44	47	7	3	3.65*
	L	44/45	-49	4	9	5.03
	L	44/45	-52	10	3	4.90
INSULAR LOBE						
anterior insula	L	13	-40	13	6	4.77
middle insula	L	13	-43	4	3	5.21
PARIETAL LOBE						
inferior parietal lobule (supramarginal gyrus)	R	40	53	-32	24	4.18
	L	40	-55	-41	24	4.58
posterior cingulate cortex	MID	23	-1	-29	21	4.24
OCCIPITAL LOBE						
cuneus	L	19	-7	-77	36	4.50
superior occipital gyrus	R/MID	18/19	5	-95	27	5.24
lingual gyrus	R	19	17	-65	1	5.06
	L	19	-25	-71	6	4.65
SUBCORTICAL						
thalamus	R	–	17	-8	15	5.80
	L	–	-16	-8	12	5.75
	L	–	-13	-11	9	5.70
putamen	R	–	23	-2	12	5.95
	L	–	-25	-2	12	6.31
globus pallidus	R	–	17	-5	0	5.27
	L	–	-26	-8	0	4.80
cerebellum	R	–	11	-77	-18	6.10
	R	–	11	-92	-21	5.94
	R	–	32	-56	-24	6.83
	MID	–	2	-71	-39	4.21
(B) MOVEMENT IMITATION TASK						
FRONTAL LOBE						
precentral gyrus	R	6/4	35	-17	27	4.88
	L	6/4	-37	-14	30	4.67
PARIETAL LOBE						
inferior parietal lobule (supramarginal gyrus)	R	40	41	-32	27	4.03
postcentral gyrus	L	40	-43	-8	21	4.09
	L	40	-61	-20	15	4.25
OCCIPITAL LOBE						
lingual gyrus	R	17	17	-65	6	4.07
	L	17	-22	-74	6	4.49
SUBCORTICAL						
thalamus	R	–	14	-14	9	4.04
	L	–	-16	-17	9	4.45

Effects of task in observation and execution

The most critical question of this study concerns coding of the meaning of the pain expressions, versus the facial movements contained in the expressions, during both the observation and execution of facial expression. We examined the differential activation induced by task (PT vs. MT) using a conjunction analysis across stimuli and response events (contrasts PT – MT (Obs∩Exec) and MT – PT (Obs∩Exec); Table 4 and Figure 5). Positive peaks associated with the pain task (contrast PT – MT (Obs∩Exec)) were found in the midline medial/superior frontal gyrus, bilaterally in the IFG, and in the posterior cingulate cortex and precuneus. Note that the IFG peak, while located in putative BA 44, was slightly more anterior to the posterior IFG peaks found in the previous contrasts. Additional peaks were observed in the posterior portion of the middle temporal gyrus (MTG) and in the left superior occipital gyrus. Subcortical activation was observed bilaterally in the cerebellum. The conjunction of observation and execution in the reverse contrast (MT – PT (Obs∩Exec)) revealed activation in bilateral clusters extending along the fundus of the postcentral sulcus from the SPL into the IPL and IPS (Table 4 and Figure 5).

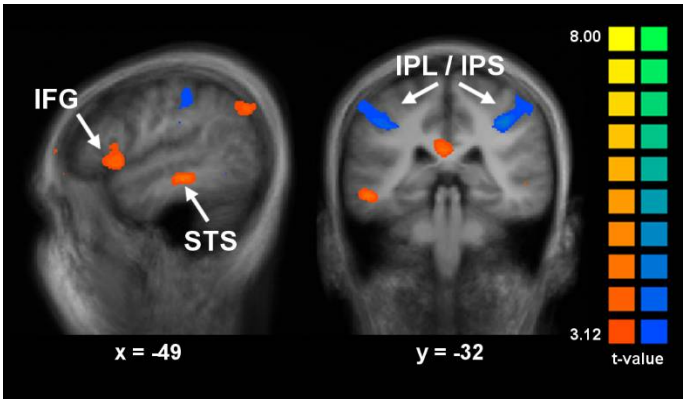

Figure 5. Effects of task during both observation and execution of pain expressions. For the pain task (PT – MT (Obs∩Exec); orange), a cluster of activation was observed in the left IFG, while bilateral clusters were observed in the IPL for the movement task (MT – PT (Obs∩Exec); blue) ($p \leq 0.005$, uncorrected). Analysis included pain expressions only, no neutrals. See Table 4 for coordinates and t-values of peaks.

Table 4. Main effects of task during both observation and execution (pain expressions only†):

Peak values for areas of significant BOLD response change during both the viewing and performance of pain expressions, in the pain expression task condition (A) (PT – MT (Obs∩Exec)), versus the movement imitation task condition (B) (MT – PT (Obs∩Exec)). See note in Table 2 regarding identification and labeling of brain regions. *p < 0.002. † Results are reported for pain expressions only. Similar results were obtained when including the neutral condition with only one exception, in the right IFG (‡ : t=2.31; not significant).

Anatomical location	Hemisphere	BA	x	y	z	t-value
(A) PAIN TASK > MOVEMENT TASK (pain expressions)						
FRONTAL LOBE						
medial/superior frontal gyrus	MID	6	-4	10	60	4.98
inferior frontal gyrus	R	44	47	19	0	3.44*‡
	L	44	-49	13	3	4.12*
TEMPORAL LOBE						
middle temporal gyrus (posterior portion)	L	21	-52	-32	-9	4.72
PARIETAL LOBE						
precuneus	L	31	-7	-74	30	3.93
posterior cingulate gyrus	L/MID	23/31	-4	-41	19	4.81
OCCIPITAL LOBE						
superior occipital gyrus	L	19	-43	-71	39	4.74
SUBCORTICAL						
cerebellum	R	–	35	-77	-42	4.29
	L	–	-31	-74	-42	4.57
(B) MOVEMENT TASK > PAIN TASK (pain expressions)						
PARIETAL LOBE						
inferior parietal lobule / intraparietal sulcus	R	40	35	-35	39	5.06
	L	40	-29	-41	39	4.88
	L	40	-55	-29	45	3.96*
postcentral gyrus	R	1/2/3	50	-23	36	4.70
	L	1/2/3	-58	-23	33	3.94*

The supplementary analysis of the interaction of pain expression (vs neutral) and task showed effects in several regions during the observation phase, and some of these regions also showed a similar effect during the execution phase, as revealed by the conjunction analysis of observation and execution on the interaction term (see Table S4). Areas showing stronger activation for pain expression (vs neutral) in the pain task included the left medial frontal gyrus, bilateral IFG, posterior cingulate cortex, left middle and inferior temporal gyri and the left cerebellum; whereas peaks of stronger activation for pain expression (vs neutral) in the movement task were observed bilaterally in the IPL/IPS. Peaks in the IFG and IPL/IPS closely matched those found in the conjunction of task effects.

DISCUSSION

The results of the current study reinforce, and move beyond, those of our earlier work in several important ways. For the first time, we investigated the overlap in brain response to the observation and execution of pain expressions, in an experimental protocol using dynamic pain expressions depicting different levels of pain. Importantly, the execution phase was separated temporally from the observation phase, allowing us to test the overlap (conjunction) between activation patterns with no overt motor confound in the observation phase and no overt visual confound in the execution phase. Results showed brain responses common to observed and executed facial expressions, consistent with "mirroring" properties and with previous studies on facial imitation [15,17,18,20,33]. More significantly, we investigated whether overlapping responses in different brain areas to both observation and execution of pain expressions may reflect either the processing of surface details of the expression, such as the movement or configuration of the facial features (movement task), or a deeper processing of the overall emotional meaning of the expression (pain task). This task contrast demonstrates that the decoding (observation) and the encoding (execution) of the meaning of the expression relies more strongly on the STS/MTG and the IFG, brain areas previously identified as responsive to biological motion [34,35,36,37,38] and motor observation and imitation [12,39], respectively, whereas attention to movement relies more on the IPL, another area previously identified as involved in the observation of motor actions [39,40]. Together, these findings

support the broader notion that mirroring processes support perception of emotional expressions – pain expressions, in this case; and demonstrate how the neural representation of emotional meaning may be partly segregated from the representation of the facial movements that constitute the expression.

As in previous studies [3,5,6,7,8,9,41], including our own [1], we found that regions of the supracallosal ACC and bilateral aINS are activated in response to pain in others (Pain:Obs(PT); see Table S1), but these effects were seen only when subjects were attending to the meaning of the expressions, and not when they attended to the motor aspects (Pain:Obs(MT); see Table S2). The locations of the peaks we observed in these regions are consistent with the activation observed in response to acute self-pain [42]. Furthermore, we were able to replicate the functional dissociation between the IFG and IPL during the observation of pain faces [1], with the IFG being more robustly activated when subjects focused on the meaning of the pain expression, and the IPL being more engaged when subjects focused on the facial movements.

Decoding pain expression: the role of mirroring

The first main objective of this study was to test whether areas of activation in the IFG and the IPL found during the observation of pain faces [1] were also involved in the delayed execution of pain expressions. Both regions are part of a putative human mirror neuron system [10], responding to both observed and executed actions. Although some studies have looked at the involvement of mirroring areas in the perception of facial expressions of emotions such as happiness, fear, disgust, sadness, or anger [15,17,18,20] and/or non-emotional mouth movements such as biting, chewing, or blowing out the cheeks [12,17], in most cases the execution phases of the experimental protocols occurred at the same time as the observation (i.e. imitation of the stimuli occurred simultaneously to the presentation of the stimuli) [15,18]; in only one study were the observation and execution phases temporally separated[17]. Here, we found robust, bilateral activation in the posterior IFG and the IPL, and we demonstrated significant involvement across observation and execution phases that were separated temporally in order to reduce confounding effects. This conjunction of stimuli and responses in the PT revealed not only the IFG and IPL, but also the ACC and aINS, areas which have been associated with affective mirroring for pain and disgust [1,3,6,7,43]. These

results confirm our hypothesis that the IFG and IPL, two components of the 'fronto-parietal human mirror neuron system' [10], show mirror-type responses for pain expressions, and fit with the hypothesis that an IFG/IPL 'core circuit' of imitation interacts with the INS to form a system for affective mirroring that supports social cognition [10], perhaps via an effective link between the IFG and the aINS [44]. That we can demonstrate a common response of these areas during both observation and execution of pain expressions supports the notion that mirroring of both emotional states and motor movements underlies the perception of pain in others via facial expression.

Additionally, we identified an area of the supracallosal ACC and adjacent supplementary motor area (SMA) that showed common activation for both observation and execution. This area was revealed in our previous study as coding for pain (vs. neutral) and showing modulatory effects of perceived pain intensity [1]. In the current study, this area also demonstrated a greater response to pain expressions, during both observation and execution. This subregion of the supracallosal ACC has been discussed in relation to the control of movement in response to aversive stimuli such as pain [45,46], including motor facilitation of withdrawal, and inhibition of approach [47,48], as well as pain expression (Kunz et al., 2011). Interestingly, recent work has demonstrated involvement of this region during voluntary motor responses in both painful and non-painful contexts, but not in painful contexts lacking the motor response [49]. Together with the SMA, an area supporting motor control of movements [29] and movement preparation [50,51], ACC involvement in the response to signals of pain in others may reflect motor readiness or priming. Whether this priming is for withdrawal behaviors or pain expression [52,53], its occurrence in response to both observed and executed pain expressions is consistent with the concept of a mirroring mechanism.

Extracting meaning from faces: task effects

The second main objective of this study was to investigate how the brain processes the meaning of a pain expression and the mirroring activations that occur during the observation of pain faces, by using two different tasks to direct attention toward either the pain communicated via the expression (i.e. meaning), or the constituent movements. Although each task required a different response from the subject – "express pain" vs. "imitate movements" – the stimuli in both conditions were the same, thus differences in the brain activation between

tasks reflect the different processing requirements. As hypothesized, mirroring activity in the IFG and the STS/MTG was stronger when attention was directed to the meaning of the expression (pain task), and mirroring activity in the IPL was stronger when attention was directed to the movements. However, the greater IFG activation seen during the pain task was significant only when the neutral expressions were excluded from the analysis (PT – MT (Obs∩Exec); Table 4). Neutral expressions, in containing no pain, have less 'meaning' to consider, and thus there would be less difference in the task requirements for those stimuli. This interpretation is further supported by the observation that the IFG shows a significantly increased response to pain expressions (vs. neutral) in the PT trials, but not during the MT trials (see Tables S1 and S2, as well as the interaction analysis results shown in Table S4). These results are consistent with those of our previous studies, in which the IFG responded more strongly when subjects rated pain than when they evaluated facial movement [1], as well as when subjects evaluated images of limbs in painful, vs. non-painful situations, and images of pain, vs. neutral, facial expressions [54]. The IFG has been reported in several studies using facial movement and expressions [15,17,18,33], and a recent study has also implicated this area in the processing of semantic meaning of both speech and communicative gestures, finding greater IFG response when subjects listened to meaningful speech vs. an unfamiliar language, and when they viewed meaningful vs. nonsense gestures [55]. Importantly, the slightly more anterior position of this peak, compared with those of the other contrasts, is consistent with the idea that the function of the IFG is organized such that the more anterior portion is relatively more involved with the processing of semantic meaning, while the posterior portion is more involved with motor mirroring [56]. These results, together with those previously described, support the idea that the IFG is recruited more strongly when the meaning of a stimulus is being considered, not only in the case of pain expressions, but also in the broader context of other emotional expressions.

While most studies investigating imitation or observation and execution of emotional facial expressions have found a robust response of the IFG, the IPL is less commonly described. However, the IPL, as well as the SPL, have been widely reported in work looking at action observation and imitation [39], and the results of one meta-analysis strongly support a major role of both regions in imitation [57]. Here, bilateral IPL regions demonstrated strong common activation during both observation and execution of expressions in PT, consistent

with the earlier findings on imitation. However, the IPL responded most strongly when subjects attended to the motor aspects of the expressions – i.e. the movements of the facial features– rather than when they attended to the affective content of the expressions (see as well the results of the interaction analysis, in Table S4). Thus, while it is obviously involved when subjects attend to the meaning of the expressions, it may not be responding primarily to the emotional meaning of the expressions. Interestingly, there is evidence that the IPL may be involved in pain coding during hand-object interactions, responding more strongly when subjects grasped painful vs. non-painful objects [1]. However, another study found pain-related IPL response for images involving hands and feet, but not for facial expressions of pain [2], suggesting that motor-related IPL responses may be reinforced by salient consequences of an action (e.g. pain). In the current study, the lack of IPL response in the pain task could be due to the lack of information about such consequences. These results, together with those previously described, support the idea that the motor mirroring functions of these parietal regions may support, but are not sufficient for, the understanding of emotional expressions in others.

We also noted greater activation in visual areas for trials featuring pain faces (vs. neutral), as well as for PT trials (vs. MT), showing that the visual cortex responded more strongly not only to emotional stimuli, but also when attention was directed towards the meaning of the stimuli. Both cases may reflect the effects of positive feedback from higher-order executive areas, and is consistent with other work showing stronger responses of basic sensory regions to emotional stimuli [58]. It is possible that a similar positive feedback loop may also contribute to the increased response of regions to the pain expressions, such as the STS/MTG and the ACC/SMA complex.

Potential limitations

In our previous study focusing on the observation phase, we noted stronger recruitment of the medial prefrontal cortex (mPFC) during the evaluation of pain, in comparison to the evaluation of movement. Here, task-related effects in this region were restricted to the most anterior part of the mPFC (see Table S3). This region is theorized to have a major role in social cognition via the process of mentalizing, i.e. thinking about what others are thinking, and typically described in the context of intentions, thoughts, and beliefs, rather than feeling

states or emotional states [59,60,61]. The fact that it was not similarly recruited for both observation and execution of the expressions in the present study is in line with an interpretation of mentalizing as a separate, yet complementary, evaluative process from emotional mirroring [see [62]].

Additionally, the inclusion of the execution phase in the current paradigm, while a strength of the study, introduces the potential confound of motor preparation or covert motor responses. These processes might produce motor-related activity during the observation phase. However, while they might contribute to any observed overlap between observation and execution, they do not compromise the interpretation of task differences.

