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Investigations of the role of the human anterior cingulate cortex in observing others' pain

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INVESTIGATIONS OF THE ROLE OF THE HUMAN ANTERIOR CINGULATE CORTEX IN OBSERVING OTHERS' PAIN

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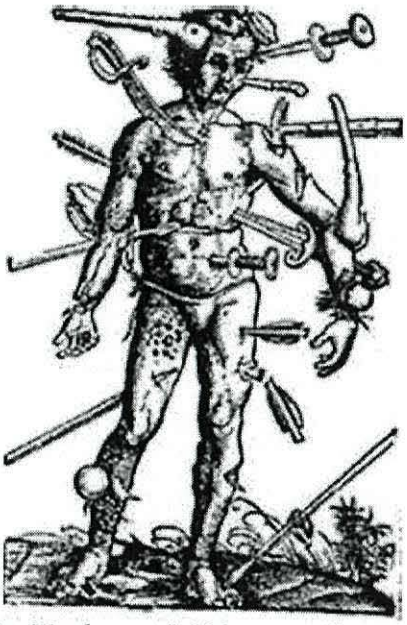


"Der Wundermann", 16th century illustration of a variety of lacerations and puncture wounds (German, artist unknown)

"...the executioner struck no blow that the people did not follow with a plaintive cry and exclamation, as if everyone had lent his own sense of feeling to that carcass."

Michel de Montaigne, *Of cruelty,* 1583
(describing an execution and quartering he witnessed during a visit to Rome)

Summary

This thesis takes a basic approach to empathy by focusing on the role of the anterior cingulate cortex (ACC) during observation of the pain-related situations of other people. It seeks to place this role in terms of the ACC's more general involvement in the preparation and selection of motor responses on the basis of motivational relevance. In doing so, the thesis introduces the conceptual and empirical bases for current prevailing hypotheses about interpersonal representations, empathy, and pain, especially those centering on human neuroimaging evidence (Chapter I). Integral to the interpretation of this evidence is a dimensional model of pain processing in which motivational-affective and sensory-discriminative components are dissociable. The current understanding of the role of cingulate cortex in pain processing and other functions is also described (Chapters I and VII).

The studies presented in the experimental chapters elucidate the role of the cingulate in pain observation, including its relevant processing dimensions (Chapter II), the anatomical localization of visual pain-related responses (Chapters II ,III, IV and VI), stimulus features upon which these depend (Chapters III, IV and VI), and the relationship of pain observation to behavior and functions of the cingulate dealing with selecting, preparing, and executing motor responses (Chapters V and VI). The findings of these studies indicate that both feeling pain directly and seeing others' apparent injury give rise to activations in the dorsal ACC (dACC) and midcingulate (MCC) cortices. The converging behavioral and neuroanatomical results presented here also reinforce the relationship between pain observation and motor processing in medial premotor areas of the human brain.

CHAPTER I[1]:

INTRODUCTION

"What have you done to it?" asked Ursula, who had been aching to put the question for the last half hour.

"To my hand?" said Gerald. "I trapped it in some machinery."

"Ugh!" said Ursula. "And did it hurt much?"

"Yes," he said. "It did at the time. It's getting better now. It crushed the fingers."

"Oh," cried Ursula, as if in pain, "I hate people who hurt themselves. I can *feel* it." And she shook her hand.

— D.H. Lawrence, *Women in Love,* chapter XIV ("Water-party")

[1] Portions of this chapter are adapted from a book chapter in press: Morrison, I., Motivational-affective processing and the neural foundations of empathy. In T. Farrow and P. Woodruff, Eds., *Empathy in Mental Illness and Health.* Cambridge: Cambridge University Press.

I. Conceptual foundations of empathy and pain

One of the essential issues at the core of "empathy" is that of knowledge. If each person is a psychically bounded entity with privileged access only to his or her own mental or emotional experience, how is it possible to *know* what another person experiences? In addressing such a multifarious subject as "empathy", cognitive neuroscience inherits a concept that began as a hybrid of early psychological theories of perception, and philosophical theories dealing with phenomenology (the subjective contents of experience) and epistemology (what makes knowledge of these contents possible). The modern "empathy" concept as it comes to us is relatively young, but nevertheless represents the complex product of multiple conceptual influences that acted on it from the late nineteenth century— when experimental psychology was finding its feet— to today, when theories of mind-brain are dominated by representationalist models of information processing.

The studies presented in this thesis are directed towards an understanding of the basic neural mechanisms that may ultimately underlie our ability to "empathize" in the sense of having relatively reliable, subjectively-flavored knowledge of another person's probable mental state, on the basis of perceiving objective features of their circumstances or behavior. But in studying empathy empirically it is important to be aware that the object of study is not a straightforward phenomenon, or even a well-delineated construct, but rather is a vernacular concept of which certain aspects have been implicitly or explicitly highlighted in hypothesis-testing. For example, the studies in this thesis posit that empathy chiefly applies to the domain of

unpleasant experiences, and thus investigates it through the narrower lens of pain.

It is not possible to give a complete account of all that the vernacular concept of empathy entails. It is similarly difficult to encapsulate the nature of pain. Pain, like empathy, is a complex concept, having both subjective, phenomenal aspects and objective, physical aspects that are difficult to reduce into a single theoretical framework. However, in the absence of a comprehensive definition, it is useful to identify some of the elements of the "empathy" concept that inform the approach taken in the following chapters. Likewise, there are key features of current models of pain processing which have direct bearing on the study of "pain empathy," especially for the recent studies using neuroimaging techniques. This chapter outlines the main elements of the empathy concept and pain-processing models that lie behind the stance taken in the rest of the thesis.

Historically, two of these elements have taken the form of paradoxes: the first could be called the "problem of foreign experience": how is it possible to "sense", "feel", or "know" *others'* subjective experience in a firsthand manner? The second, related issue could be called the "sense-datum problem of pain": how is it possible to "sense" or "feel" a bodily sensation like pain in the absence of a direct physical cause? The conceptual foundations of these two issues are covered in this section, and are relevant to the more empirical issues in this chapter which review research on empathy, pain, and associated brain regions.