Finally, we have approached the facial expression of pain only as an indicator of emotional state, and the subjects' brain responses only as the decoding of an emotional message. This experimental paradigm does not allow us to consider the impact of pain decoding on the observer (i.e. pain communication as a transaction; see [63]). The brain responses we observed may in fact reflect a type of priming response that prepares the observer to act, either defensively against the threat of self-pain, or solicitously in the face of another's need for aid. Future work in this area would thus benefit from additional investigation of effects of observed pain on subsequent actions, in order to investigate the potential influence these mirror-type responses have on intentions and motivational states, and to shed further light on the social function of pain expressions, beyond the simple communication of an affective state.

Conclusion

In summary, we first confirmed findings from earlier studies that imply a role for the ACC and aINS in the perception of pain in others via facial expression. In addition, these regions, along with the IFG and IPL, were involved in both observation and execution of pain expressions, implicating all of these areas as parts of a broadly construed mirroring system for pain expression. The IFG and IPL have been proposed as a fronto-parietal "core circuit" for imitation which, in various combinations with other regions, form the neural basis for different functions of social cognition such as imitation and imitative learning, as well as empathy and affective mirroring [10]. Importantly, we found that IFG and IPL involvement was dependent on task requirements, with a functional dissociation between these two regions in the

mirroring of emotional vs. motor components of pain expressions. The IFG, together with the MTG and STS/STG, two areas implicated in the perception of biological motion, were more strongly recruited when subjects attended to the meaning of the expressions, whereas the IPL was more strongly recruited when subjects attended to the movements. Together, these findings provide evidence that areas involved in motor mirroring contribute to a brain network underlying the perception of pain in others. However, the perception of the affective meaning in these expressions requires a deeper level of processing and more robustly recruits higher-order association regions involved in the perception of biological motion and semantic meaning. These results add to the growing body of research that suggests overlapping neural representations underlie the processing of both self and other experiences, allowing us to understand the internal state of another individual via the recreation of some aspects of that internal state within ourselves.

Acknowledgements

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SUPPORTING INFORMATION

Table S1. Effects of pain expression during observation in pain expression task.
Peak values for areas of significant BOLD response change identified by analysis of pain minus neutral, during stimuli events, in the pain task trials (Pain:Obs(PT)). Note regarding identification and labeling of brain regions: coordinates for activation peaks are given in Talairach Space according to the Talairach atlas incorporated into the BrainVoyager QX software package. Brodmann area (BA) labels identified using the original Talairach atlas [1] and the online application for the Talairach Daemon (TD) database [2]. $P < 0.001$ (uncorrected) unless otherwise indicated.

Anatomical location	Hemisphere	BA	x	y	z	t-value
FRONTAL LOBE						
superior /medial frontal gyrus	R/MID	6	2	-2	51	6.89
	L	6	-7	-5	59	7.26
superior frontal gyrus	L	6	-10	1	54	7.87
ACC (supracallosal)	R	24	3	7	42	5.48
	L	24	-4	7	39	6.32
	L/MID	23	-7	-14	33	5.49
precentral gyrus	R	6	44	-8	39	4.99
	L	6	-49	-11	36	5.43
	L	6	-43	1	30	5.47
	L	6	-52	4	21	5.78
	L	6	-46	1	12	5.36
	L	6	-20	-11	49	4.96
inferior frontal gyrus	L	44	-49	10	0	5.56
INSULAR LOBE						
anterior insula	R	13	34	7	-5	5.58
	R	13	29	4	-9	7.90
	L	13	-37	13	3	5.37
	L	13	-40	4	0	5.60
	L	13	-34	0	-9	5.77
PARIETAL LOBE						
inferior parietal lobule	R	40	32	-41	33	5.27
	L	40	-34	-55	36	4.63
	L	40	-43	-38	30	6.28
	L	39/40	-49	-41	24	6.02
posterior cingulate cortex	R	23	14	-26	33	4.95
	L/MID	23	-7	-35	24	5.53
postcentral gyrus	R	1/2/3	38	-21	33	4.30
	L	1/2/3	-43	-23	33	5.15
precuneus/paracentral lobule	R	7	17	-74	33	4.77
	L/MID	7	-7	-74	36	5.08
precuneus	R	31	23	-68	24	4.87
TEMPORAL LOBE						
superior temporal gyrus	R	22/41/42	53	-35	18	4.99
	R	22/41/42	35	-32	12	5.41
	R	22/41/42	35	-23	0	5.81
	L	22/41/42	-58	-38	15	6.10

	L	22/41/42	-34	-35	12	5.70
superior temporal gyrus (temporal pole)	R	38	32	7	-18	8.57
	L	38	-43	13	-18	7.57
OCCIPITAL LOBE						
lingual gyrus	R	17	17	-68	9	5.17
	L	17	-22	-74	6	4.82
middle occipital gyrus	R	19	50	-68	-5	7.39
	L	19	-55	-71	-3	8.41
inferior occipital gyrus	R	18/19	35	-86	-21	8.25
	L	18/19	-31	-92	-21	7.91
SUBCORTICAL						
thalamus	R	–	14	-13	9	6.43
	L	–	-10	-14	6	6.56
globus pallidus/putamen	R	–	17	-22	6	10.52
	L	–	-19	-2	6	10.03
cerebellum	R	–	32	-56	-24	6.83

Table S2. Effects of pain expression during observation in movement imitation task. Peak values for areas of significant BOLD response change identified by analysis of pain minus neutral, during stimuli events, in the movement task trials (Pain:Obs(MT)). See note in Table S1 regarding identification and labeling of brain regions.

Anatomical location	Hemisphere	BA	x	y	z	t-value
FRONTAL LOBE						
medial frontal gyrus	R	4	14	-20	54	6.41
	L	4	-13	-14	51	5.48
precentral gyrus (extending into central sulcus)	L	3/4/6	-43	-11	30	5.24
PARIETAL LOBE						
postcentral gyrus	R	1/2	38	-20	27	6.04
	L	1/2	-49	-20	33	5.15
inferior parietal lobule (supramarginal gyrus)	R	40	38	-35	27	5.74
	L	40	-43	-32	24	4.69
TEMPORAL LOBE						
superior temporal gyrus (posterior portion)	R	42/22	53	-32	21	4.27
	L	40	-51	-38	18	5.02
	L	40/42	-61	-35	15	5.74
superior temporal gyrus (temporal pole)	R	38	35	16	-21	8.10
	L	38	-40	16	-24	7.41
inferior temporal gyrus (occipitotemporal junction)	R	37/39	50	-65	0	5.47
	L	37/39	-55	-68	0	5.51
OCCIPITAL LOBE						
lingual gyrus	R	17	20	-62	6	4.39
	L	17	-22	-74	9	4.49
SUBCORTICAL						
globus pallidus / putamen	R	–	17	-2	3	7.00
	L	–	-25	-5	3	7.29
thalamus	R	–	14	-17	6	4.98
	L	–	-10	-14	3	5.15

Table S3. Main effects of task during observation.
Peak values for areas of significant BOLD response change during viewing of the facial expression stimuli in (A) the pain expression task condition (PT – MT (Obs)) versus (B) the movement imitation task condition (MT – PT (Obs)). See note in Table S1 regarding identification and labeling of brain regions.

Anatomical location	Hemisphere	BA	x	y	z	t-value
(A) PAIN TASK > MOVEMENT TASK						
FRONTAL LOBE						
superior frontal gyrus (dorsal)	R	6	11	10	57	5.45
	L	6	-10	7	60	6.70
superior frontal gyrus (lateral)	R	6/8	17	22	51	5.02
	L	6/8	-10	25	51	4.51
middle frontal gyrus	R	6	38	10	45	4.80
	L	6	-28	10	45	5.15
anterior cingulate (supracallosal)	L/MID	32	-1	25	33	4.15
inferior frontal gyrus	L	44	-46	13	33	4.57
	L	44	-49	16	27	4.82
medial frontal gyrus	R/MID	10	2	55	6	5.16
	L/MID	10	-4	49	-3	5.22
PARIETAL LOBE						
inferior parietal lobule	L	39	-40	-71	36	8.11
precuneus	L/MID	23/31	-4	-56	30	6.40
posterior cingulate gyrus	R	31	2	-47	27	5.46
	L	31	-7	-41	27	5.7
TEMPORAL LOBE						
temporo-parietal junction	R	39	44	-65	30	6.78
	L	39	-55	-62	24	10.63
superior temporal gyrus	R	41	41	-20	6	4.71
	L	41	-41	-23	6	5.51
superior/middle temporal gyrus	R	21/38	41	10	-21	4.61
	R	21/38	44	19	-24	5.31
	L	21/38	-43	22	-25	7.23
middle temporal gyrus	R	21	53	-35	0	4.21
	L	21	-58	-32	-6	8.36
	L	21	-49	-11	-18	6.26
	L	21/38	-46	4	-21	7.70
	L	21	-52	4	-27	7.49
inferior temporal gyrus	R	21	53	-2	-30	4.26
parahippocampal gyrus	R	35/36	25	-20	-18	3.89
	L	35/36	-25	-29	-18	4.77
OCCIPITAL LOBE						
lingual gyrus	R	30	26	-47	-3	5.07
cuneus	MID	18	0	-74	24	6.11

	L	18	-7	-71	24	6.65
inferior occipital gyrus	R	18	35	-89	-12	7.15
	L	18	-31	-92	-15	6.21
SUBCORTICAL						
cerebellum	R	–	29	-77	-42	7.56
	L	–	-28	-74	-39	5.58
(B) MOVEMENT TASK > PAIN TASK						
FRONTAL LOBE						
precentral gyrus	R	6	62	-2	27	3.84
	L	6	-52	-2	30	4.37
PARIETAL LOBE						
postcentral gyrus	R	2	59	-26	45	5.21
	R	3	59	-17	33	6.11
	L	1/2/3	-64	-20	39	4.44
	L	3	-58	-23	33	4.77
inferior parietal lobule	R	40 40 40	35	-35	39	4.99
	L	40	-40	-32	39	5.42
	L	40	-28	-41	36	5.40

Table S4. Interaction of pain and task.

Peak values for areas of significant BOLD response change for the interaction of pain and task: [pain(1,2,3)-pain(0)]PT – [pain(1,2,3)-pain(0)]MT, during the observation of pain expressions (Obs). See note in Table S1 regarding identification and labeling of brain regions. *p < 0.002. † Significant peak t-values are reported for the conjunction of observation and execution (Obs∩Exec) in the same structures as the peaks, or within the corresponding cluster of activated voxels, identified in the pain x task interaction during observation only (Obs).

		observation (Obs)					conjunction (Obs∩Exec)†
Anatomical location	**Hemisphere**	**BA**	**x**	**y**	**z**	**t-value**	**t-value**
(A) PAIN TASK > MOVEMENT TASK							
FRONTAL LOBE							
superior /medial frontal gyrus	R	6	8	10	57	8.04	
	L	6	-4	10	51	5.66	
	L	6	-10	7	60	9.66	4.91
middle frontal gyrus	R	6	38	10	45	4.73	
	L	6	-28	10	51	6.70	
	L	6	-43	13	39	5.74	
precentral gyrus	R	6	44	-2	42	4.55	
ACC (supracallosal)	MID/L	24/32	-4	17	38	4.84	
ACC (posterior)	MID/L	23	-4	-17	33	5.92	
inferior frontal gyrus	R	44	50	10	0	4.41	4.08
	L	44	-49	13	3	5.23	5.05
PARIETAL LOBE							
inferior parietal lobule	R	77	38	-62	30	6.18	
	L	7	-34	-65	36	5.70	
precuneus	L	31	-7	-62	36	5.43	
posterior cingulate gyrus	MID/L	23/30	-1	-41	21	6.46	3.81
angular gyrus	L	39	-58	-59	18	6.52	
TEMPORAL LOBE							
superior temporal gyrus (temporal pole)	L	38	35	4	-21	5.26	
middle temporal gyrus (posterior portion)	R	21	41	-32	-6	4.78	
	L	21	-55	-35	-6	6.14	3.82
	L	21	-49	-30	-6	5.66	
	L	21	-55	-17	-9	5.40	
inferior temporal gyrus (posterior portion)	L	20	-64	-47	-15	5.75	5.44
inferior temporal gyrus (temporal pole)	R	38	41	22	-24	5.02	
	L	38	-46	19	-27	5.93	
	L	38	-52	-5	-24	5.04	
OCCIPITAL LOBE							
cuneus	L	17	-1	-92	15	4.83	
inferior occipital gyrus	R	18	39	-78	-8	4.47	
	R	18/19	26	-83	-21	7.43	
	L	18/19	-31	-92	-15	6.08	
SUBCORTICAL							
cerebellum	R	–	32	-65	-24	5.06	
	R	–	29	-53	-30	5.07	4.12
	R	–	26	-74	-36	4.66	3.66*
(B) MOVEMENT TASK > PAIN TASK							

PARIETAL LOBE							
postcentral gyrus	R	1/2/3	59	-14	26	4.28	
supramarginal gyrus	R	40	59	-17	33	5.83	
	L	40	-55	-23	30	3.51*	3.52*
inferior parietal lobule / intraparietal sulcus	R	7	35	-35	42	4.81	4.49
	L	7	-46	-29	42	4.77	4.33

References for Supporting Information

1. Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain : 3-dimensional proportional system : an approach to cerebral imaging. Stuttgart; New York: G. Thieme: Thieme Medical Publishers.

2. Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, et al. (2000) Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 10: 120-131.

REFERENCES

1. Budell L, Jackson P, Rainville P (2010) Brain responses to facial expressions of pain: emotional or motor mirroring? Neuroimage 53: 355-363.

2. Price DD (2000) Psychological and neural mechanisms of the affective dimension of pain. Science 288: 1769-1772.

3. Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, et al. (2004) Empathy for pain involves the affective but not sensory components of pain. Science 303: 1157-1162.

4. Morrison I, Lloyd D, di Pellegrino G, Roberts N (2004) Vicarious responses to pain in anterior cingulate cortex: is empathy a multisensory issue? Cogn Affect Behav Neurosci 4: 270-278.

5. Jackson PL, Meltzoff AN, Decety J (2005) How do we perceive the pain of others? A window into the neural processes involved in empathy. Neuroimage 24: 771-779.

6. Botvinick M, Jha AP, Bylsma LM, Fabian SA, Solomon PE, et al. (2005) Viewing facial expressions of pain engages cortical areas involved in the direct experience of pain. Neuroimage 25: 312-319.

7. Saarela MV, Hlushchuk Y, Williams AC, Schurmann M, Kalso E, et al. (2007) The compassionate brain: humans detect intensity of pain from another's face. Cereb Cortex 17: 230-237.

8. Lamm C, Nusbaum HC, Meltzoff AN, Decety J (2007) What are you feeling? Using functional magnetic resonance imaging to assess the modulation of sensory and affective responses during empathy for pain. PLoS One 2: e1292.

9. Lamm C, Decety J, Singer T (2011) Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. Neuroimage 54: 2492-2502.

10. Iacoboni M (2005) Neural mechanisms of imitation. Curr Opin Neurobiol 15: 632-637.

11. Iacoboni M, Dapretto M (2006) The mirror neuron system and the consequences of its dysfunction. Nat Rev Neurosci 7: 942-951.

12. Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, et al. (2001) Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. Eur J Neurosci 13: 400-404.

13. Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, et al. (1999) Cortical mechanisms of human imitation. Science 286: 2526-2528.

14. Kilner JM, Neal A, Weiskopf N, Friston KJ, Frith CD (2009) Evidence of mirror neurons in human inferior frontal gyrus. J Neurosci 29: 10153-10159.

15. Leslie KR, Johnson-Frey SH, Grafton ST (2004) Functional imaging of face and hand imitation: towards a motor theory of empathy. Neuroimage 21: 601-607.

16. Hetu S, Mercier C, Eugene F, Michon PE, Jackson PL (2011) Modulation of brain activity during action observation: influence of perspective, transitivity and meaningfulness. PloS one 6: e24728.

17. van der Gaag C, Minderaa RB, Keysers C (2007) Facial expressions: what the mirror neuron system can and cannot tell us. Soc Neurosci 2: 179-222.

18. Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL (2003) Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proc Natl Acad Sci U S A 100: 5497-5502.