The third main element will be taken up in the subsequent section (section II). It addresses a more recent, neuroscientifically-centered concern: the

functional link or mechanism relating the perception of externally-caused sensory events (*eg* through vision) to the body-centered, first-person processing which may be accompanied by subjective feeling states. This third issue will be referred to as the "functional mechanism problem."

The problem of foreign experience

The phenomenologist philosopher Edith Stein first articulated the "problem of foreign experience" in the context of empathy (Stein, 1917/1989). The basic problem for Stein was to show empathy as the perceiving of foreign (others') experience as ultimately "primordial" (as if it were part of our own present subjective experience). She described empathy in phenomenological terms, in which present phenomenal experience is primary to other more removed forms of knowledge, and integral to perceiving and acting in the world (rather than, for example, being a consequence or by-product of perceiving and acting). For her, there was a difference between knowledge derived from inference, memory, and other such processes, and phenomenological "givenness", with givenness being more fundamental. Her project was to explore the respects in which the phenomenal experience of others is subjectively "given" upon perception of their acts, expressions, utterances, etc.

Stein's analysis does not emphasize the means by which perception of these acts and what they elicit in the consciousness of the observer are bridged. This is because her concern was not one of explaining mechanical causation, which she and other phenomenologists (such as her teacher Edmund Husserl) viewed as an inappropriate criterion for addressing matters

of a psychical or "spiritual" nature. Instead, she concentrates on the epistemological status of empathy, and concludes that it is not reducible to representation, inference, association, or other less "given" forms of perception and knowledge. The importance of her treatise to the modern conception of empathy lies mainly in her bringing its subjective quality and immediacy to the fore.

For Stein, the issue of whether the phenomenal character of foreign experience in empathy was accurate or justified was not essential. However, for later philosophers and current theorists, this issue regarding "other minds" is central (*eg* Eisenberg, Murphy, & Shepard, 1997; Batson, Early, & Salvarani, G, 1997). For example, do we know what the other person is feeling, or do we know how the other person's situation makes *us* feel? The latter has been referred to as "personal distress" which may be elicited by seeing someone else in pain (*eg* Lawrence, Shaw, Giampietro, Surguladze, Brammer, & David, 2006). Even if perceiving others' pain is a direct phenomenal perception and not an inference, it still begs the question of whether the observer is *really* justified in claiming that the other person is *actually* in pain (Fodor, 1981). For many, the question becomes more refined: how is *type-identical* subjective experience of others' pain possible?

The position taken in this thesis is that what is perceived, as it were, is more along the lines of a probability than a certainty. The importance of the accuracy question depends on the function of empathy and the processes leading to it. Here, and in the chapters that follow, I provisionally take the function of the processes leading to empathy to be heuristic, subserving learning about pain and the circumstances surrounding it, rather than learning

about the other's mental state *per se* (although the latter may be a consequence of the former). From this perspective, the probability that the other person is in pain is sufficiently instructive, even if the observer always subjectively *experiences* it as a certainty. The question becomes one of how these probabilities are detected and interpreted, and what factors weight the estimation of their certainty in the subjective experience. In my view, this is an empirical question, and mainly eludes *post hoc* theoretical analysis. A first step in the empirical direction is to establish the functional properties of the brain's responses to others' pain, which the studies in this thesis attempt to do.

The sense-datum problem

But problems in characterizing the subjective aspects of perception can arise even in the first-person case, without any foreign experiencer on the scene. The "sense-datum problem of pain" stems from the problem of applying traditional ideas of sensation and representation (derived mainly from the example of vision) to the very broad and very fuzzy domain of bodily sensation. Many theorists and philosophers from Descartes onwards have been bothered by the question of exactly *what* is perceived during pain (*eg,* Dretske, 2005; Fodor, 1981; Tye, 2005, Hardcastle, 1999). First of all, pain is private as few other categories of perception are. Everyone can directly see the coffee mug sitting on the table, but only I can directly feel the pain of the hot ceramic when I grasp it. Second, abnormal sense-datum/representation relationships are very conspicuous and common in pain, such as chronic pain syndromes in which pain is felt in the absence of an

actual peripheral cause, phantom pain which is felt in the absence of a body part, and analgesia in which a physical cause is present but pain is not experienced.

If a sensation is nothing more than a representation of a sense-datum, then pain is almost disqualified from being a sensation at all. Pain's wealth of exceptions from the classical sense-datum/representation rule poses obstacles for any theory aiming for a direct, realist account of pain perception (Aydede, 2005). One salient reason is because seemingly non-physical— or at least non-physically-caused— factors often appear to intervene between the sense-datum and its perception (*eg* in chronic pain, allodynia, or hyperalgesia), and even with acute pain the relationship can be non-veridical, as with referred pain (*eg*, is it a heart attack, or indigestion?). Pain sensation can be viewed both as an object (*eg* a pinprick to the finger) and as a subjective experience (*eg* the unpleasant feeling resulting from the pinprick). Indeed, Armstrong (1962) categorized pains as "intransitive" bodily sensations for which it is often not possible to assign an objective sensory cause external to our own subjective experience. Some theorists have addressed this "sense-datum" problem with a framework of "indirect realism," in which the thing that is *perceived* is not a sense-datum, but a phenomenal state *instigated* by a sense-datum— yet the presence of a stimulus does not *necessarily* lead to such perception (Aydede, 2005).

For the purposes of this thesis, the important aspect of this debate is that "pain" extends beyond the sense-datum/representation relationship as traditionally conceived. This decoupling of pain from direct sense-datum/representation relationships means that in principle, sources of pain-

related information are not limited to the activity of nerve fibers at the periphery. For philosophers, the question may never be settled. Scientists studying pain, however, have taken a more pragmatic approach. The International Association for the Study of Pain (IASP) officially unanchored the pain from the stimulus in 1986, operationally defining pain as "...an unpleasant sensory and emotional experience associated with actual or potential tissue damage, described in terms of such damage...Pain is always subjective...Activity induced in the nociceptor and nociceptive pathways is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause" (International Association for the Study of Pain Subcommittee on Taxonomy, 1986).