19. Schulte-Ruther M, Markowitsch HJ, Fink GR, Piefke M (2007) Mirror neuron and theory of mind mechanisms involved in face-to-face interactions: a functional magnetic resonance imaging approach to empathy. J Cogn Neurosci 19: 1354-1372.

20. Lee TW, Josephs O, Dolan RJ, Critchley HD (2006) Imitating expressions: emotion-specific neural substrates in facial mimicry. Social cognitive and affective neuroscience 1: 122-135.

21. Iacoboni M, Molnar-Szakacs I, Gallese V, Buccino G, Mazziotta JC, et al. (2005) Grasping the intentions of others with one's own mirror neuron system. PLoS Biol 3: e79.

22. Noppeney U (2008) The neural systems of tool and action semantics: a perspective from functional imaging. Journal of physiology, Paris 102: 40-49.

23. Simon D, Craig KD, Gosselin F, Belin P, Rainville P (2008) Recognition and discrimination of prototypical dynamic expressions of pain and emotions. Pain 135: 55-64.

24. Kunz M, Chen JI, Lautenbacher S, Vachon-Presseau E, Rainville P (2011) Cerebral regulation of facial expressions of pain. The Journal of neuroscience : the official journal of the Society for Neuroscience 31: 8730-8738.

25. Ekman P, Rosenberg EL (1997) What the face reveals : basic and applied studies of spontaneous expression using the facial action coding system (FACS). New York: Oxford University Press. xvi, 495 p. p.

26. Kunz M, Gruber A, Lautenbacher S (2006) Sex differences in facial encoding of pain. The journal of pain : official journal of the American Pain Society 7: 915-928.

27. Kunz M, Chatelle C, Lautenbacher S, Rainville P (2008) The relation between catastrophizing and facial responsiveness to pain. Pain 140: 127-134.

28. Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, et al. (1996) A unified statistical approach for determining significant signals in images of cerebral activation. Human brain mapping 4: 58-73.

29. Picard N, Strick PL (1996) Motor areas of the medial wall: a review of their location and functional activation. Cereb Cortex 6: 342-353.

30. Picard N, Strick PL (2001) Imaging the premotor areas. Curr Opin Neurobiol 11: 663-672.

31. Paus T (2001) Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nature reviews Neuroscience 2: 417-424.

32. Fink GR, Frackowiak RS, Pietrzyk U, Passingham RE (1997) Multiple nonprimary motor areas in the human cortex. Journal of neurophysiology 77: 2164-2174.

33. Montgomery KJ, Haxby JV (2008) Mirror neuron system differentially activated by facial expressions and social hand gestures: a functional magnetic resonance imaging study. J Cogn Neurosci 20: 1866-1877.

34. Allison T, Puce A, McCarthy G (2000) Social perception from visual cues: role of the STS region. Trends Cogn Sci 4: 267-278.

35. Beauchamp MS (2005) See me, hear me, touch me: multisensory integration in lateral occipital-temporal cortex. Current opinion in neurobiology 15: 145-153.

36. Saygin AP (2007) Superior temporal and premotor brain areas necessary for biological motion perception. Brain : a journal of neurology 130: 2452-2461.

37. Hein G, Knight RT (2008) Superior temporal sulcus--It's my area: or is it? Journal of cognitive neuroscience 20: 2125-2136.

38. Wheaton KJ, Thompson JC, Syngeniotis A, Abbott DF, Puce A (2004) Viewing the motion of human body parts activates different regions of premotor, temporal, and parietal cortex. NeuroImage 22: 277-288.

39. Caspers S, Zilles K, Laird AR, Eickhoff SB (2010) ALE meta-analysis of action observation and imitation in the human brain. Neuroimage 50: 1148-1167.

40. Grezes J, Armony JL, Rowe J, Passingham RE (2003) Activations related to "mirror" and "canonical" neurones in the human brain: an fMRI study. NeuroImage 18: 928-937.

41. Lamm C, Batson CD, Decety J (2007) The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. J Cogn Neurosci 19: 42-58.

42. Duerden EG, Albanese MC (2013) Localization of pain-related brain activation: a meta-analysis of neuroimaging data. Human brain mapping 34: 109-149.

43. Wicker B, Keysers C, Plailly J, Royet JP, Gallese V, et al. (2003) Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. Neuron 40: 655-664.

44. Jabbi M, Keysers C (2008) Inferior frontal gyrus activity triggers anterior insula response to emotional facial expressions. Emotion 8: 775-780.

45. Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, et al. (2011) The integration of negative affect, pain and cognitive control in the cingulate cortex. Nature reviews Neuroscience 12: 154-167.

46. Dum RP, Levinthal DJ, Strick PL (2009) The spinothalamic system targets motor and sensory areas in the cerebral cortex of monkeys. The Journal of neuroscience : the official journal of the Society for Neuroscience 29: 14223-14235.

47. Morrison I, Peelen MV, Downing PE (2007) The sight of others' pain modulates motor processing in human cingulate cortex. Cereb Cortex 17: 2214-2222.

48. Morrison I, Poliakoff E, Gordon L, Downing P (2007) Response-specific effects of pain observation on motor behavior. Cognition 104: 407-416.

49. Perini I, Bergstrand S, Morrison I (2013) Where pain meets action in the human brain. The Journal of neuroscience : the official journal of the Society for Neuroscience 33: 15930-15939.

50. Cunnington R, Windischberger C, Moser E (2005) Premovement activity of the pre-supplementary motor area and the readiness for action: studies of time-resolved event-related functional MRI. Human movement science 24: 644-656.

51. Cunnington R, Windischberger C, Deecke L, Moser E (2002) The preparation and execution of self-initiated and externally-triggered movement: a study of event-related fMRI. NeuroImage 15: 373-385.

52. Vachon-Presseau E, Martel MO, Roy M, Caron E, Jackson PL, et al. (2011) The multilevel organization of vicarious pain responses: effects of pain cues and empathy traits on spinal nociception and acute pain. Pain 152: 1525-1531.

53. Mailhot JP, Vachon-Presseau E, Jackson PL, Rainville P (2012) Dispositional empathy modulates vicarious effects of dynamic pain expressions on spinal nociception, facial responses and acute pain. The European journal of neuroscience 35: 271-278.

54. Vachon-Presseau E, Roy M, Martel MO, Albouy G, Chen J, et al. (2012) Neural processing of sensory and emotional-communicative information associated with the perception of vicarious pain. NeuroImage 63: 54-62.

55. Straube B, Green A, Weis S, Kircher T (2012) A supramodal neural network for speech and gesture semantics: an FMRI study. PloS one 7: e51207.

56. Press C, Weiskopf N, Kilner JM (2012) Dissociable roles of human inferior frontal gyrus during action execution and observation. NeuroImage 60: 1671-1677.

57. Molenberghs P, Cunnington R, Mattingley JB (2009) Is the mirror neuron system involved in imitation? A short review and meta-analysis. Neuroscience and biobehavioral reviews 33: 975-980.

58. Vuilleumier P (2005) How brains beware: neural mechanisms of emotional attention. Trends in cognitive sciences 9: 585-594.

59. Amodio DM, Frith CD (2006) Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci 7: 268-277.

60. Frith CD, Frith U (2006) The neural basis of mentalizing. Neuron 50: 531-534.

61. Frith U, Frith CD (2003) Development and neurophysiology of mentalizing. Philos Trans R Soc Lond B Biol Sci 358: 459-473.

62. Van Overwalle F, Baetens K (2009) Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. Neuroimage 48: 564-584.

63. Hadjistavropoulos T, Craig KD, Duck S, Cano A, Goubert L, et al. (2011) A biopsychosocial formulation of pain communication. Psychological bulletin 137: 910-939.

64. Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain : 3-dimensional proportional system : an approach to cerebral imaging. Stuttgart; New York: G. Thieme: Thieme Medical Publishers.

65. Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, et al. (2000) Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 10: 120-131.

Chapter 3: General Discussion

How we understand – quickly and often seemingly automatically – the emotional state of another person, simply by observing their facial expression, is a fascinating and long-standing question in cognitive neuroscience. One central idea is that the perception of emotions in others is linked to the perception of emotions in the self, via the generation of an internal representation of the observed emotion. This concept originates from simulation theory, which describes how observers use their own minds and experiences, as opposed to a set of external laws, to understand the actions and experiences of others (Gordon, 1986). Simulation theory originated in philosophy and cognitive science, then was considered in light of findings in neuroscience, including the discovery of mirror neurons – motor neurons that respond to both observed and executed actions (Gallese and Goldman, 1998). This basic concept of simulation as a basis for understanding others has been interpreted, expanded, and reiterated into several different models, such as the shared circuits model (Hurley, 2008, 2006), the perception-action model (Preston and de Waal, 2002), or embodied simulation (Keysers and Gazzola, 2006), and has additionally been referred to by different phrases such as shared representations, vicarious activation, and mirroring. Gallese and Goldman first described how mirror neurons – certain motor neurons in monkeys that respond to both observed and executed actions – could support simulation in humans, linking observation of an experience to a neural representation of that experience in the observer (Gallese and Goldman, 1998). Although classical mirror neurons are motor, the idea that there may be neurons, populations of neurons, or networks of brain regions that respond in a similar fashion to self and other experiences has been used to explain how humans are able to understand not only the actions of others, but also mental states including emotions, thoughts, and beliefs (see review, (Keysers and Gazzola, 2006)).

Returning to the specific case of pain empathy, a model for pain communication was presented in the introduction, describing a three-part process by which a pain experience is represented in the self and then encoded and expressed via behavioral responses. Some aspects of the third step – decoding – were also discussed, namely that it involves overlap with processes for encoding, and that this overlap can be observed in brain imaging work. In this chapter, the discussion of decoding is continued, in order to consider how the brain processes the pain message via facial expression specifically, and concludes that this is done via a

mixture of emotional resonance, motor mirroring, and mentalizing. Figure 1, below, shows a model schema for this process as it occurs in the experimental protocols of the two studies:

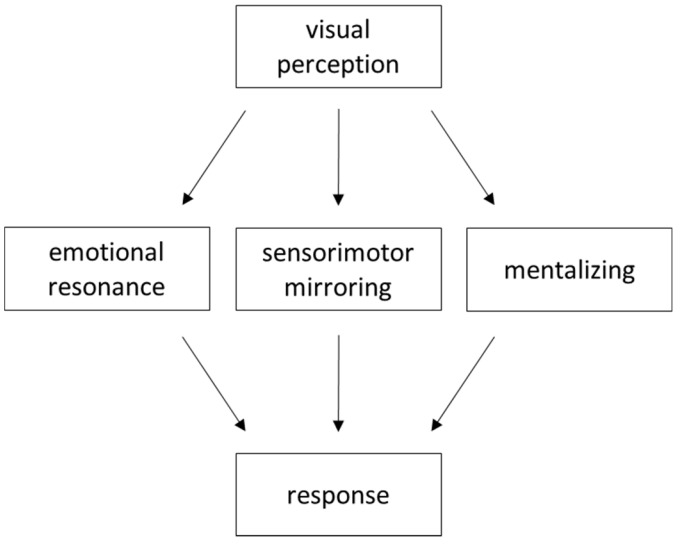

Figure 3.1. General model for perception of pain via facial expression, as used in this work.
Visual perception of facial expressions of pain leads to decoding and interpretation of the expression via three complementary functions: emotional resonance, sensorimotor mirroring, and mentalizing. This schema shows a generic version of the process that does not take into account the different tasks and response methods used in each study. Specific task demands influence the relative contribution of each function into the subsequent response. Feedback loops may exist between the three functions, as well as between these functions and the initial visual perception, although these are not addressed in this work.

3.1. Restatement of objectives

The objective of this thesis was to investigate the cerebral mechanisms behind the perception of facial expressions of pain and, specifically, to examine the potential role played in this process by the neural systems supporting self-pain processing, as well as those supporting the perception of the thoughts and feelings of others. The first study, reported in the first article (Chapter 3, Article 1) looked at brain responses to facial expressions of pain during explicit rating of pain intensity and compared them to those generated during a control

task, with the goal of distinguishing between those regions involved in processing observed pain and those generally involved in processing dynamic facial stimuli. The second study, reported in the second article (Chapter 3, Article 2), was designed to build upon results of the first work that suggested the involvement of mirroring and mentalizing systems during the perception of pain in others. In this chapter, the following sections will summarize the results of these two works, address a few differences observed in their results, and then discuss their significance in light of the current literature on the perception of pain in others, as well as in a broader context of social cognition, specifically in regard to the mechanisms of mirroring and mentalizing. Finally, limitations of these studies will be addressed and possible future directions for this work will be explored, as well as the contributions it could offer toward a better understanding of pathological conditions in which perception of emotion in others is abnormal.

3.2. Summary of results

This thesis comprises two studies examining the brain mechanisms behind the perception of facial expressions of pain in others, using dynamic visual stimuli and a dual-task paradigm that allowed the analysis to distinguish between activation related to the processing of the emotional content presented in the stimuli and processing of the physical movement. The same stimuli set was used for both studies and comprised a set of 1-second video clips in which several male and female models performed expressions of pain of varying intensities, as well as neutral expressions. Two different tasks were used to manipulate attentional emphasis on emotional evaluation (mentalizing) versus sensorimotor representation (mirroring): in the pain task, subjects evaluated the intensity of the pain displayed in each clip; in the movement task, subjects evaluated the facial movements. In Study 1, responses to both tasks were provided using a visual scale; subjects manipulated an onscreen slider on the scale to register their response. In Study 2, subjects provided responses to both tasks using their own faces (and with no visual feedback about these responses).

The hypotheses of the two studies were closely linked and comprised two main themes – overlap with self-pain areas, and engagement of regions involved in motor mirroring and in mentalizing. Recruitment of regions involved in processing self-pain was expected to occur in

response to pain versus neutral expressions during the explicit evaluation of pain and, in Study 1, it was hypothesized that a subset of these regions would also show a parametric effect in response to the perceived pain intensity (Study 2 did not look for this parametric effect). Furthermore, this recruitment of self-pain areas would not occur in response to pain expressions during the movement evaluation task condition.

In regard to task effects, it was hypothesized in Study 1 that explicit evaluation of the meaning of the expressions would reveal greater responses in midline cortical regions involved in thinking about the mental states of others, whereas evaluation of the movement shown in the expressions would result in greater responses in motor regions identified in action observation and motor mirroring. While the first study included only observational conditions, the experimental protocol of Study 2 added an execution condition to allow greater confidence in the identification of 'mirroring' processes. Following the results of the first study, it was expected that attending to the meaning of the expressions would more strongly engage the frontal portions of the action observation/mirroring network, whereas attending to the movement in the expressions would more strongly engage parietal regions of this network.

3.2.1. Effects of pain

To investigate the effects of pain, contrasts were used that subtracted brain responses to neutral expressions from those for pain expressions. In the first study this was done only during the observation of facial expressions, and in the second study this was done during both observation and execution of expressions. Overall, the results of the two studies were consistent with each other. As reported in many earlier studies looking at pain empathy and the perception of pain in others, both studies found increased activation of the supracallosal ACC and the anterior insula associated with the perception of pain expressions (versus neutral expressions) and, in Study 1, the magnitude of the responses of these regions was found to scale with the perceived pain intensity (this parametric effect was not assessed in Study 2). This effect of pain versus neutral was only seen when subjects were evaluating pain; during the control tasks, when subjects focused on the facial movements, there was no increased response of these regions to pain expressions (see Tables 2 and S1 in (Budell et al., 2010); and Tables S1 and S2 in (Budell et al., 2015)). Additionally, significantly stronger responses to

pain expressions were also noted in several regions not typically described as pain-related, including the SFG (premotor region), the ventral IFG, the IPL, and the posterior STG/MTG.

3.2.2. Effects of task

In both studies, the movement task was in part intended as a control task that could be used to remove the effects of perceived movement in order to isolate the effects of observing pain. However, the contrasts comparing brain response to each task produced intriguing results that revealed the different processing requirements for each task. Specifically, the results of Study 1 revealed that, during observation of stimuli in the pain task condition, a greater response was observed bilaterally in the medial and superior PFC, and the subgenual ACC, as well as in the left hemisphere in the posterior STG, ventral IFG, and the temporal pole. During the movement evaluation task, greater activation was observed bilaterally in the inferior and superior parietal lobules, and the SFG. In Study 2, the results of contrasts looking at task effects during stimuli observation were generally consistent with those from Study 1, with observation of the stimuli during the pain task condition producing a greater response in the medial and superior PFC, the posterior STG, and the left IFG. Additionally, the supracallosal ACC/SMA, the precuneus, and the bilateral TPJ also showed a stronger response during the evaluation of pain. During the movement task, greater activation was observed bilaterally in the inferior parietal lobule, as well as pre- and post-central gyri. Additionally, the paradigm in the second study allowed examination of these contrasts during both observation and execution of pain expressions. Here, a conjunction analysis across both stimuli and response events identified stronger responses for the pain task in the medial/superior frontal gyrus, the left IFG, the precuneus and posterior cingulate, and the posterior MTG.

3.2.3. Differences between the two studies

While the results of these two studies were consistent with each other, some differences were noted between equivalent analysis contrasts, mainly in regard to differences between the tasks. The most notable such difference was observed when comparing the effects of pain in each task condition. Both studies looked at pain effects during the observation of the

expressions by contrasting pain versus neutral expressions, and doing so separately for each task. In Study 1, this contrast produced significant results only for the pain task, (see Tables 2 and S1 in (Budell et al., 2010)), showing increased activation in the supracallosal ACC and the anterior insula, as hypothesized. Here, these results suggest that the perception of affective content of the expressions is linked with attention and task demands, with minimal effects of pain when subjects observed the stimuli in preparation for the movement discrimination task.

In Study 2, however, this contrast of pain vs. neutral during stimuli observation produced significant results in both task conditions (see Table S1 and S2; (Budell et al., 2015)). While increased ACC and INS responses for pain expressions were only observed during the pain task (as in Study 1), viewing pain expressions during the movement imitation task did elicit significant responses in several other regions that showed a stronger response to pain during the pain task, notably the bilateral MFG (SMA), superior frontal gyrus, pre- and post-central gyri, inferior parietal lobule (supramarginal gyrus), and the superior temporal gyrus.

One possible explanation for these differences concerns the type of task and rating method that was used in each study, and the effects of response preparation, which may be seen during observation of the stimuli even if the stimuli presentation and the response window are separated by a short pause (as was done in Study 2). While the tasks were similar – evaluation of pain and evaluation of movement – the physical method of reporting the responses in each study differed, with a visual analog scale controlled via a hand-operated response box used in one protocol versus the production of facial expressions in the other. The subjects in Study 1 were required to translate their perception of a motor event involving a face into a representation of an abstract, linear scale, whereas the subjects in the second study could use the more direct route of reporting the perceived facial motion with facial responses; doing so may have led to greater response of motor processing areas. During the observation of stimuli, this activation would represent motor preparation and, given that pain expressions contain more movement than the neutral expressions, mimicking pain expressions would result in greater motor responses than mimicking neutral expressions.

Additionally, the Study 1 movement task required subjects to compare two regions of facial movement, whereas in Study 2 subjects did not make such a comparison. It is possible that, instead of movement discrimination, they instead provided a more general magnitude

estimation comprising all components of facial movement. Thus, a greater response to pain expressions is observed also during the movement task, yet does not necessarily reflect the greater *affective* (pain) content.

3.3. Pain communication via facial expression engages brain systems implicated in pain in the self (emotional resonance)

The work described here demonstrates that perception of pain in others involves systems responsible for the representation of pain in the self. In the introduction of this manuscript, a brief story of pain communication demonstrated how it is not necessary for an observer to see an actual pain event in order to understand that another person has experienced pain; observing pain behaviors are sufficient to convey the message that someone is suffering pain. However, most of the work representing the background literature for Study 1 involved stimuli that provided the observer with information about the sensory aspects of the pain experience, such as images of limbs in painful situations. The results presented here demonstrate that previous findings in pain empathy research implicating self-pain brain mechanisms in the perception of pain in others are replicable using pain expressions alone: the facial expression stimuli used in Studies 1 and 2 provide information only about the pain response, yet this information is sufficient to elicit activation of self-pain networks in the observers, namely, the anterior INS and the supracallosal ACC. Further, the parameter of pain intensity is included in this information and is also coded in the response of these regions of the self-pain network.

3.3.1. Role of aINS during perception of facial expression of pain

The role of the aINS during the perception of other pain is similar to its role during self-pain: as discussed in the introduction, the insula builds a representation of the negative sensory state, particularly one entailing disruption to homeostasis. In the case of observed pain expressions, information about the sensory aspects of the observed pain experience is not available; only information about the pain response is communicated to the observer. Thus,

one question is how the insula builds a representation of physical saliency when lacking any indication of physical stimuli.

The insula is generally responsive to emotional stimuli, including emotional expressions, and particularly aversive stimuli (Phan et al., 2004, 2002); thus one possible explanation is that the aINS, rather than showing somatic resonance specific to pain, is simply responding to and processing negative emotional stimuli that reference the physical self/state. However, pain expressions do provide information about the *response* to a sensory state, even if not about the details leading up to that state, and this information may therefore be sufficient to recruit insula involvement via learned associations between pain expressions and the physical experiences that typically lead to those expressions. In other words, the observation of pain expressions may evoke memories of self-pain experience or personal distress. These internally-generated representations might reference personal recollections of highly specific painful events (e.g. "I remember hitting my head on a sharp corner"), or a more general, prototypical idea of pain or physical discomfort (e.g. "that is a pain face; pain is a hot sharp sensation; pain hurts"]. Interestingly, patients with congenital insensitivity to pain (CIP) show the same aINS response during observation of pain in others as do healthy controls (Danziger et al., 2009), despite being unable to experience pain themselves. Their ability to do so appears to rely more heavily on generalized emotional empathy, recruiting the vmPFC and the posterior cingulate, two regions associated with empathy and mentalizing (Amodio and Frith, 2006; Ochsner et al., 2008; Saxe, 2006; Völlm et al., 2006; Wicker et al., 2003). In healthy subjects, these regions are recruited more heavily in response to images of pain expressions than to images of limbs in painful situations (with the aINS responding to both) (Vachon-Presseau et al., 2012), and show greater functional connectivity with the aINS during perception of other pain versus self-pain (Zaki et al., 2007). This is consistent with the idea that the processing of pain expressions in the absence of sensory-specific information requires more generalized emotional empathy.

3.3.2. Role of ACC during perception of facial expression of pain

As discussed in the introduction in Chapter 1, it has been hypothesized that the role of the supracallosal ACC during both observed and felt pain is to influence behavior, particularly

motor responses, by orienting attention and creating motivational drives. During observed pain, the ACC may play a similar role, influencing attentional orientation and contributing to behavioral responses via the generation of motivational drives and participating in motor preparation. Most recently, Perini and colleagues have suggested activity in this area may even be more motor- than pain-related, after showing a correlation between reaction times and ACC response for both for painful and non-painful conditions. They concluded that perhaps the ACC is not just sharing a representation of pain for self and others, but instead is demonstrating motor response preparation that occurs in response to two distinct, though similar, phenomena (pain in self, pain in others) (Perini et al., 2013). This association between ACC and motor response preparation is further supported by the finding that ACC responses reflect the facilitation of motor responses to self-pain by observation of pain in others [Morrison et al., 2007a, 2007b]. In short, the self/other overlap in the role of the ACC could be described as shared response readiness, or 'motivated motor preparation.' Further, the observation in Study 1 that ACC was modulated by perceived pain intensity is consistent with this interpretation, suggesting that greater pain intensity would be associated with greater motivation to act.

While it may be the case that the ACC plays a more purely motor role during pain, responding only when an action is performed (Perini et al., 2013), it is important to note that in Study 2, while various other motor regions responded more strongly to pain versus neutral expressions in both tasks, the ACC only did so during the pain task. This pattern suggests that the motor role played by this region may be invoked only during 'motivated' actions, an idea that fits with earlier work that found this region of the ACC to be more active for voluntary, self-initiated movements versus externally-triggered movements (Deiber et al., 1999). In Study 2, the difference between the facial responses in the two tasks could be described similarly; in the pain task, subjects' responses were generated based on an internal idea of a pain experience, resulting in a self-initiated movement, whereas the movement task required subjects to imitate an externally-provided example.

Finally, the fact that both the ACC and the aINS only responded to pain expression during the pain task shows that this involvement is not automatic, but is in fact sensitive to attentional demands. Interestingly, this may be true for both emotional and sensory cues; Gu and colleagues found that aINS response to images of fingers in painful conditions

disappeared when subjects counted the fingers, compared to when they rated pain intensity (X Gu and Han, 2007). This modulation of emotional resonance by attentional factors may be one explanation for inter-individual variability in pain empathy and in the assessment of other pain that is observed in behavioral studies, as well as the phenomena of medical caregivers suppressing pain empathy towards patients (Decety et al., 2010).

3.3.3. Specificity for pain: is it pain or sensory salience?

Thus far, the results of these two studies have been described as supporting the hypotheses that for both self- and other- pain, the anterior INS is involved in representing physical saliency of a painful or potentially painful stimulus or situation, and the role of the ACC is to create motivational drives influencing behavior, in particular motor responses. However, as mentioned in the introduction of this manuscript (Chapter 1), the argument has been put forth that what is believed to be activation of a specific 'pain matrix' in fact represents a more general 'salience detection network' for bodily stimuli (Legrain et al., 2011; Mouraux et al., 2011). Similarly, the combination of the ACC and aINS have previously been proposed as key components of a generalized network sensitive to the degree of personal salience, regardless of task demands (Seeley et al., 2007).

The results presented here are not inconsistent with this idea of a generalized salience detection network, as it is not possible to claim specificity for pain with a protocol that includes only pain faces. Further, while there is some evidence that observation of pain stimuli applied to a particular body part – such as a muscle of the hand – leads to altered sensorimotor representation of that part in the self (Avenanti et al., 2005), the idea of a general sensory threat detection system is more allowing of a scenario using stimuli that do not contain information about specific pain events, such as facial expressions.

Ultimately, this work cannot answer the question of whether this activation is specific to pain or if it represents a broader type of 'salience detection.' In one sense the question is irrelevant, in that the answer could be either or both: pain is sensory *and* salient, both in self and in others (although pain expressions *are* specific and allow discrimination between pain and other emotions, as discussed in the introduction). The results of these two studies are consistent with the hypothesis that overlapping, shared representations underlie felt and seen

pain; the overlap is clear. Within these overlapping representations, it also seems clear that the ACC/SMA is coding for motivational urges and/or motor readiness for avoidance behaviors in relation to adverse sensory events including, but not necessarily limited to, pain (see (Perini et al., 2013); these studies show that this coding occurs during the perception of pain in others, as well. Similarly, the aINS is a key region for the processing of adverse sensory events, both in self and others, and in the latter this occurs even when the only information provided about the event is in regard to the affective dimension of the experience and the response. Finally, this work demonstrates that if the observer is not attending to the pain content, the emotional resonance effect does not occur.

3.4. Pain communication via facial expression engages brain systems implicated in motor mirroring and mentalizing

Perception of pain expressions is a part of pain empathy, and so the previous section discussed the results of this work within the context of emotional resonance for pain. However, pain perception is also part of the broader topic of social cognition, which – alongside the perception of emotion – includes action understanding and mental state attribution. In this field, two mechanisms have been described that contribute to our understanding of others. The first, motor mirroring, falls under the heading of simulation, mentioned earlier in this manuscript, and is the phenomenon of an overlap in motor processing of a particular action when it is both observed and executed. The second mechanism is mentalizing, also referred to as Theory-of-Mind (ToM), and describes what occurs when an observer recognizes the thoughts, beliefs, and intentions of others, and understands the perspective of the other as being different from their own. Typically, research into motor mirroring employs protocols in which subjects observe models and imitate or execute their actions, such as body movements and facial expressions, whereas mentalizing is studied using tasks that require subjects to think about the mental states of others and assess or determine their beliefs, knowledge, or intentions.

The two studies presented here suggest that both mirroring and mentalizing are involved in the perception of pain in others. Specifically, several contrast models identified the

IFG and the IPL, two regions heavily implicated in the human mirror neuron system, as responding significantly during observation of the pain expressions in both studies, as well as during execution of the expressions in the second study. Additionally, several regions known to be involved in the process of mentalizing were also identified in both studies, namely, the mPFC, the TPJ, the precuneus, and the posterior STG/STS. Participation of these regions, however, was shown to differ according to task demands. Thus, these results are able to shed further light on mechanisms of motor mirroring and mentalizing, specifically in the context of pain perception.

3.4.1. Motor mirroring

3.4.1.1. Classical mirror neurons: monkeys reaching for goals

Classical mirror neurons were discovered in the early 1990s, when researchers recording the activity of macaque motor neurons during grasping motions discovered that certain neurons would fire not only when the monkey reached for an object, but also when the monkey observed a human researcher performing the same motion (Gallese et al., 1996; Rizzolatti et al., 1996). Subsequent work revealed that some of these neurons are sensitive to movement goals, responding even when target objects are blocked from view, and that others are sensitive to mouth movements and facial movements and expressions ((Ferrari et al., 2003), also see review (Rizzolatti and Craighero, 2004)). The behavior of these motor neurons was posited to be a possible neural mechanism for action understanding, by creating internal representations – simulations – of observed actions, which allow understanding of the goals and intentions behind motor acts.

3.4.1.2. Mirroring in humans: evidence, theories, and caveats

After their discovery, mirror neurons quickly became a very popular topic of study. Inevitably, researchers began to question if the human brain also contained mirror neurons and, if so, whether they could be a key mechanism underlying a wide range of social cognitive abilities, such as imitation and language acquisition, and even empathy (Gallese et al., 2007;

Gallese and Goldman, 1998). However, due to methodological limitations – single-neuron recordings are more difficult to perform in humans – the evidence for motor mirror neurons in humans is, for the most part, provided by indirect methods such as fMRI (though see (Mukamel et al., 2010) for evidence from direct intracellular recordings of action mirroring neurons in human SMA). An important caveat that must then be mentioned is that it is usually not possible to conclude that individual neurons within the activation clusters observed in human imaging studies are displaying properties consistent with the 'classic' mirror neurons identified in monkey research. Studies investigating the 'human mirror neuron system' and presenting maps of overlapping BOLD activation for both felt and seen actions are in fact showing overlapping clusters of activation across voxels for group-level effects, not the activity of individual neurons, and it is possible that the 'mirroring' revealed by these clusters is the result of distinct, though adjacent, populations of neurons.

Despite these issues, human brain researchers are using the term "mirroring" to refer to a putative human mirror neuron system similar to that found in monkeys. Evidence to support the existence of such a system comes primarily from imaging studies, in which areas where clusters of activation appear for both observed and experienced actions are described as showing "mirroring" behavior. These results have been described for hand actions, facial actions (e.g. chewing), facial expressions, and whole-body movements, and have implicated three areas in particular – the ventral/posterior IFG (BA 44 and 6), the IPL, and the posterior STS/MTG ((Carr et al., 2003; Cross et al., 2006; Kilner et al., 2009; Leslie et al., 2004; Montgomery and Haxby, 2008; van der Gaag et al., 2007); see also reviews: (Iacoboni et al., 1999; Iacoboni and Mazziotta, 2007; Keysers and Gazzola, 2006)). Corroborating evidence comes from fMRI adaptation protocols using repetition suppression: this method assumes that, given a population of neurons responsive to a given stimulus, repetition of that stimulus will lead to a decreased or adapted BOLD signal as the population adapts to the stimulus (Malach, 2012). Thus, repetition suppression effects provoked in a brain region by observation and execution (or vice-versa) of the same action would suggest mirroring activity. Such results have been described in regions of the IFG, for finger and hand movements (Dinstein et al., 2007; Kilner et al., 2009; Press et al., 2012), as well as in the IPL (Chong et al., 2008). Finally, studies using transcranial magnetic stimulation (TMS) have shown that inducing temporary

perturbations in the IFG interferes with imitation of observed actions (see review: (Fadiga et al., 2005)), further implicating this region in the representation of observed actions.