The introduction of the word "potential" into the relationship with tissue damage in this definition is crucial for the idea of empathy presented in this thesis. It reflects the important trend in current scientific models of pain to consider pain not simply as a sensation but as an essentially psychological and affective phenomenon. Further, it de-emphasizes the phenomenological mystery of pain affect to ask what the function of its encompassing affective quality might be.

For example, the pioneering neuroscientist Charles Scott Sherrington characterized pain as a heuristic category of perception, referring to its role in learning about tissue damage through specialized channels of perception (Sherrington, 1948). Later, Melzack and Wall's (1968) gate control theory was the first scientific model of pain that specifically included modulatory mechanisms between the nerve endings in peripheral tissue and central pain processing in the brain, via excitatory and inhibitory mechanisms in the

dorsal horn of the spinal cord. Melzack and Wall's neurophysiological model of intervening modulatory processes paved the way for further hypotheses which aimed to account for the dissociations between the sensory discrimination of pain— more likely to be tied to the stimulus and more amenable to a traditional representationalist framework— and the motivational-affective aspects involved in pain's less straightforward, contentful subjective dimension (Melzack & Casey, 1968; Wall, 1999). Pain now is not just a sort of sensory push to which the organism replies with a behavioral pull. Its characterization has become that of a labile, modulatory coalition of mechanisms in which subjective affective experience plays an indispensable role in relating harmful events to behavior.

II. Pain processing pathways in the brain: motivation and affect

In this spirit, the neurophysiological encoding of pain is considered to be divisible into two major, dissociable dimensions (Rainville, Duncan., Price, Carrier, & Bushnell, 1997; Rainville, Carrier, Hofbauer, Bushnell, & Duncan, 1999; Rainville, 2002; Ploner, Freund, Schnitzler,1999; Craig, Reiman, Evans, & Bushnell, 1996; Coghill, Sang, Maisog, & Iadarola, 1999; Ploghaus, Tracey, Gati, Clare, Menon, Matthews., & Rawlins, 1999; Sawamoto, Honda, Okada, Hankawa, Kanda, Fukuyama, & Shibasai, 2000; Price, 2000; Derbyshire, Whalley, Stenger, & Oakley, 2004). The sensory-discriminative dimension supports the spatial localization and intensity encoding of painful stimuli. The motivational-affective dimension is involved in coding the unpleasantness and motivational relevance of nociceptive information (Hofbauer, Rainville, Duncan, & Bushnell, 2001). Other

dimensions have been identified, such as the negative hedonic (Sewards & Sewards, 2002) and the cognitive-evaluative (Ingvar, 1999), but it is the sensory-discriminative and motivational-affective dimensions that have emerged as major axes in neuroimaging studies of pain processing.

This section outlines some of the important models and empirical findings about central pain processing with respect to these two dimensions. It is not intended to be an exhaustive review, but to cover those points that are most relevant to the remainder of this chapter and the ensuing experimental chapters. It emphasizes the motivational-affective dimension and role of a brain region designated as the anterior cingulate cortex (ACC) in its coding.

Pain motivates behavior

Mammals have evolved learning mechanisms that go beyond reactive affective responses— mechanisms which play essential roles in evaluating and learning complex contingencies as well as in selecting, changing, and controlling relevant response elements. "Motivation" is a general concept used by behavioral neuroscientists in hypotheses about the many ways in which organisms change their behavior. (It should be noted that the concept of motivation has a rich history in social psychology too. The concept of motivation used here is the neuroscientist's.) Essentially in the service of bioregulation, motivation in the behaving organism often manifests in learning processes that contribute to the ways in which behavior becomes modified with respect to rewarding or aversive objects or situations (Berridge & Robinson, 2003; Berridge, 2004).

Clark (2005) delineated an array of possible ways in which the motivational-affective component of pain interacts with or influences behavior (from Clark, 2005, p 185):

- *desire*: to avoid the pain, to reduce it, or have it stop
- *drive*: the urgency to do something about it; the degree to which the motivations aroused by pain override all others
- *interest*: the degree to which pain grabs and holds attention, and prevents one from attending to other projects or plans; the degree to which one can be distracted from the pain
- *preference*: the extent to which presence of pain changes preferences among alternative sets of affairs
- *incentive*: the degree to which reduction of pain provides a reward for other behaviors
- *reinforcer*: the degree to which pain decreases the probability of some behaviors (aversive conditioning and avoidance learning)

The neural pathways subserving these elements in the central nervous system are complex and multi-tiered (especially when they include associative processes that modulate pain responses in the absence of actual nociceptive input, such as in memory, anticipation, or learning). In the presence of a painful stimulus, nociception begins at the spinal level. Dorsal root ganglion cells receive signals from free-ended nerves at the periphery which respond to chemical cues from damaged cells (Toates, 2001). Of these specialized peripheral afferents, the most relevant are thinly myelinated Aδ fibers (comparatively fast), and unmyelinated C fibers (slow) (Julius & Basbaum, 2001). There is evidence that cells in laminae I-II and IV-VI of the

dorsal horn of the spinal cord perform basic computations as to the nature and location of pain on the basis of signals from these peripheral fibers (Price, Barrell, & Rainville, 2002).

From the spinal cord, the pathways to subcortical and cortical regions separate into sensory-discriminative and motivational-affective routes at a relatively early stage (Sewards & Sewards, 2002). On the whole, sensory-discriminative processing has been associated with fibers ascending through lateral nuclei of the thalamus, while motivational-affective processing is associated primarily with medial thalamic pathways (Sewards & Sewards 2002, 2003; Vogt & Sikes, 2000, Craig 2003a). With the exception of a few key human neuroimaging studies (Rainville *et al*, 1997, 1999; Craig *et al* 1996; Price *et al*, 2000, Kulkarni, Bentley, Elliott, *et al*, 2005), evidence for the functional distinction between motivational-affective and sensory-discriminative dimensions of pain processing has come from mammals such as rats and monkeys (*eg*, Johansen, Fields, & Manning, 2001).