Thus, it is possible to broaden the definition of mirroring to include overlapping clusters of activation, particularly when observed in a group of areas which may be functioning as a network, allowing a discussion of mirroring in humans even when there is little data reported on true 'classic' mirror neurons. In addition, it is possible to move beyond the motor cortex, and beyond physical actions, to consider both sensory and emotional processing; in fact, mirroring is also used to refer to a wider range of overlapping activations underlying the representation of both self and other sensory and emotional experiences, beyond the purely motor (Keysers and Fadiga, 2008). The term 'mirroring' can then be used to refer not only to the classical motor mirroring for actions, but also to overlapping responses to felt and seen sensory and affective phenomena, without implying the detection of responses from identical populations of neurons. This manuscript, then, does not assert that the evidence discussed here reveals the existence of individual motor neurons that respond both to observed and performed behaviors. Instead, the term "mirroring" is used to discuss brain regions where clusters of activation for observed versus performed actions overlap; instead of neurons mirroring, it is voxels. This could mean that specific populations or subpopulations of neurons within a region are coding for both observed and performed actions, but it does not prove it.

3.4.1.3. Role of IFG during perception of facial expression of pain: mirroring for meaning?

In the two studies presented here, the IFG was recruited more strongly during the pain evaluation tasks, when the social meaning of the pain expressions was being considered. Additionally, its response was modulated by the perceived pain intensity, though only when subjects attended to the pain content of the expressions. Similar results have been observed when using images of hands in painful conditions, where the IFG response was stronger when subjects rated pain intensity, thus focusing on the pain content of the images compared to when they counted the number of fingers shown in each image (X Gu and Han, 2007). Other work has found the IFG responds preferentially to painful, versus neutral, content of images of

both sensory pain (limbs) and communicative pain (expressions) (Gu et al., 2010; Vachon-Presseau et al., 2012).

In addition to motor mirroring, the IFG has also been implicated in empathy and the perception, imitation, and execution of emotional expressions (Carr et al., 2003; Hennenlotter et al., 2005; Iacoboni et al., 1999; Leslie et al., 2004; Liakakis et al., 2011; Sabatinelli et al., 2011; Seitz et al., 2008; van der Gaag et al., 2007). Some specific findings consistent with the idea of IFG sensitivity to affective meaning include IFG responses to both hand and face actions. For example, while the IFG responds during observation, imitation, and execution of hand actions, it shows a significantly stronger response to meaningful actions versus those presented without context (Iacoboni et al., 2005). Another study found that across three task conditions – viewing, imitating, and executing actions – the IFG responded more strongly in all conditions for facial expressions than to hand actions (Montgomery and Haxby, 2008), a result that the authors attributed to the greater affective content of facial expressions. Moreover, correlations have been found between higher scores on personality tests measuring emotional empathy and IFG response to observed actions (Kaplan and Iacoboni, 2006). Finally, it has been shown that lesions of the IFG are associated with reductions in emotional empathy, as revealed by both diminished performance on emotion perception tasks as well as reduced trait empathy test scores (Shamay-Tsoory et al., 2009). Overall, these findings are consistent with the hypothesis that, during both observation and execution of emotional expressions, the IFG is coding information relevant to their affective meaning.

In summary, the results of both Study 1 and Study 2 showed the IFG to respond more strongly to facial expressions of pain when the meaning of the expressions was being considered. Together with previous evidence supporting a role for the IFG in motor mirroring as well as in the perception of emotional stimuli, these results are consistent with the hypothesis that this region contributes to emotion perception and empathy via a role in motor representation.

3.4.1.4. Role of IPL during perception of facial expression of pain: mirroring for movement?

In both Study 1 and Study 2, bilateral regions of the IPL (BA 40) were more responsive during observation of pain expressions during the movement evaluation tasks, when subjects attended to the specific movements of facial features rather than the emotional content of the faces. Additionally, in Study 2, this region showed the same movement-related response during both observation and execution of pain faces.

In contrast to these results, previous works examining brain response during observation of pain faces did not report significant IPL activation during passive viewing of pain expressions (Botvinick et al., 2005; Saarela et al., 2007). This may in part be due to differences in the cognitive demands of passive viewing versus active evaluation of the stimuli, in that the latter condition may elicit a stronger response. More significantly, the task comparison that revealed IPL sensitivity to movement discrimination – allowed by the dual-task paradigm in the two current studies – was not possible in those earlier studies. This comparison allows the analysis to tease out the effects of action versus emotion. Note that in Study 1, the IPL did show a parametric response to pain expressions during the pain evaluation task, which, together with the results of the task comparison, supports the idea that this region is responding primarily to the movement components of the expression.

Subsequent work has reported increased IPL response to images of facial expressions of pain, painful versus non-painful stimuli to hands and feet (Vachon-Presseau et al., 2012), and painful hand-object interactions (Morrison et al., 2013). In the former study, the IPL showed greater response to the images of limbs compared to those of facial expressions, which the authors concluded indicates that the IPL's role is more related to the coding of sensorimotor information. Likewise, Morrison and colleagues reported that IPL response was greater for images of limbs receiving painful versus non-painful stimuli and similarly hypothesized that the IPL is involved in the predictive coding of the sensory consequences of actions – specifically, in this case, coding for noxiousness associated with object interactions (Morrison et al., 2013). In both cases, these results have been interpreted as demonstrating that IPL response represents sensorimotor resonance, an explanation that is consistent with the findings presented here. Interestingly, a meta-analysis of studies examining brain response to

pain in others identified this region as responsive to other pain when the painful stimuli are portrayed in relation to the affected body parts but not when pain in others is suggested by abstract cues (Lamm et al., 2011). This distinction is also suggestive of sensorimotor, rather than affective, resonance.

Beyond pain processing, the IPL has long been known to play a role in action observation and imitation (Buccino et al., 2001; Caspers et al., 2010; Iacoboni et al., 1999; Molenberghs et al., 2009). An early study found significant parietal responses to videos of hand, foot, and mouth actions, both object- and non-object-related, compared to static images of limbs and faces (Buccino et al., 2001). A meta-analysis on motor imitation reported IPL/SPL activation during imitation and observation of hand and foot movements (Molenberghs et al., 2009). In a later meta-analysis, Caspers and colleagues further demonstrated that multiple subregions of this area are involved in the observation of hand, foot, face, and full body movements, in task conditions including passive observation, observation and imitation, and various types of discrimination (Caspers et al., 2010). These findings support the hypothesis that the IPL is primarily involved in processing the movement component of pain expressions; it is likely that the motor role of the IPL during the perception of pain in the current studies is magnified during the movement task conditions, when subjects are focused more specifically on the facial movements.

Further, the IPL is a multimodal sensory integration region that plays an important role in visuospatial processing, integrating elements of the visual field into a coherent whole: patients with damage to the IPL display spatial neglect, famously demonstrated by patient drawings lacking one side of the target image (Driver and Mattingley, 1998; Mattingley et al., 1998). In the context of facial expression perception, this would entail integrating individual facial parts into a coherent whole that can then be assessed for meaning.

3.4.1.5. From motor mirroring to pain empathy

The results of Study 1 and 2 suggest that the putative human MNS plays a role in pain communication. Motor mirroring occurring during the perception of pain expressions may thus contribute to the perception of other pain via a process of mental simulation. This neurological phenomenon is reflected in two behavioral concepts: automatic mimicry and

facial feedback. The first, automatic mimicry, occurs when one person observes the gestures, facial expressions, speech patterns, and body postures of another, and displays similar gestures, expressions, etc., often doing so unconsciously and unintentionally. This phenomenon is referred to as the "chameleon effect" (Chartrand and Bargh, 1999), and can often be readily observed with the naked eye. Even when not overtly displayed, and when subjects are unaware of their responses, electromyography (EMG) has been used to detect micro-movements of the face that reflect the expression of the other (Dimberg et al., 2000). People who score high on empathy tests display greater automatic mimicry during interactions with others (Chartrand and Bargh, 1999; Sonnby-Borgstrom, 2002). The second concept, the facial feedback hypothesis, states that performing an emotional expression leads to the bodily feeling of that emotion (see, for example (Niedenthal et al., 2010)). Simply performing facial expressions of an emotion can lead to autonomic nervous system responses appropriate to that emotion, as well as the subjective report of feeling that emotion (Ekman et al., 1983; Levenson et al., 1990); facial expression may increase subjective feelings of emotion during an emotional experience (Adelmann and Zajonc, 1989; Dimberg, 1987). Thus, an observer who mimics an observed facial expression of pain, even subconsciously, may then experience some degree of the expressed emotion. Both mimicry and facial feedback are mechanisms consistent with the broader theory of embodied simulation, mentioned in the introduction of this chapter, which describes how the observed actions, sensations, and emotions of others are understood via internal representations of these phenomena in the self (Keysers and Gazzola, 2006).

3.4.2. Mentalizing

Mentalizing is the process of thinking about the mental state of another person, such as their thoughts, beliefs, or intentions, and recognizing the mental state of the other as separate from one's own; it is also referred to as having a 'Theory of Mind' (ToM) (Premack and Woodruff, 1978). It is an underlying requirement for 'cognitive empathy', which is the (usually) conscious effort to recognize and understand the emotional state of another person. While it is similar to emotional empathy/resonance in that it involves perceiving the internal state of another, mentalizing requires both perspective taking and making the distinction between the self and the other. Additionally, it is concerned with the mental state of the other

rather than the physical state. Though the latter can inform the process of mentalizing, it is not necessary; in fact, mentalizing can occur in the absence of information about a target's physical or motor state, such as in a written narrative describing thoughts, beliefs, or feelings (Frith and Frith, 2003).

Similarly, the underlying neural networks for mentalizing differ from those for emotional resonance and motor mirroring. Brain regions associated with mentalizing processes are the medial prefrontal cortex (mPFC), the temporo-parietal junction (TPJ), the posterior STS, and the temporal poles (Frith and Frith, 2006; Gallagher and Frith, 2003; Saxe and Kanwisher, 2003). This network overlaps with that identified as the 'default network', which is active when subjects have self-referential thought (Buckner et al., 2008), and which could be described as mentalizing about one's own mental states.

In the two studies presented here, regions identified as part of the mentalizing network were observed to show significant responses while subjects observed pain expressions, but only during the pain evaluation task; observation of the expressions during movement evaluation did not produce the same response. Additionally, in Study 2, mentalizing regions showed an overlapping response during both observation and execution of the pain expressions (again, only during the pain evaluation task), suggesting that mentalizing is utilized in both conditions. In both studies, the demands of the pain evaluation task are consistent with the definition of a mentalizing task: subjects were asked to consider, and quantify, the mental/emotional state of the other. This is in contrast to the movement evaluation task, in which subjects only had to consider the physical aspects of the expressions, with no requirement to account for the underlying state. These results demonstrate that the general process of mentalizing – thinking about the mental state of another – is in effect during the evaluation of pain expressions, in addition to the emotional and motor resonance discussed in the previous two subsections. The fact that the stimuli remained the same in both task conditions reveals that mentalizing is not an automatic process, but rather one that can be easily disrupted by attentional demands.

What mentalizing brings to the phenomena of pain empathy is the recognition of the other as an intentional agent distinct from the self, and recognition of the perspective of the other. While mentalizing may not be required to recognize pain in others, it is nonetheless a common component of the full experience of pain empathy, and it is necessary for the

production of helping behaviors aimed at the other, as well as self-protecting avoidance behaviors aimed at the self.

3.4.3. Mirroring vs mentalizing in the perception of facial expression of pain

Mirroring and mentalizing are clearly two different processes, each supported by a distinct neuroanatomical network, and the question of whether these processes are cooperative, independent, or even perhaps competitive is still being explored (Keysers and Gazzola, 2007; Spunt and Lieberman, 2012a, 2012b; Uddin et al., 2007; Van Overwalle and Baetens, 2009). In support of independence is evidence from studies showing each network activated in the absence of the other and/or showing differential responses according to the type of target stimuli provided (Brass et al., 2007; Spunt et al., 2011). Overwalle and Baetens describe the two functions as separate, though complementary, and theorize that the mirroring system is recruited when there is input about moving body parts, whereas mentalizing is recruited when this type of information is not available (Van Overwalle, 2009; Van Overwalle and Baetens, 2009). However, other studies have shown co-activation of networks for both mirroring and mentalizing (Zaki and Ochsner, 2012), as well as connectivity between their member regions (Lombardo et al., 2010), supporting a more complementary/cooperative model. Following this, it has been shown that activation of both networks is correlated with empathic accuracy of subjects tasked with identifying positive versus negative emotional states experienced by targets recounting autobiographical events (Zaki et al., 2009). Further, some work has even suggested the two systems are competitive to some degree, with activation of one inhibiting the other (Fox et al., 2005; Spengler et al., 2009).

In the more specific context of pain empathy, Lamm and colleagues have suggested a divide between networks responding to other pain that depends on how the pain information is presented to the observer, comparing picture-based to cue-based paradigms (Lamm et al., 2011). In the former, subjects view images or video clips of body parts receiving painful stimuli, whereas in the latter, subjects see cues indicating that a painful stimuli will be applied to another, but do not see the event themselves. They investigated this idea with a meta-analysis of nine pain empathy studies and concluded that a core pain empathy network

comprising the ACC and aINS is supplemented with either the mirroring regions (i.e. IFG and aIPL) that are engaged for pictures showing body parts receiving pain, or ToM regions (i.e. vmPFC, TPJ, pSTS, PCC/precuneus, and temporal poles) that are engaged for cues indicating, but not showing, painful stimuli. In other words, they concluded that mirroring can only occur when there is specific sensory information to mirror and when there is not, mentalizing is required to imagine the painful event. Overwalle and Baetens have described a similar distinction, proposing that mirroring occurs when body parts are in view, and mentalizing occurs when they are not; they conclude that the two functions are separate, though complementary, (Van Overwalle, 2009; Van Overwalle and Baetens, 2009).

In all of these previous works, however, the distinction is explored via the use of different types of stimuli to portray or describe painful events: for example, Lamm and colleagues compare images of body parts in painful conditions versus cues signaling a partner has received pain. In the work presented here, this distinction is created not by changing the stimuli, but by changing how subjects must evaluate the stimuli: either they must assess the pain content of the stimuli – i.e. the pain experience of the model – or the physical movements. In the pain task of Study 1, in fact, subjects are explicitly directed to mentalize, that is, to think about what the model is feeling ("How much pain?"). Thus, these findings provide additional support to the argument that mirroring predominates when there is a physical, biological model to mirror, while mentalizing predominates when there is no such model. Importantly, they expand on this idea by demonstrating that this dissociation between mirroring and mentalizing can also be revealed by simply directing the subject's attention to or away from the internal mental state of the model. Additionally, as the stimuli used in the current studies depict pain responses only, rather than pain stimuli or painful events, these results also demonstrate that both mirroring and mentalizing can occur in the absence of specific sensory information about the painful stimuli.

As described above, some authors have argued that mirroring predominates when there is an observable physical model to mirror, whereas mentalizing takes over when there is no such model. The findings here suggest that this same fluctuation between mirroring and mentalizing can be provoked simply by directing attention either to the external physical aspects or the internal/mental experience of the model. This work shows that both functions are involved in the perception of pain expressions, but the relative contribution of each

depends on task demands. Both versions of the pain evaluation task used in these studies rely more heavily on mentalizing, as subjects must consider the internal emotional state of the model. Similarly, both versions of the movement task rely more heavily on motor mirroring, as subjects must focus on the physical movements of the models and do not have to consider the internal state at all. However, it is unlikely that the subjects do not perceive the movements in the pain task, or that they do not consider or notice the internal state in the movement task at least to some small degree. Thus, these protocols are not able to dissociate completely these two functions and, as concluded by other authors (for example, (Spunt and Lieberman, 2012b)), the most likely answer is that both mirroring and mentalizing are important for pain empathy and the perception of pain in others.

3.5. Limitations

As with all research, limitations of these two studies fall into two categories: methodological considerations and the conceptual and theoretical interpretation of the findings.

Certain general methodological limitations apply to both of these studies as well as to fMRI work overall. Although fMRI is generally accepted as providing an accurate measure of brain activity related to a task, it is an indirect measure of brain activity, measuring blood flow changes rather than actual neural activity. Furthermore, areas identified by BOLD signal changes as "active" during a target condition may not actually be required for a task; lesions studies (with patients) and TMS protocols (in which temporary lesions are invoked in healthy subjects) are better at identifying direct links between specific brain regions and behavior. FMRI also does not provide the spatial resolution necessary to detect the activity of individual neurons, so protocols looking for mirror neurons are not able to detect overlapping activation at the level of individual neurons or neural populations, as is possible with, for example, micro-electrode recordings. However, in order to move forward with neuroimaging work, these limitations are generally accepted, and various measures such as meta-analyses and comparative reviews can mitigate them by aggregating the results of numerous individual studies together.