In the sensory-discriminative encoding of pain, the majority of ascending inputs from the lateral pain system project to somatosensory cortices (Peyron, Garcia-Larrea, Gregoire, *et al*, 2000; Ploner *et al*, 1999; Bushnell, Duncan, Hofbauer, Ha, Chen, & Carrier, 1999; Treede *et al* 1999). Regardless of the exact nature of their respective contributions to spatial localization and sensory encoding of pain (Timmermann, Ploner, Haucke, Schmitz, Baltissen, & Schnitzler, 2001), nociception in both SI and SII is distinct from tactile discrimination (Ploner, Schmitz, Freund, & Schnitzler, 2000). Many neuroimaging studies show spatial summation for painful stimuli in SI with respect to the amount of the body surface stimulated (Peyron *et al*, 2000a). In

monkeys and other mammals, sensory-discriminative neurons tend to have small receptive fields and steep stimulus-response functions (Davis, Taylor, Crawley, Wood, Mikulis, 1997; Peyron *et al*2000a; Kanda, M., Nagamine, T., Ikeda, *et al,* 2000).

Motivational aspects of pain, on the other hand, are those that ultimately pertain to desires, urges, or impulses to avoid or terminate a painful experience. These are reflected in voluntary or involuntary behaviors such as freezing, escape (also "wild flight"), and avoidance (Sewards & Sewards, 2002). This definition can include reflexive or conditioned responses but also includes cortical mechanisms involved in learning about the context and nature of painful stimuli. A chief function of motivational pain pathways is to provide inputs to premotor and motor structures involved in the planning and execution of movement (Devinsky, Morrell, & Vogt, 1995, Sewards & Sewards, 2002; Vogt, Berger, & Derbyshire, 2003).

The hedonic side of motivation

A further distinction is often made between motivational-affective and negative-hedonic processing. Both can be subjectively associated with feelings of unpleasantness. In contrast to motivational-affective processing associated with skeletomotor output, negative hedonic outputs can possibly be utilized by other systems as well (for example, autonomic and neuroendocrine systems). Nociceptive processing performed by cells in dorsal horn laminae I and II are considered to belong under the "negative-hedonic" heading before becoming destined as motivational-affective afferents in laminae VII and VIII (Sewards & Sewards 2002). Further,

Sewards and Sewards posit that the negative hedonic aspect is represented *independently* in *lateral* pathways.

Since motivational urges can also be experienced as unpleasantness or discomfort, especially when the motivated behaviors fail to relieve the pain, this account implies some blending on the subjective level between unpleasantness from motivational-affective and hedonic sources. The possibility that different neural and functional pathways can produce sensations which are difficult to distinguish subjectively may be an important consideration in analyzing the neural correlates of "unpleasantness" apart from sensory coding, for instance in studying empathy in terms of a wholesale separation between sensory-discriminative and motivational-affective dimensions. Indeed, the inextricability of the relationship between stimulus intensity and unpleasantness is part of Fields' (1999) criticism of the dimensional dichotomy. He suggests the alternative term "algosity" for the unpleasantness associated with pain intensity, other sensory phenomena such as itch, and unpleasant sensations not easily describable in terms of actual or potential tissue damage (*eg* "electrical" or "crawling"; Fields, 1999).

The motor side of motivation and the role of ACC

The nature of the ACC's contribution to motivational-affective processing in pain is well-illustrated by the case of a patient with selective damage to the right postcentral gyrus and parietal operculum, which include somatosensory areas for the skin of the hands (Ploner *et al*, 1999). When stimulated with a laser, the patient was unable to localize a painful stimulus on the left (contralateral) hand. However, he appeared to have intact motivational

processing, identifying the painful sensation as "something he wanted to avoid" despite not being able to discriminate its sensory characteristics (Ploner *et al*, 1999). Damage to the ACC, a cortical target for medial fiber projections, can alter pain perception without impairing localization, yet intracortical microstimulation does not produce feelings of pain (Davis, Hutchison, Lozano, & Dostrovsky, 1994; Hutchison, Davis, Lozano, Tasker, & Dostrovsky,1999). This implies that the ACC's role in nociception is not simply in detecting painful stimuli. Stimulation of anterior cingulate cortex in humans, on the other hand, *does* produce reports of unspecific motivation or urges, and feelings of "wanting or planning to do something" (Bancaud & Talairach, 1992).

The human ACC is a region of the cingulate gyrus and sulcus that extends anterior from about the anterior commissure (AC) plane and curves around the genu of the corpus callosum. It includes Brodmann's areas 25, 24, 32, and 33 (see Fig. 1). It is cytologically distinct from posterior cingulate cortex (PCC) portions that extend posterior to the posterior commissure (PC) plane and curve around the splenium of the corpus callosum (Vogt *et al*, 1995; Vogt & Sikes, 2000). Within the ACC itself numerous cytologically distinct regions also exist (Vogt, Wiley, & Jensen, 1995; Vogt *et al*, 2003). These are partly reflected in broad functional differences between supracallosal and subcallosal regions, with the latter more often implicated in emotional tasks and the former in cognitive tasks (Bush, Luu, & Posner, 2000). This is supported by differences in connectivity. Subcallosal regions have numerous inputs and reciprocal connections with limbic structures (such as the amygdala; Morecraft & van Hoesen, 1997). Supracallosal regions, on the

other hand, lack such a strong limbic influence and their caudal areas in particular are predominantly connected with prefrontal and medial and lateral premotor areas, as well as parietal cortex (Matelli, Luppino, & Rizzolatti, 1991; G. Rizzolatti & Luppino, 2001; Rizzolatti, Fogassi, & Gallese, 2002). This region of cortex is often referred to as dorsal ACC (dACC).