In the specific case of the studies presented here, additional methodological limitations exist. In Study 1, the results of an informal post-scan questionnaire regarding the scanning experience (data not analyzed nor published) suggested that many subjects found the movement task more difficult than the pain task. It is then possible that some of the activations observed during the movement task reflect a greater cognitive load and mental effort. However, as this was an unanticipated finding, and thus not addressed by the study design, there was insufficient data collected to explore this question.

In terms of conceptual and theoretical interpretation of the findings, one limit is that these results cannot be said to be specific for pain. No other emotional states were presented in either paradigm, thus the results cannot be said to represent a pain-specific emotion perception system. However, while it is not possible to say that these results are pain-specific, the validation process for the stimuli in both studies included first a comparison between pain expressions and expressions of other negative emotions: the stimuli used were selected from a larger pool based on their ratings for pain versus other negative emotions (anger, fear, and disgust) (Budell et al., 2010). Thus, while the video clips were not compared to other emotions such as disgust during the two studies described here, they were initially compared to other emotions during the validation process.

Pain is clearly a very important negative emotional state, but as mentioned in Section 3.3.3, the pain-related regions discussed here could alternatively be described as salience-detection-related, as part of a general system for the detection and avoidance of aversive stimuli. However, the main point to keep in mind is that there are basic processes sufficient to explain these results, and the "pain matrix" is still valid as it is a stable, basic, robust model consistent across different modalities, and the physiological response to pain comprises homeostasis-related functions. Finally, as the objective of this work was to investigate pain, it is a reasonable interpretation that these results show sensitivity for pain, even if not specificity for it.

3.6. Future directions

Future work investigating the differential contribution of emotional resonance, motor mirroring, and mentalizing to pain empathy, using similar dual-task paradigms as those

described here, could take this work in several different directions. Broadly speaking, additional studies could look at how the components of pain empathy are modulated by factors intrinsic to the observer and/or the pain sufferer, how self-pain is effected by the observation of pain in others ('vicarious pain facilitation'), and finally, how various pathologies might influence the brain response underlying pain empathy.

Already, much work has been done investigating the modulation of pain empathy and its underlying brain response. Several factors intrinsic to the observer are associated with differences in the perception of pain in others, such as personality traits (e.g. empathy, anxiety, or pain catastrophizing) (Goubert et al., 2009, 2008; Ochsner et al., 2008) or medical expertise (Cheng et al., 2007). Prior knowledge or impressions of the pain sufferer may also have an effect, such as perceived fairness (Singer et al., 2006) or perceived intentions (Akitsuki and Decety, 2009). Gender of the sufferer may also have an influence (Coll et al., 2012; Simon et al., 2006), as can social factors such as subject-observer racial parity/disparity or in-group/out-group membership status (Bruneau et al., 2012a; Hein et al., 2010; Xu et al., 2009). Most of these studies describe differences in emotional resonance, reflected by changes in ACC and aINS response. In some situations, decreases in emotional resonance appear to be correlated with increases in mentalizing, reflected by increased response in ToM regions such as the TPJ: for example, increased familiarity with painful procedures is associated with less emotional resonance and greater mentalizing in medical practitioners (Cheng et al., 2007). However, few of these modulation studies have discussed motor mirroring, utilized the type of observation/execution paradigms designed to identify this type of activation, or attempted to modulate the amount of mirroring that occurs. Thus, one area for exploration is how these three components of pain empathy – emotional resonance, motor mirroring, and mentalizing – are differentially influenced by a variety of psychological and sociological factors already known to affect pain empathy.

Another potential topic that has already received some attention is vicarious pain facilitation – i.e. the modulation of felt pain by observed pain – and the implications of this phenomenon for understanding the function of pain empathy. Viewing pain in others can lead to increased sensitivity for self-pain, as measured by different methods such as self-report, pain expression, and spinal reflexes. For example, viewing images of painful stimuli applied to others lowers the threshold for reflexive spinal responses to self-pain (Vachon-Presseau et al.,

2011). This effect is modulated by trait empathy, induced compassion, and information about the other's pain condition (e.g. sensory versus affective cues) (Loggia et al., 2008; Mailhot et al., 2012; Vachon-Presseau et al., 2011), and does not appear to be based simply on affective modulation (Roy et al., 2013). That the observation of pain cues and pain in others can influence the perception of self-pain and facilitate self-pain responses may illustrate one function of pain empathy – to avoid harm to oneself. It would be useful to investigate which components of pain empathy are most associated with vicarious facilitation of pain, and whether this phenomenon is, like emotional resonance, susceptible to attentional demands.

Finally, all of the aforementioned topics could be translated into work with clinical populations, to explore if and how pain empathy, specifically, is disrupted in patients with certain pathologies known to cause abnormal emotional perception, such as autism or schizophrenia. Further, it would be interesting to investigate whether, and how, interventions designed to increase accuracy of emotion perception in these populations could modulate pain empathy and its component parts.

3.7. Conclusion

The complex interaction of a distributed brain network and ascending and descending spinal pathways build the neural basis for the perception of pain in the self. Pain is a multidimensional experience with sensory, affective, and motivational components; during pain communication, information about the pain experience can be transmitted from a sufferer to an observer via multiple channels, including facial expression. An observer is able to perceive the internal emotional state of the other without receiving explicit information about the pain experience, such as the type of stimulus or the affected body part, by decoding the pain behaviors displayed by the other. Here, dynamic videos showing modelled pain expressions were used to explore the brain mechanisms in healthy subjects that support the perception of other pain and the evaluation of its intensity.

The results of this work reveal that perception of pain in others involves an interaction between mechanisms underlying the perception of self-pain and emotional resonance, those implicated in action understanding and motor mirroring, and those involved in mentalizing. While these mechanisms are distinct from one another, they are highly interconnected, both in

terms of the cognitive functions they support as well as the underlying neural networks. The extent of the contribution of each appears to be modulated by attentional demands: when the task directed subjects' attention away from the affective content of these expressions, self-pain-related brain responses were significantly reduced. However, explicit evaluation of pain expressions, while involving both mirroring and mentalizing, drew more heavily on the latter.

In conclusion, this work thus makes a relevant contribution to the question of how the brain reacts to facial cues communicating a noxious threat. As these findings are potentially applicable to other emotions, particularly negative emotions with a sensory component such as disgust, this work may also contribute to the broader field of empathy and perception of emotions in others.

Bibliography

Adelmann, P.K., Zajonc, R.B., 1989. Facial efference and the experience of emotion. Annual review of psychology 40, 249–280.

Akitsuki, Y., Decety, J., 2009. Social context and perceived agency affects empathy for pain: an event-related fMRI investigation. NeuroImage 47, 722–734.

Albe-Fessar, D., Berkley, K.J., Kruger, L., Ralston, H.J., Willis, W.D., 1985. Diencephalic mechanisms of pain sensation. Brain Research Reviews 9, 217–296.

Allison, T., Ginter, H., McCarthy, G., Nobre, A.C., Puce, A., Luby, M., Spencer, D.D., 1994. Face recognition in human extrastriate cortex. Journal of Neurophysiology 71, 821–825.

Allison, T., Puce, A., McCarthy, G., 2000. Social perception from visual cues: role of the STS region. Trends in Cognitive Sciences 4, 267–278.

Amodio, D.M., Frith, C.D., 2006. Meeting of minds: the medial frontal cortex and social cognition. Nature Reviews Neuroscience 7, 268–277.

Apkarian, A.V., Bushnell, M.C., Treede, R.-D.D., Zubieta, J.-K.K., 2005. Human brain mechanisms of pain perception and regulation in health and disease. European Journal of Pain 9, 463–484.

Avenanti, A., Bueti, D., Galati, G., Aglioti, S.M., 2005. Transcranial magnetic stimulation highlights the sensorimotor side of empathy for pain. Nature Neuroscience 8, 955–960.

Bornhövd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C., Büchel, C., 2002. Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. Brain 125, 1326–1336.

Botvinick, M., Jha, A.P., Bylsma, L.M., Fabian, S.A., Solomon, P.E., Prkachin, K.M., 2005. Viewing facial expressions of pain engages cortical areas involved in the direct experience of pain. NeuroImage 25, 312–319.

Boucher, J.D., 1969. Facial displays of fear, sadness and pain. Perceptual and Motor Skills 28,

239–42.

Brass, M., Schmitt, R.M., Spengler, S., Gergely, G., 2007. Investigating Action Understanding: Inferential Processes versus Action Simulation. Current Biology 17, 2117–2121.

Brooks, J.C.W., Zambreanu, L., Godinez, A., Craig, A.D., Tracey, I., 2005. Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. NeuroImage 27, 201–209.

Bruneau, E.G., Dufour, N., Saxe, R., 2012a. Social cognition in members of conflict groups: behavioural and neural responses in Arabs, Israelis and South Americans to each other's misfortunes. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences 367, 717–730.

Bruneau, E.G., Pluta, A., Saxe, R.R., 2012b. Distinct roles of the "shared pain" and "theory of mind" networks in processing others' emotional suffering. Neuropsychologia 50, 219–231.

Buccino, G., Binkofski, F., Fink, G.R., Fadiga, L., Fogassi, L., Gallese, V., Seitz, R.J., Zilles, K., Rizzolatti, G., Freund, H.J., Parma, Á., Volturno, V., Parma, I.-, 2001. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. European Journal of Neuroscience 13, 400–404.

Büchel, C., Holmes, a P., Rees, G., Friston, K.J., 1998. Characterizing stimulus-response functions using nonlinear regressors in parametric fMRI experiments. NeuroImage 8, 140–8.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Annals of the New York Academy of Sciences 1124, 1–38.

Budell, L., Jackson, P., Rainville, P., 2010. Brain responses to facial expressions of pain: emotional or motor mirroring? NeuroImage 53, 355–363.

Budell, L., Kunz, M., Jackson, P.L., Rainville, P., 2015. Mirroring pain in the brain: emotional expression versus motor imitation. PloS One 10, e0107526.

Bushnell, M.C., Duncan, G.H., Hofbauer, R.K., Ha, B., Chen, J.I., Carrier, B., 1999. Pain perception: is there a role for primary somatosensory cortex? Proceedings of the National Academy of Sciences of the United States of America 96, 7705–9.

Byrne, J.H., Dafny, N. (Eds.), 1999. Pain Tracts and Sources, in: *Neuroscience Online: An Electronic Textbook for the Neurosciences*. Department of Neurobiology and Anatomy, The University of Texas Medical School at Houston (UTHealth).

Carr, L., Iacoboni, M., Dubeau, M.C., Mazziotta, J.C., Lenzi, G.L., 2003. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proceedings of the National Academy of Sciences of the United States of America 100, 5497–5502.

Caspers, S., Zilles, K., Laird, A.R., Eickhoff, S.B., 2010. ALE meta-analysis of action observation and imitation in the human brain. NeuroImage 50, 1148–1167.

Cauda, F., D'Agata, F., Sacco, K., Duca, S., Geminiani, G., Vercelli, A., 2011. Functional connectivity of the insula in the resting brain. NeuroImage 55, 8–23.

Chang, L.J., Yarkoni, T., Khaw, M.W., Sanfey, A.G., 2013. Decoding the role of the insula in human cognition: Functional parcellation and large-scale reverse inference. Cerebral Cortex 23, 739–749.

Chartrand, T.L., Bargh, J.A., 1999. The chameleon effect: the perception-behavior link and social interaction. Journal of Personality and Social Psychology 76, 893–910.

Cheng, Y., Lin, C.-P., Liu, H.-L., Hsu, Y.-Y., Lim, K.-E., Hung, D., Decety, J., 2007. Expertise modulates the perception of pain in others. Current Biology 17, 1708–1713.

Chong, T.T.J., Cunnington, R., Williams, M.A., Kanwisher, N., Mattingley, J.B., 2008. fMRI Adaptation Reveals Mirror Neurons in Human Inferior Parietal Cortex. Current Biology 18, 1576–1580.

Coghill, R.C., Sang, C.N., Maisog, J.M., Iadarola, M.J., 1999. Pain intensity processing within the human brain: a bilateral, distributed mechanism. Journal of Neurophysiology 82, 1934–1943.

Coghill, R.C., Talbot, J.D., Evans, A.C., Meyer, E., Gjedde, A., Bushnell, M.C., Duncan, G.H., 1994. Distributed processing of pain and vibration by the human brain. The Journal of Neuroscience 14, 4095–4108.

Coll, M.-P.P., Budell, L., Rainville, P., Decety, J., Jackson, P.L., 2012. The role of gender in the interaction between self-pain and the perception of pain in others. The Journal of Pain 13, 695–703.

Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nature Reviews Neuroscience 3, 655–666.

Craig, A.D., 2009. How do you feel--now? The anterior insula and human awareness. Nature Reviews Neuroscience 10, 59–70.

Craig, A.D.B., 2003. Pain mechanisms: labeled lines versus convergence in central processing. Annual Review of Neuroscience 26, 1–30.

Craig, K.D., Hadjistavropoulos, H.D., Grunau, R. V, Whitfield, M.F., 1994. A comparison of two measures of facial activity during pain in the newborn child. Journal of Pediatric Psychology 19, 305–18.

Craig, K.D., Prkachin, K.M., Grunau, R.E., 2011. The facial expression of pain., in: Turk, D., Melzack, R. (Eds.), *Handbook of Pain Assessment*. Guilford Press, pp. 117–133.

Critchley, H.D., Corfield, D.R., Chandler, M.P., Mathias, C.J., Dolan, R.J., 2000. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. The Journal of Physiology 523 Pt 1, 259–270.

Critchley, H.D., Mathias, C.J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B.K., Cipolotti, L., Shallice, T., Dolan, R.J., 2003. Human cingulate cortex and autonomic control: Converging neuroimaging and clinical evidence. Brain 126, 2139–2152.

Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. Nature Neuroscience 7, 189–195.

Cross, E.S., Hamilton, A.F., Grafton, S.T., 2006. Building a motor simulation de novo: observation of dance by dancers. NeuroImage 31, 1257–1267.

Danziger, N., Faillenot, I., Peyron, R., 2009. Can we share a pain we never felt? Neural correlates of empathy in patients with congenital insensitivity to pain. Neuron 61, 203–212.

Danziger, N., Prkachin, K.M., Willer, J.-C., 2006. Is pain the price of empathy? The perception of others' pain in patients with congenital insensitivity to pain. Brain 129, 2494–507.

Decety, J., Yang, C.-Y., Cheng, Y., 2010. Physicians down-regulate their pain empathy response: an event-related brain potential study. NeuroImage 50, 1676–82.

Deen, B., Pitskel, N.B., Pelphrey, K.A., 2011. Three systems of insular functional connectivity identified with cluster analysis. Cerebral Cortex 21, 1498–1506.

Deiber, M.P., Honda, M., Ibanez, V., Sadato, N., Hallett, M., 1999. Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: effect of movement type and rate. Journal of Neurophysiology 81, 3065–3077.

Dimberg, U., 1987. Facial reactions, autonomic activity and experienced emotion: a three component model of emotional conditioning. Biological Psychology 24, 105–122.

Dimberg, U., Thunberg, M., Elmehed, K., 2000. Unconscious facial reactions to emotional facial expressions. Psychological Science 11, 86–89.

Dinstein, I., Hasson, U., Rubin, N., Heeger, D.J., 2007. Brain areas selective for both observed and executed movements. Journal of Neurophysiology 98, 1415–1427.

Driver, J., Mattingley, J.B., 1998. Parietal neglect and visual awareness. Nature Neuroscience 1, 17–22.

Dubé, A.A., Duquette, M., Roy, M., Lepore, F., Duncan, G., Rainville, P., 2009. Brain activity associated with the electrodermal reactivity to acute heat pain. NeuroImage 45, 169–180.

Duerden, E.G., Albanese, M.C., 2013. Localization of pain-related brain activation: a meta-analysis of neuroimaging data. Human Brain Mapping 34, 109–149.