The nomenclature of human cingulate areas is variable, and studies reporting ACC activations frequently refer to widely different subregions. Moreover, the designation of Brodmann's areas are not often in agreement with recent findings in connectivity and cytoarchitecture (Vogt *et al,* 1995). Talairach and Tournoux's anatomical atlas also has weaknesses in the designation of areas with respect to anatomical landmarks (Vogt *et al,* 1995; Vogt *et al,* 2003), and in accurately representing the cortical volume of this region (Rushworth, Walton, Kennerley, & Bannerman, 2004). A relatively recent division of the cingulate into anterior and middle cingulate cortex (ACC and MCC) has been proposed by Vogt on the basis of connectivity, cytoarchitecture, and neuroendocrine differences (Vogt *et al,* 2003). This distinction is adopted here because it is relevant to issues of pain as well as motor processing.

The MCC includes cortex situated between the AC and PC planes, inferior to SMA and pre-SMA. Vogt has distinguished these as subregions 24a', 24b', 24c', 24d, and 32' (see Fig. 1). MCC is heavily implicated in pain processing in humans. Although activations occur here during painful stimulation, tasks involving negative emotions activate this area only infrequently (Vogt *et al,* 2003), indicating that its functional role in pain processing does not simply involve the representation of generally negative affective coding. MCC also

contains regions with premotor properties. These are referred to as the CMAs in monkeys and the cingulate motor zones (CMZs) or rostral and caudal cingulate zones (RCZ and CCZ) in humans (Paus, Petrides, Evans, & Meyer, 1993; Dum & Strick 1996; Picard & Strick, 2001; Vogt *et al,* 1995; Isomura &Takada, 2004; Koski & Paus, 2000).

In monkeys, four mesial premotor areas have been identified, two in the SMA and pre-SMA and two in the cingulate (Matelli *et al,* 1991; Deiber, Honda, Ibanez, Sadato, & Hallett, 1999; Tanji, 1996). Cingulate motor areas have been identified in rostral and caudal parts of the gyrus and suclus, with the former associated with complex tasks and the latter with relatively simple tasks. In the human the CMZs are associated with quick hand responses and fast, self-triggered movements (Deiber, *et al,* 1999). Projections from MCC reach supplementary motor, premotor, primary motor cortices, and the spinal cord, influencing the selection of skeletomotor responses to painful stimuli (Devinsky *et al,* 1995; Matelli *et al,* 1991; Vogt *et al,* 1995).

If this motivated feeling of wanting to move corresponds subjectively to what we would label an urge, the MCC is well-situated to perform such functions— namely to relate reward outcomes to motor responses. Intriguingly, converging evidence from human and nonhuman primate literature suggests that these areas of the MCC/dACC are indeed involved in numerous tasks involving the linkage of relevant contextual information with action (Badre & Wagner, 2004; Bush *et al,* 2000; Deiber *et al,* 1999; Kerns, Cohen, MacDonald, Cho, Stenger, & Carter, 2004; Bush, Vogt, Holmes, Dale, Greve, Jenike, & Rosen, 2002). This includes the learning and

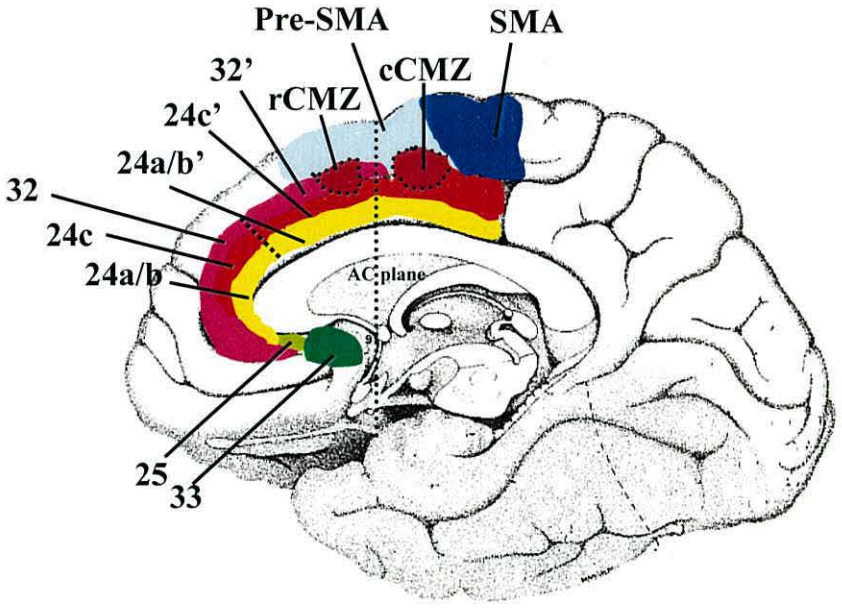


Figure 1. Areas within human cingulate cortex and neighboring medial cortex. The vertical dotted line denotes the plane of the anterior commissure (AC); the small oblique dotted line indicates the boundary of Brodmann areas 32, 24a/c, and 24c with 32', 24a/c', and 24c'. The rostral and caudal cingulate motor zones (rCMZ and cCMZ) are circled with dotted lines. Figure based on Vogt *et al* (2003), Bush *et al* (2000), Rushworth *et al* (2004), and Paus (2002).

performance of new behavior (Raichle, 1998; Jueptner, Stephan, Frith, Brooks, Frackowiak, & Passingham, 1997), and the detection of errors and monitoring of response conflict in ongoing behavior (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Menon, Adleman, White, Glover, & Reiss, 2001; van Veen, Holroyd, Cohen, Stenger, & Cameron, 2004). For example, cingulate areas show activations when it is necessary to suppress a prepotent or overlearned motor response (Carter, Macdonald, Botvinick, Ross, Stenger, Noll, & Cohen, 2000), or when freely choosing among alternative actions (Walton, Devlin, & Rushworth, 2003). Consistent with this, they are also involved in tasks which involve making voluntary decisions based on

fluctuating reward frequencies (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006; Williams, Bush, Rauch, Cosgrove & Eskandar, 2004; Bush *et al,* 2002; O'Doherty, Critchley, Deichmann, & Dolan, 2003; Gehring & Willoughby, 2002). Pain-related neurons have been found among the same populations as reward-related neurons (Koyama, Kato, Tanaka, & Mikami, 2001) and those that anticipate painful stimuli (Koyama, T., Tanaka, Y.Z., & Mikami, A., 1998; Porro, Cettolo, Francescato, & Baraldi, 2003). The role of MCC and related dACC regions in pain and reward-based action selection is consistent with a view of ACC function in evaluating stimuli with respect to potential consequences.