Dum, R.P., Levinthal, D.J., Strick, P.L., 2009. The spinothalamic system targets motor and sensory areas in the cerebral cortex of monkeys. The Journal of Neuroscience 29, 14223–

14235.

Dum, R.P., Strick, P.L., 2005. Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. The Journal of Neuroscience 25, 1375–1386.

Ekman, P., Friesen, W. V., 1978. *The Facial Action Coding System.*, Consulting Psychologists.

Ekman, P., Levenson, R.W., Friesen, W. V, 1983. Autonomic nervous system activity distinguishes among emotions. Science 221, 1208–1210.

Fadiga, L., Craighero, L., Olivier, E., 2005. Human motor cortex excitability during the perception of others' action. Current Opinion in Neurobiology.

Ferrari, P.F., Gallese, V., Rizzolatti, G., Fogassi, L., 2003. Mirror neurons responding to the observation of ingestive and communicative mouth actions in the monkey ventral premotor cortex. European Journal of Neuroscience 17, 1703–1714.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proceedings of the National Academy of Sciences of the United States of America 102, 9673–8.

Frith, C.D., Frith, U., 2006. The neural basis of mentalizing. Neuron 50, 531–534.

Frith, U., Frith, C.D., 2003. Development and neurophysiology of mentalizing. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences 358, 459–473.

Frot, M., Faillenot, I., Mauguière, F., 2014. Processing of nociceptive input from posterior to anterior insula in humans. Human Brain Mapping.

Frot, M., Magnin, M., Mauguière, F., Garcia-Larrea, L., 2007. Human SII and posterior insula differently encode thermal laser stimuli. Cerebral Cortex 17, 610–620.

Frot, M., Mauguiere, F., Magnin, M., Garcia-Larrea, L., 2008. Parallel processing of nociceptive A-delta inputs in SII and midcingulate cortex in humans. The Journal of

Neuroscience 28, 944–952.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., Benedetti, F., Abbamonte, M., Gasparotti, R., Barale, F., Perez, J., McGuire, P., Politi, P., 2009. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. Journal of Psychiatry and Neuroscience 34, 418–432.

Gallagher, H.L., Frith, C.D., 2003. Functional imaging of "theory of mind." Trends in Cognitive Sciences 7, 77–83.

Gallese, V., Eagle, M.N., Migone, P., 2007. Intentional attunement: mirror neurons and the neural underpinnings of interpersonal relations. Journal of the American Psychoanalytic Association 55, 131–176.

Gallese, V., Fadiga, L., Fogassi, L., Rizzolatti, G., 1996. Action recognition in the premotor cortex. Brain 119 (Pt 2, 593–609.

Gallese, V., Goldman, A., 1998. Mirror neurons and the simulation theory of mind-reading. Trends in Cognitive Sciences 2, 493–501.

Garcia-Larrea, L., 2012. The posterior insular-opercular region and the search of a primary cortex for pain. Neurophysiologie Clinique.

Garcia-Larrea, L., Perchet, C., Creac'H, C., Convers, P., Peyron, R., Laurent, B., Mauguire, F., Magnin, M., 2010. Operculo-insular pain (parasylvian pain): A distinct central pain syndrome. Brain 133, 2528–2539.

Garcia-Larrea, L., Peyron, R., 2013. Pain matrices and neuropathic pain matrices: a review. Pain 154 Suppl, S29-43.

Geday, J., Gjedde, A., Boldsen, A.S., Kupers, R., 2003. Emotional valence modulates activity in the posterior fusiform gyrus and inferior medial prefrontal cortex in social perception. NeuroImage 18, 675–684.

Gingold, S.I., Greenspan, J.D., Apkarian, A. V, 1991. Anatomic evidence of nociceptive inputs to primary somatosensory cortex: relationship between spinothalamic terminals

and thalamocortical cells in squirrel monkeys. The Journal of Comparative Neurology 308, 467–490.

Gordon, R.M., 1986. Folk Psychology as Simulation. Mind & Language 1, 158–171.

Goubert, L., Vervoort, T., Cano, A., Crombez, G., 2009. Catastrophizing about their children's pain is related to higher parent-child congruency in pain ratings: an experimental investigation. European Journal of Pain 13, 196–201.

Goubert, L., Vervoort, T., Sullivan, M.J., Verhoeven, K., Crombez, G., 2008. Parental emotional responses to their child's pain: the role of dispositional empathy and catastrophizing about their child's pain. The Journal of Pain 9, 272–279.

Grill-Spector, K., Knouf, N., Kanwisher, N., 2004. The fusiform face area subserves face perception, not generic within-category identification. Nature Neuroscience 7, 555–562.

Grunau, R. V, Craig, K.D., 1987. Pain expression in neonates: facial action and cry. Pain 28, 395–410.

Gu, X., Han, S., 2007. Attention and reality constraints on the neural processes of empathy for pain. NeuroImage 36, 256–267.

Gu, X., Han, S., 2007. Neural substrates underlying evaluation of pain in actions depicted in words. Behavioural Brain Research 181, 218–223.

Gu, X., Liu, X., Guise, K.G., Naidich, T.P., Hof, P.R., Fan, J., 2010. Functional dissociation of the frontoinsular and anterior cingulate cortices in empathy for pain. The Journal of Neuroscience 30, 3739–3744.

Hadjistavropoulos, T., Craig, K.D., Duck, S., Cano, A., Goubert, L., Jackson, P.L., Mogil, J.S., Rainville, P., Sullivan, M.J., De, C.W.A.C., Vervoort, T., Fitzgerald, T.D., 2011. A biopsychosocial formulation of pain communication. Psychological Bulletin 137, 910–939.

Haxby, J. V., Hoffman, E.A., Gobbini, M.I., 2000. The distributed human neural system for face perception. Trends in Cognitive Sciences.

Haxby, J. V, Haxby, J. V, Hoffman, E. a, Hoffman, E. a, Gobbini, M.I., Gobbini, M.I., 2002.

Human neural systems for face recognition and social communication. Biological Psychiatry 51, 59–67.

Hein, G., Silani, G., Preuschoff, K., Batson, C.D., Singer, T., 2010. Neural responses to ingroup and outgroup members' suffering predict individual differences in costly helping. Neuron 68, 149–160.

Hennenlotter, A., Schroeder, U., 2006. Partly dissociable neural substrates for recognizing basic emotions: a critical review. Progress in Brain Research 156, 443–456.

Hennenlotter, A., Schroeder, U., Erhard, P., Castrop, F., Haslinger, B., Stoecker, D., Lange, K.W., Ceballos-Baumann, A.O., 2005. A common neural basis for receptive and expressive communication of pleasant facial affect. NeuroImage 26, 581–591.

Hofbauer, R.K., Rainville, P., Duncan, G.H., Bushnell, M.C., 2001. Cortical representation of the sensory dimension of pain. Journal of Neurophysiology 86, 402–11.

Horn, C., Blischke, Y., Kunz, M., Lautenbacher, S., 2012. Does pain necessarily have an affective component? Negative evidence from blink reflex experiments. Pain Research and Management 17, 15–24.

Humphreys, K., Avidan, G., Behrmann, M., 2007. A detailed investigation of facial expression processing in congenital prosopagnosia as compared to acquired prosopagnosia. Experimental Brain Research 176, 356–73.

Hurley, S., 2006. Active perception and perceiving action: The shared circuits hypothesis, in: *Perceptual Experience*. pp. 205–259.

Hurley, S., 2008. The shared circuits model (SCM): how control, mirroring, and simulation can enable imitation, deliberation, and mindreading. Behavioral and Brain Sciences 31, 1–58.

Hutchison, W.D., Davis, K.D., Lozano, A.M., Tasker, R.R., Dostrovsky, J.O., 1999. Pain-related neurons in the human cingulate cortex. Nature Neuroscience 2, 403–405.

Iacoboni, M., Mazziotta, J.C., 2007. Mirror neuron system: basic findings and clinical applications. Annals of Neurology 62, 213–218.

Iacoboni, M., Molnar-Szakacs, I., Gallese, V., Buccino, G., Mazziotta, J.C., Rizzolatti, G., 2005. Grasping the intentions of others with one's own mirror neuron system. PLoS Biology 3, e79.

Iacoboni, M., Woods, R.P., Brass, M., Bekkering, H., Mazziotta, J.C., Rizzolatti, G., 1999. Cortical mechanisms of human imitation. Science 286, 2526–2528.

IASP, 2012. IASP Taxonomy 2012 update [WWW Document]. IASP Taxonomy. URL https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698

Isomura, Y., Takada, M., 2004. Neural mechanisms of versatile functions in primate anterior cingulate cortex. Reviews in the Neurosciences 15, 279–291.

Jabbi, M., Bastiaansen, J., Keysers, C., 2008. A common anterior insula representation of disgust observation, experience and imagination shows divergent functional connectivity pathways. PLoS One 3, e2939.

Jabbi, M., Swart, M., Keysers, C., 2007. Empathy for positive and negative emotions in the gustatory cortex. NeuroImage 34, 1744–1753.

Jackson, P.L., Meltzoff, A.N., Decety, J., 2005. How do we perceive the pain of others? A window into the neural processes involved in empathy. NeuroImage 24, 771–779.

Johnson, M.H., Senju, A., Tomalski, P., 2015. The two-process theory of face processing: modifications based on two decades of data from infants and adults. Neuroscience and Biobehavioral Reviews 50, 169–79.

Kanwisher, N., McDermott, J., Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. The Journal of Neuroscience 17, 4302–11.

Kaplan, J.T., Iacoboni, M., 2006. Getting a grip on other minds: mirror neurons, intention understanding, and cognitive empathy. Social Neuroscience 1, 175–183.

Kemp, R., McManus, C., Pigott, T., 1990. Sensitivity to the displacement of facial features in negative and inverted images. Perception 19, 531–543.

Kenshalo, D.R., Giesler, G.J., Leonard, R.B., Willis, W.D., 1980. Responses of neurons in

primate ventral posterior lateral nucleus to noxious stimuli. Journal of Neurophysiology 43, 1594–1614.

Keysers, C., Fadiga, L., 2008. The mirror neuron system: new frontiers. Social Neuroscience 3, 193–198.

Keysers, C., Gazzola, V., 2006. Towards a unifying neural theory of social cognition. Progress in Brain Research 156, 379–401.

Keysers, C., Gazzola, V., 2007. Integrating simulation and theory of mind: from self to social cognition. Trends in Cognitive Sciences 11, 194–196.

Kilner, J.M., Neal, A., Weiskopf, N., Friston, K.J., Frith, C.D., 2009. Evidence of mirror neurons in human inferior frontal gyrus. The Journal of Neuroscience 29, 10153–10159.

Kober, H., Barrett, L.F., Joseph, J., Bliss-Moreau, E., Lindquist, K., Wager, T.D., 2008. Functional grouping and cortical-subcortical interactions in emotion: A meta-analysis of neuroimaging studies. NeuroImage 42, 998–1031.

Kong, J., White, N.S., Kwong, K.K., Vangel, M.G., Rosman, I.S., Gracely, R.H., Gollub, R.L., 2006. Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity. Human Brain Mapping 27, 715–721.

Kress, T., Daum, I., 2003. Developmental prosopagnosia: a review. Behavioural Neurology 14, 109–121.

Kulkarni, B., Bentley, D.E., Elliott, R., Youell, P., Watson, A., Derbyshire, S.W.G., Frackowiak, R.S.J., Friston, K.J., Jones, A.K.P., 2005. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. European Journal of Neuroscience 21, 3133–3142.

Kunz, M., Chatelle, C., Lautenbacher, S., Rainville, P., 2008a. The relation between catastrophizing and facial responsiveness to pain. Pain 140, 127–134.

Kunz, M., Faltermeier, N., Lautenbacher, S., 2012a. Impact of visual learning on facial expressions of physical distress: a study on voluntary and evoked expressions of pain in congenitally blind and sighted individuals. Biological Psychology 89, 467–476.

Kunz, M., Gruber, A., Lautenbacher, S., 2006. Sex differences in facial encoding of pain. The Journal of Pain 7, 915–928.

Kunz, M., Lautenbacher, S., LeBlanc, N., Rainville, P., 2012b. Are both the sensory and the affective dimensions of pain encoded in the face? Pain 153, 350–358.

Kunz, M., Mylius, V., Schepelmann, K., Lautenbacher, S., 2004. On the relationship between self-report and facial expression of pain. The Journal of Pain 5, 368–376.

Kunz, M., Mylius, V., Schepelmann, K., Lautenbacher, S., 2008b. Impact of age on the facial expression of pain. Journal of Psychosomatic Research 64, 311–318.

Kunz, M., Rainville, P., Lautenbacher, S., 2011. Operant conditioning of facial displays of pain. Psychosomatic Medicine 73, 422–431.

Lamm, C., Decety, J., Singer, T., 2011. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. NeuroImage 54, 2492–2502.

LeDoux, J., 2003. The emotional brain, fear, and the amygdala. Cellular and Molecular Neurobiology.

Legrain, V., Iannetti, G.D., Plaghki, L., Mouraux, A., 2011. The pain matrix reloaded: a salience detection system for the body. Progress in Neurobiology 93, 111–24.

LeResche, L., Dworkin, S.F., Wilson, L., Ehrlich, K.J., 1992. Effect of temporomandibular disorder pain duration on facial expressions and verbal report of pain. Pain 51, 289–295.

Leslie, K.R., Johnson-Frey, S.H., Grafton, S.T., 2004. Functional imaging of face and hand imitation: towards a motor theory of empathy. NeuroImage 21, 601–607.

Levenson, R.W., Ekman, P., Friesen, W. V, 1990. Voluntary facial action generates emotion-specific autonomic nervous system activity. Psychophysiology 27, 363–384.

Liakakis, G., Nickel, J., Seitz, R.J., 2011. Diversity of the inferior frontal gyrus--a meta-analysis of neuroimaging studies. Behavioural Brain Research 225, 341–7.

Loggia, M.L., Mogil, J.S., Bushnell, M.C., 2008. Empathy hurts: compassion for another increases both sensory and affective components of pain perception. Pain 136, 168–176.

Lombardo, M. V., Chakrabarti, B., Bullmore, E.T., Wheelwright, S.J., Sadek, S.A., Suckling, J., Baron-Cohen, S., 2010. Shared Neural Circuits for Mentalizing about the Self and Others. Journal of Cognitive Neuroscience 22, 1623–1635.

Mailhot, J.P., Vachon-Presseau, E., Jackson, P.L., Rainville, P., 2012. Dispositional empathy modulates vicarious effects of dynamic pain expressions on spinal nociception, facial responses and acute pain. European Journal of Neuroscience 35, 271–278.

Malach, R., 2012. Targeting the functional properties of cortical neurons using fMR-adaptation. NeuroImage 62, 1163–1169.

Mattingley, J.B., Husain, M., Rorden, C., Kennard, C., Driver, J., 1998. Motor role of human inferior parietal lobe revealed in unilateral neglect patients. Nature 392, 179–182.

Mazzola, L., Isnard, J., Mauguière, F., 2006. Somatosensory and pain responses to stimulation of the second somatosensory area (SII) in humans. A comparison with SI and insular responses. Cerebral Cortex 16, 960–968.

Mazzola, L., Isnard, J., Peyron, R., Guénot, M., Mauguière, F., 2009. Somatotopic organization of pain responses to direct electrical stimulation of the human insular cortex. Pain 146, 99–104.

McNeil, J.E., Warrington, E.K., 1993. *Prosopagnosia: a face-specific disorder.*, The Quarterly Journal of Experimental Psychology.

Mesulam, M.M., Mufson, E.J., 1982. Insula of the old world monkey. III: Efferent cortical output and comments on function. Journal of Comparative Neurology 212, 38–52.

Molenberghs, P., Cunnington, R., Mattingley, J.B., 2009. Is the mirror neuron system involved in imitation? A short review and meta-analysis. Neuroscience and Biobehavioral Reviews 33, 975–980.

Montgomery, K.J., Haxby, J. V, 2008. Mirror neuron system differentially activated by facial expressions and social hand gestures: a functional magnetic resonance imaging study. Journal of Cognitive Neuroscience 20, 1866–1877.