However, it is important to note that motivational urges in themselves may not intrinsically specify a particular effector. Cortical motivational-affective regions like the dACC do not contain a clearly delineated topography of the body as sensory-discriminative regions do (Vogt *et al,* 1995; Vogt, *et al,* 2003; Barch, Braver, Akbudak, Conturo, Ollinger, & Snyder, 2001). The cingulate and nearby supplementary motor regions in human and nonhuman primates have been associated with a rough somatotopic organization, with motor fields corresponding to manual, forelimb, facial, and vocal responses (Isomura & Takada, 2004).

Outside of these midcingulate motor areas, though, any "mapping" may be conceived more in terms of motivational salience, and in any case is not especially spatially acute (Mesulam, 1999). This squares well with the uncomfortable but ill-localized subjective experience of vicarious pain, which could be considered of a variety vividly termed "all-overishness" by William James: "If our friend goes near to the edge of a precipice, we get the well-

known feeling of 'all-overishness', and we shrink back, although we positively *know* him to be safe, and have no distinct imagination of his fall" (James, 1892/1985). Because this type of motivational salience is not tied to strictly sensory nociceptive stimulation but is open to multiple sources of mediation, it is this dimension of pain processing— carrying its uncomfortable, squeamish, urgish feel— that leaves open the possibility that pain information can be derived from *extrapersonal* sources as well as from direct pain experience. The evidence from studies of cingulate cortex indicates that these sources include heuristic ones such as the temporal relationships surrounding painful events, objects and situations that may predict painful outcomes. Critically, they may also include the behavior of other people.

The functional mechanism problem

This leads to the "functional mechanism" problem: if information about others' pain and their probable painful mental state is available to an observer, how is this accomplished? Current theories of empathy (and closely-related issues in theory-of-mind or "mentalizing") share trends with theories contemporary with Titchener's coinage of the English word "empathy" in 1909 (Titchener, 1909; see *A note on terminology* below). One trend is that empathy is conceived as a route to knowledge about the other person's subjective mental contents, desires, intentions, or motives. Another trend concerns the nature of the mechanism, psychological or neural, by which this is accomplished. Namely, witnessing others' behavior is proposed to cause "resonance" of similar systems or behavioral dispositions in the observer

(Rizzolatti, Fadiga, Fogassi, & Gallese, 1999; Gallese 2001, 2003), or "mappings" of perceptual input about others onto self-related representations (Meltzoff, 2002; Preston & de Waal).

At the late nineteenth and the beginning of the twentieth century, theorists such as Lipps (1903) and Titchener (1909, 1921) were pursuing epistemological concerns about the nature of perception. One major thread in their thought could be formulated as the question: how do we derive the content of perception from the act of sensation? Titchener (1909) and Lipps (1903) each considered the idea that the object of perception is understood by means of kinesthetic imagery. For Titchener, kinesthetic imagery could serve as a vehicle for propositional thought about, and understanding of, the object via the motoric attitude evoked by the object. Even for abstract dispositional attributes such as "gravity and modesty and pride and courtesy and stateliness," Titchener wrote, "I feel or act them in the mind's muscles" (Titchener, 1909). This kinesthetic "resonance" with the object had epistemological value, and when the object was another person, kinesthetic imagery could similarly set up a perception-knowledge relationship in the mind of the senser/perceiver, including any ensuing feelings or aesthetic experience.

For Lipps, the idea of empathy was linked to a similar idea of "inner imitation" (*innere Nachahmung*, Lipps, 1903), which was also kinesthetically-based. A major difference between Lipps' and Titchener's ideas is that for Lipps, empathy and inner imitation were means to *impart* feelings to objects of perception (including other people), and for Titchener, kinesthetic imagery was more a means to *derive* propositional meanings and

feelings from objects. One of the underlying assumptions of each, akin to Stein's analysis, is that we have privileged epistemological access to our own mental states. In these early kinesthetic theories empathy hovered between being an *explanadum* in its own right and an *explanans* in theories of perception. However, they have in common a conception of empathy as a route to knowledge though motor-related reactions in the observer, which also bear some relation to feeling or emotion.

These themes are echoed in modern theories about how object perception relates to interpersonal representation and empathy. Nowadays the question takes a slightly different form: how do we derive *self*-related subjective representations from *nonself*-related visual information? One of the most important recent advances in this regard is the discovery of mirror neurons in monkey premotor and parietal cortices (di Pellegrino, Fadiga, Fogassi, Gallese ,& Rizzolatti, 1992; Gallese, Fadiga, Fogassi, & Rizzolatti,1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996; Rizzolatti & Craighero, 2004). Mirror neurons are a type of visuomotor cell that fires both during the generation of a goal-directed action and also during the observation of a similar action made by someone else. Evidence for homologous functions in premotor cortex has also been found in humans (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995; Iacoboni, Woods,Brass, Bekkering, Mazziotta, & Rizzolatti, 1999; Nishitani & Hari, 2000; Hari, Forss, Avikainen, Kirveskari, Salenius, & Rizzolatti, 1998; Grèzes, Costes, & Decety, 1999; Grèzes, Armony, Rowe, & Passingham, 2003; Buccino, Vogt, Ritzl, Fink, Zilles, Freund, Rizzolatti, 2004).