Morecraft, R.J., Mcneal, D.W., Stilwell-Morecraft, K.S., Gedney, M., Ge, J., Schroeder, C.M.,

Van Hoesen, G.W., 2007. Amygdala interconnections with the cingulate motor cortex in the rhesus monkey. Journal of Comparative Neurology 500, 134–165.

Morecraft, R.J., Stilwell-Morecraft, K.S., Rossing, W.R., 2004. The motor cortex and facial expression: new insights from neuroscience. The Neurologist 10, 235–249.

Morrison, I., Downing, P.E., 2007. Organization of felt and seen pain responses in anterior cingulate cortex. NeuroImage 37, 642–651.

Morrison, I., Lloyd, D., di Pellegrino, G., Roberts, N., 2004. Vicarious responses to pain in anterior cingulate cortex: is empathy a multisensory issue? Cognitive, Affective, & Behavioral Neuroscience 4, 270–278.

Morrison, I., Peelen, M. V., Downing, P.E., 2007a. The sight of others' pain modulates motor processing in human cingulate cortex. Cerebral Cortex 17, 2214–2222.

Morrison, I., Poliakoff, E., Gordon, L., Downing, P., 2007b. Response-specific effects of pain observation on motor behavior. Cognition 104, 407–416.

Morrison, I., Tipper, S.P., Fenton-Adams, W.L., Bach, P., 2013. "Feeling" others' painful actions: the sensorimotor integration of pain and action information. Human Brain Mapping 34, 1982–1998.

Mouraux, A., Diukova, A., Lee, M.C., Wise, R.G., Iannetti, G.D., 2011. A multisensory investigation of the functional significance of the "pain matrix". NeuroImage 54, 2237–49.

Mufson, E.J., Mesulam, M. -Marsel, 1982. Insula of the old world monkey. II: Afferent cortical input and comments on the claustrum. Journal of Comparative Neurology 212, 23–37.

Mukamel, R., Ekstrom, A.D., Kaplan, J., Iacoboni, M., Fried, I., 2010. Single-neuron responses in humans during execution and observation of actions. Current Biology 20, 750–756.

Müri, R.M., 2016. Cortical control of facial expression. Journal of Comparative Neurology.

Niedenthal, P.M., Mermillod, M., Maringer, M., Hess, U., 2010. The Simulation of Smiles

(SIMS) model: Embodied simulation and the meaning of facial expression. The Behavioral and Brain Sciences 33, 417-433-480.

Ochsner, K.N., Zaki, J., Hanelin, J., Ludlow, D.H., Knierim, K., Ramachandran, T., Glover, G.H., Mackey, S.C., 2008. Your pain or mine? Common and distinct neural systems supporting the perception of pain in self and other. Social Cognitive and Affective Neuroscience 3, 144–160.

Ostrowsky, K., Magnin, M., Ryvlin, P., Isnard, J., Guenot, M., Mauguière, F., 2002. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation., Cerebral Cortex.

Palermo, R., Willis, M.L., Rivolta, D., McKone, E., Wilson, C.E., Calder, A.J., 2011. Impaired holistic coding of facial expression and facial identity in congenital prosopagnosia. Neuropsychologia 49, 1226–35.

Patrick, C.J., Craig, K.. D., Prkachin, K.M., 1986. Observer judgments of acute pain: facial action determinants. Journal of Personality and Social Psychology 50, 1291–8.

Paus, T., 2001. Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nature Reviews Neuroscience 2, 417–424.

Paus, T., Koski, L., Caramanos, Z., Westbury, C., 1998. Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: a review of 107 PET activation studies. Neuroreport 9, R37–R47.

Perini, I., Bergstrand, S., Morrison, I., 2013. Where pain meets action in the human brain. The Journal of Neuroscience 33, 15930–15939.

Peyron, R., García-Larrea, L., Grégoire, M.C., Costes, N., Convers, P., Lavenne, F., Mauguière, F., Michel, D., Laurent, B., 1999. Haemodynamic brain responses to acute pain in humans. Sensory and attentional networks. Brain 122, 1765–1779.

Peyron, R., Laurent, B., Garcia-Larrea, L., 2000. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiologie clinique / Clinical Neurophysiology 30, 263–288.

Phan, K.L., Fitzgerald, D.A., Gao, K., Moore, G.J., Tancer, M.E., Posse, S., 2004. Real-time fMRI of cortico-limbic brain activity during emotional processing. Neuroreport 15, 527–532.

Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. NeuroImage 16, 331–48.

Phillips, M.L., Young, A.W., Scott, S.K., Calder, A.J., Andrew, C., Giampietro, V., Williams, S.C., Bullmore, E.T., Brammer, M., Gray, J.A., 1998. Neural responses to facial and vocal expressions of fear and disgust. Proceedings of the Royal Society of London. Series B, Biological Sciences 265, 1809–1817.

Phillips, M.L., Young, A.W., Senior, C., Brammer, M., Andrew, C., Calder, A.J., Bullmore, E.T., Perrett, D.I., Rowland, D., Williams, S.C., Gray, J.A., David, A.S., 1997. A specific neural substrate for perceiving facial expressions of disgust. Nature 389, 495–498.

Picard, N., Strick, P.L., 1996. Motor areas of the medial wall: a review of their location and functional activation. Cerebral Cortex 6, 342–353.

Piché, M., Arsenault, M., Rainville, P., 2010. Dissection of perceptual, motor and autonomic components of brain activity evoked by noxious stimulation. Pain 149, 453–462.

Ploner, M., Freund, H.J., Schnitzler, A., 1999. Pain affect without pain sensation in a patient with a postcentral lesion. Pain 81, 211–214.

Pomares, F.B., Faillenot, I., Barral, F.G., Peyron, R., 2013. The “where” and the “when” of the BOLD response to pain in the insular cortex. Discussion on amplitudes and latencies. NeuroImage 64, 466–475.

Porro, C. a, Cettolo, V., Francescato, M.P., Baraldi, P., 1998. Temporal and intensity coding of pain in human cortex. Journal of Neurophysiology 80, 3312–20.

Premack, D., Woodruff, G., 1978. Does the chimpanzee have a theory of mind? Behavioral and Brain Sciences 1, 515–526.

Press, C., Weiskopf, N., Kilner, J.M., 2012. Dissociable roles of human inferior frontal gyrus during action execution and observation. NeuroImage 60, 1671–1677.

Preston, S.D., de Waal, F.B.M., 2002. Empathy: Its ultimate and proximate bases. Behavioral and Brain Sciences 25, 1–71.

Price, D.D., 2000. Psychological and neural mechanisms of the affective dimension of pain. Science 288, 1769–1772.

Price, D.D., Harkins, S.W., Baker, C., 1987. Sensory-affective relationships among different types of clinical and experimental pain. Pain.

Prkachin, K.M., 1992. The consistency of facial expressions of pain: a comparison across modalities. Pain 51, 297–306.

Prkachin, K.M., Craig, K.D., 1995. Expressing pain: The communication and interpretation of facial pain signals. Journal of Nonverbal Behavior 19, 191–205.

Rainville, P., Carrier, B., Hofbauer, R.K., Bushnell, M.C., Duncan, G.H., 1999. Dissociation of sensory and affective dimensions of pain using hypnotic modulation. Pain 82, 159–171.

Rainville, P., Duncan, G.H., Price, D.D., Carrier, B., Bushnell, M.C., 1997. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277, 968–971.

Rizzolatti, G., Craighero, L., 2004. The mirror-neuron system. Annual Review of Neuroscience 27, 169–192.

Rizzolatti, G., Fadiga, L., Gallese, V., Fogassi, L., 1996. Premotor cortex and the recognition of motor actions. Cognitive Brain Research 3, 131–141.

Roy, C., Fiset, D., Taschereau-Dumouchel, V., Gosselin, F., Rainville, P., 2013. A refined examination of the facial cues contributing to vicarious effects on self-pain and spinal responses. The Journal of Pain 14, 1475–1484.

Rubia, K., Russell, T., Overmeyer, S., Brammer, M.J., Bullmore, E.T., Sharma, T., Simmons, A., Williams, S.C., Giampietro, V., Andrew, C.M., Taylor, E., 2001. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. NeuroImage 13, 250–261.

Rushworth, M.F.S., Behrens, T.E.J., Rudebeck, P.H., Walton, M.E., 2007. Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. Trends in Cognitive Sciences 11, 168–76.

Saarela, M. V, Hlushchuk, Y., Williams, A.C., Schurmann, M., Kalso, E., Hari, R., 2007. The compassionate brain: humans detect intensity of pain from another's face. Cerebral Cortex 17, 230–237.

Sabatinelli, D., Fortune, E.E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W.T., Beck, S., Jeffries, J., 2011. Emotional perception: meta-analyses of face and natural scene processing. NeuroImage 54, 2524–2533.

Saxe, R., 2006. Uniquely human social cognition. Current Opinion in Neurobiology.

Saxe, R., Kanwisher, N., 2003. People thinking about thinking people. The role of the temporo-parietal junction in "theory of mind." NeuroImage 19, 1835–1842.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. The Journal of Neuroscience 27, 2349–2356.

Seitz, R.J., Schäfer, R., Scherfeld, D., Friederichs, S., Popp, K., Wittsack, H.J., Azari, N.P., Franz, M., 2008. Valuating other people's emotional face expression: a combined functional magnetic resonance imaging and electroencephalography study. Neuroscience 152, 713–722.

Sergent, J., Ohta, S., MacDonald, B., 1992. Functional neuroanatomy of face and object processing. A positron emission tomography study. Brain 115 Pt 1, 15–36.

Shackman, A.J., Salomons, T. V., Slagter, H.A., Fox, A.S., Winter, J.J., Davidson, R.J., 2011. The integration of negative affect, pain, and cognitive control in the cingulate cortex. Nature Reviews Neuroscience 12, 154–167.

Shamay-Tsoory, S.G., Aharon-Peretz, J., Perry, D., 2009. Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. Brain 132, 617–627.

Simon, D., Craig, K.D., Gosselin, F., Belin, P., Rainville, P., 2008. Recognition and discrimination of prototypical dynamic expressions of pain and emotions. Pain 135, 55–64.

Simon, D., Craig, K.D., Miltner, W.H., Rainville, P., 2006. Brain responses to dynamic facial expressions of pain. Pain 126, 309–318.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not sensory components of pain. Science 303, 1157–1162.

Singer, T., Seymour, B., O'Doherty, J.P., Stephan, K.E., Dolan, R.J., Frith, C.D., 2006. Empathic neural responses are modulated by the perceived fairness of others. Nature 439, 466–469.

Sonnby-Borgstrom, M., 2002. Automatic mimicry reactions as related to differences in emotional empathy. Scandinavian Journal of Psychology 43, 433–443.

Spengler, S., Von Cramon, D.Y., Brass, M., 2009. Control of shared representations relies on key processes involved in mental state attribution. Human Brain Mapping 30, 3704–3718.

Spunt, R.P., Lieberman, M.D., 2012a. Dissociating modality-specific and supramodal neural systems for action understanding. The Journal of Neuroscience 32, 3575–3583.

Spunt, R.P., Lieberman, M.D., 2012b. An integrative model of the neural systems supporting the comprehension of observed emotional behavior. NeuroImage 59, 3050–3059.

Spunt, R.P., Satpute, A.B., Lieberman, M.D., 2011. Identifying the what, why, and how of an observed action: an fMRI study of mentalizing and mechanizing during action observation. Journal of Cognitive Neuroscience 23, 63–74.

Tölle, T.R., Kaufmann, T., Siessmeier, T., Lautenbacher, S., Berthele, A., Munz, F., Zieglgänsberger, W., Willoch, F., Schwaiger, M., Conrad, B., Bartenstein, P., 1999. Region-specific encoding of sensory and affective components of pain in the human brain: A positron emission tomography correlation analysis. Annals of Neurology 45, 40–47.

Torta, D.M., Cauda, F., 2011. Different functions in the cingulate cortex, a meta-analytic connectivity modeling study. NeuroImage 56, 2157–72.

Treede, R.D., Apkarian, A.V., Bromm, B., Greenspan, J.D., Lenz, F.A., 2000. Cortical representation of pain: Functional characterization of nociceptive areas near the lateral sulcus. Pain.

Treede, R.D., Kenshalo, D.R., Gracely, R.H., Jones, A.K.P., 1999. The cortical representation of pain. Pain 79, 105–112.

Tsao, D.Y., Livingstone, M.S., 2008. Mechanisms of face perception. Annual Review of Neuroscience 31, 411–437.

Uddin, L.Q., Iacoboni, M., Lange, C., Keenan, J.P., 2007. The self and social cognition: the role of cortical midline structures and mirror neurons. Trends in Cognitive Sciences 11, 153–157.

Vachon-Presseau, E., Martel, M.O., Roy, M., Caron, E., Jackson, P.L., Rainville, P., 2011. The multilevel organization of vicarious pain responses: effects of pain cues and empathy traits on spinal nociception and acute pain. Pain 152, 1525–1531.

Vachon-Presseau, E., Roy, M., Martel, M.O., Albouy, G., Chen, J., Budell, L., Sullivan, M.J., Jackson, P.L., Rainville, P., 2012. Neural processing of sensory and emotional-communicative information associated with the perception of vicarious pain. NeuroImage 63, 54–62.

van der Gaag, C., Minderaa, R.B., Keysers, C., 2007. Facial expressions: what the mirror neuron system can and cannot tell us. Social Neuroscience 2, 179–222.

Van Overwalle, F., 2009. Social cognition and the brain: a meta-analysis. Human Brain Mapping 30, 829–858.

Van Overwalle, F., Baetens, K., 2009. Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. NeuroImage 48, 564–584.

Vogt, B.A., Pandya, D.N., 1987. Cingulate cortex of the rhesus monkey: II. Cortical afferents. Journal of Comparative Neurology 262, 271–289.

Vogt, B.A., Pandya, D.N., Rosene, D.L., 1987. Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents. The Journal of Comparative Neurology 262, 256–270.

Vogt, B. a, 2005. Pain and emotion interactions in subregions of the cingulate gyrus. Nature Reviews Neuroscience 6, 533–44.

Völlm, B. a, Taylor, A.N.W., Richardson, P., Corcoran, R., Stirling, J., McKie, S., Deakin, J.F.W., Elliott, R., 2006. Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. NeuroImage 29, 90–8.

Vuilleumier, P., 2007. Neural representation of faces in human visual cortex: the roles of attention, emotion, and viewpoint, in: Osaka, N., Rentschler, I., Biederman, I. (Eds.), *Object Recognition, Attention, and Action*. Springer, pp. 119–138.

Vuilleumier, P., Driver, J., 2007. Modulation of visual processing by attention and emotion: windows on causal interactions between human brain regions. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences 362, 837–855.

Vuilleumier, P., Richardson, M.P., Armony, J.L., Driver, J., Dolan, R.J., 2004. Distant influences of amygdala lesion on visual cortical activation during emotional face processing. Nature Neuroscience 7, 1271–1278.

Wicker, B., Keysers, C., Plailly, J., Royet, J.P., Gallese, V., Rizzolatti, G., 2003. Both of us disgusted in my insula: the common neural basis of seeing and feeling disgust. Neuron 40, 655–664.

Williams, A.C., 2002. Facial expression of pain: an evolutionary account. Behavioral and Brain Sciences 25, 439–488.

Willis, W.D., Westlund, K.N., 1997. Neuroanatomy of the pain system and of the pathways that modulate pain. Journal of Clinical Neurophysiology 14, 2–31.

Xu, X., Zuo, X., Wang, X., Han, S., 2009. Do you feel my pain? Racial group membership modulates empathic neural responses. The Journal of Neuroscience 29, 8525–8529.

Zaki, J., Ochsner, K., 2012. The neuroscience of empathy: progress, pitfalls and promise.

Nature Neuroscience 15, 675–680.

Zaki, J., Ochsner, K.N., Hanelin, J., Wager, T.D., Mackey, S.C., 2007. Different circuits for different pain: patterns of functional connectivity reveal distinct networks for processing pain in self and others. Social Neuroscience 2, 276–291.

Zaki, J., Weber, J., Bolger, N., Ochsner, K., 2009. The neural bases of empathic accuracy. Proceedings of the National Academy of Sciences of the United States of America 106, 11382–7.