Mirror neurons appear to provide a compelling answer to the "functional mechanism" problem by directly transforming visual observation of others' goal-directed actions into a motor-specific vocabulary of potential actions in the observer's brain (Rizzolatti and Luppino, 2001; Rizzolatti, Fogassi, and Gallese 2002; Kakei, Hoffman, and Strick, 2003). Again, the older notion that motor resonance leads to an epistemological step— be it action recognition, action understanding, or mental state attribution— also holds in the interpretation of mirror neuron activity. Here, coding observed action in output-related terms makes mental state information available via motor response preparation processes involved in identifying goals and the consquences of action, and thence potentially to intentions, desires, and beliefs (see *eg* Gallese, Keysers, & Rizzolatti, 2004; Blakemore & Frith, 2005; but see also Jacob & Jeannerod, 2005, for an alternative view).

If visual information about the goal-directed actions of others can engage action-preparation pathways in the brains of passive observers, it suggests that we may perceive even the actions and sensations of other people though a "filter" of our own bodily representations. These results suggest a basic *type* of mechanism for the social brain to take third-person visual information about others and transform it into first-person, bodily terms. For example, Adolphs (2000) found that patients with damage to right somatosensory cortices were selectively impaired in the recognition of emotional expressions. Because the right somatosensory cortices are also implicated in the generation of emotional expressions in healthy adults (Adolphs, 2000, 2002), Adolphs reasoned that both the generation and the recognition of emotional expressions draw upon some of the same perceptual and

somatosensory resources. Many researchers have come to regard this type of mechanism as a crucial predicate for empathy (*e.g.* Gallese 2001, 2003; Keysers, Wicker, Gazzola, Anton, Fogassi, & Gallese, 2004; Decety & Jackson, 2004). Indeed, the postulated role of mirror neurons in empathy has been interpreted as being relatively direct (*eg* Carr, Iacoboni, Dubeau, Mazziotta, Lenzi, 2003; Leslie, Johnston-Frey, and Grafton, 2004, Panksepp, 2005).

A preliminary note on terminology

Definitions of empathy commonly rely on folk concepts or borrow from social psychological theories that trace their historical origins to movements such as gestalt psychology, sensationalism, or introspectionism (Wispé, 1987, 1991). The result is a comparatively elusive and fragmented concept, with almost as many definitions as there are researchers. This is partly reflected in the lack of agreement on the difference between "empathy" and "sympathy."

The word "empathy" has come into psychology and the vernacular relatively recently (Titchener, 1909) as a translation into English (via Greek roots) of Lipps' German coinage *Einfühlung,* or "feeling in to" (Lipps,1903). It has since found wide usage in personality and social psychology (Wispé, 1987). Yet recognition of the phenomenon as a serious subject for natural philosophy goes back to writers like Adam Smith and David Hume (Smith, 1759; Hume, 1779), who use the older word "sympathy" where today we might be more likely to use the more recent coinage "empathy."

Theories of empathy that predate the word "empathy" use the word "sympathy" to express the phenomenon of firsthand-like understanding of

others' feelings, desires, or interests, as in the writings of Smith and Hume. Some contemporary authors wish to distinguish between empathy and sympathy (Gruen & Mendelsohn 1986; Wispé 1991; Decety & Chaminade 2002; Preston & de Waal 2003). There is not much evident agreement among these authors. Frequently, distinctions center around the question of which of the two is automatic and involuntary and which is conscious and controlled (Levenson, 1992; Hodges & Wegner, 1997). The core concern, however, is usually the same: the shift from a third-person to a first-person perspective.

For the purposes of this literature review, "empathy" and "sympathy" are considered interchangeable when different authors employ different usage in neuroimaging studies. Because it is a more recent, deliberate coinage and widely-used, the word "empathy" is adopted when necessary throughout this thesis. Generally, however, I prefer to suspend the broad, vernacular word "empathy", except for its occasional use as a covering term. Instead, I refer to the visual modulation of body-related, egocentric neural processing by others' situations or expressions as "vicarious responding." Vicarious responding is a descriptive term intended to refer to the functional level of neural coding, rather than the psychological or phenomenological levels. It is important to note that although vicarious responding may facilitate subjective feeling states, it is *not* taken as sufficient to instigate full-blown emotions or overt actions. Neither is it exclusive to the pain domain but, as a type of mechanism, can also occur in systems associated with particular domains, such as motor action (as in the case of mirror neurons), body sensation, and affect.

In the case of pain empathy in particular, the term "pain observation" is

used here to denote circumstances in which an observer witnesses apparent injury to another person. It is used in a similar sense to "action observation" which refers to situations in which an observer witnesses the actions of another person. A further distinction is made between *pain empathy* and *pain recognition.* Pain empathy is regarded here as a compassionate affective state which the observer experiences on behalf of the sufferer, and which may result in prosocial actions. The studies in this thesis are not intended to address this subjective feeling of empathy, nor to locate its neural correlates *per se.* Rather, they aim to explore mechanisms subserving the recognition of others' pain as aversive, independently of whether this may give rise to full-blown subjective feelings of compassion. Thus *pain recognition* is simply the outcome of a basic appraisal of the pain-related nature of the sufferer's situation. Although pain recognition may be necessary for empathy, it is not sufficient for it, and may occur independently of empathy in everyday contexts.

III. Neuroimaging studies of empathy

This section discusses neuroimaging experiments that aim to elucidate the neural substrates involved in pain-related vicarious responding or other aspects of empathy. Here, the emphasis is placed on neuroimaging because this technique addresses the localization of function within the brain. This selective review excludes other recent studies of empathy which are relevant but utilize other techniques, such as lesion mapping (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Shamay-Tsoory, Tomer, Goldsher, Berger, & Aharon-Peretz, 2004; Shamay-Tsoory, Tomer, Berger, Goldsher, &

Aharon-Peretz, 2005), motor-evoked potentials (MEPs) with transcranial magnetic stimulation (TMS; Avenanti, Bueti, Galati, & Aglioti 2005; Avenanti, Paluello, Bufalari, & Aglioti, in press), fear conditioning (Olsson & Phelps, 2004), and the study of clinical populations (Shamay-Tsoory, Lester, Chisin, Israel, Bar-Shalom, Peretz, Tomer, Tsitrinbaum, & Aharon-Peretz, 2002; Blair, 2005). Also excluded from this review are published neuroimaging studies that have bearing on pain-related vicarious responding, but which constitute chapters in this thesis (Morrison, Lloyd, di Pellegrino, and Roberts, 2004; Lloyd, Morrison, & Roberts, 2006), and neuroimaging approaches to empathy not involving the processing or communicative expression surrounding sensory stimuli (Carr *et al* 2003, Farrow, Zheng, Wilkinson, Spence, Deakin, Tarrier, Griffiths, & Woodruff, 2001; Völlm, Taylor, Richardson, Corocoran, Stirling, McKie, Deakin, & Elliott, in press; Decety & Chaminade, 2002; Ruby & Decety, 2004; see also Decety & Jackson, 2004). These studies will not be reviewed specifically, but some will be taken up in the course of the following chapters and general discussion.

The studies reviewed here put forward the view that an immediate, subjective interpretation of another individual's particular sensory or affective state is accompanied by the activation of regions directly involved in the production of that sensation or emotion. Neuroimaging research in this spirit is influenced by the theoretical strains regarding action perception and "mentalizing" mentioned in the foregoing section. Viewed together, the results indicate a consistent involvement of ACC and anterior insula in pain

observation. They also imply that factors such as effector-specificity and viewpoint are, if in evidence at all, secondary to affect-related processing.

Direct comparison between pain experience and pain observation

So far, there are only three published studies which directly compare neural activity associated with feeling a painful stimulus to that associated with pain observation (Morrison *et al,* 2004; see chapter II; Singer, Seymour, O'Doherty, Kaube, Dolan, & Frith, 2004; Singer, Seymour, O'Doherty, Kaube, Dolan, & Frith, 2006). One of them warrants special examination here, because it stands as the closest counterpart to the second chapter in this thesis, and is regarded as an influential study. In this experiment by Singer *et al,* sixteen female subjects viewed their own hand alongside that of their romantic partner as electrode shocks were delivered to one or the other at either high or low levels of stimulation (Singer *et al,* 2004). The women in the scanner could view their own hand beside their partner's via a mirror mounted within the magnet bore. The couples participating in the experiment had been dating for approximately two years.

Anticipation cues of colored arrows were projected on a screen behind the hands. The arrow's position over subject or partner's hand indicated to the subject whether the shock would occur to herself or to her partner, and its color indicated whether the stimulation would be low (not painful, 0.25+- 0.02 mA) or high (painful, 1.53 +- 0.2 mA). In each trial, the pain was preceded by the anticipation cue (arrows), and the application of pain via the electrodes was jittered at a 3-4-second interval afterwards and lasted for 2 seconds. A dot matching the anticipation cue's color remained on the screen

for the duration of the stimulation. In 40/80 of the 9.5-second trials, no stimulation occurred but participants fixated on a cross, and no task was required in any of the trials.

The experimenters performed a conjunction analysis to locate areas in which activation was present for both felt and seen pain. Activity in the rostral anterior cingulate cortex (ACC) and the anterior insula was shared between the self and other conditions when the shock was painful. Activity in the ACC also correlated with scores on two empathy questionnaires designed to quantify the degree of empathy with which a subject might typically respond to others' distress. These were Davis' Interpersonal Reactivity Index (IRI; Davis, 1996) and Mehabrian's Balanced Emotional Empathy Scale (BEES; Mehabrian & Epstein, 1972). For example, the BEES questionnaire asks subjects to agree or disagree with statements such as: "I cannot relate to the crying and sniffling at weddings," and "It pains me to see young people in wheelchairs."

The authors emphasize the importance of the result that self-other pain overlaps were seen in the ACC and insula, but not in somatosensory areas. These overlapping regions are associated with the motivational-affective components of pain mentioned in the foregoing section (Rainville, 1999; Kulkarni *et al,* 2005). This result is similar to that of Morrison *et al,* (2004; chapter II). Both the overlapping areas and the somatosensory cortices receive information about pain through relatively distinct pathways that can be viewed as mapping onto the motivational-affective and sensory-discriminative dimensions of pain processing, respectively (Kulkarni *et al,* 2005). The somatosensory cortex receives projections from fibers that carry

information from nociceptors about the spatial localization, intensity, and other sensory-discriminative components of the stimulus, ascending through lateral thalamic nuclei. As previously mentioned, motivational-affective processing is associated primarily with medial thalamic pathways, with terminations in cortical areas including the ACC and insula (Sewards & Sewards, 2002, 2003; Vogt & Sikes, 2000). (For more detail see the following section on pain processing.) Singer *et al* also emphasize the anterior insula's postulated role in higher-level representations of body-related afferent inputs (Craig 2003b; Damasio, 1999; Critchley , Wiens, Rotshtein, Öhman,,& Dolan, 2004).

The absence of somatosensory activation in this study implies that when we see someone else in pain, our response is of an affective nature, rather than being more along the lines of a sensory readout of where and how the other person is undergoing injury. This interpretation employs the logic described in the "functional mechanism" section in that it posits a transformation or mapping of third-person information onto first-person processing in a certain domain. In this case, the relevant domain is the affective component of pain. Others' pain may instigate vivid affective representations from which feelings and beliefs about the other person's pain state can be derived (because here, as Adams puts it, "the 'belief box' is in the 'feel closet'"; Adams, 2001). This interpretation also takes phenomenal affective experience about pain as epistemically "given", much in the same vein as theories of empathy and perspective-taking beginning with Lipps and Stein. The contention in Singer *et al* (2004) and Morrison *et al* (2004; chapter II) is that since sensory-discriminative areas do not show a statistical

conjunction between felt and seen pain, they have minimal or no involvement in this other-to-self mapping. However, so far no other research has explicitly addressed whether such absence of evidence is really evidence of absence.

An advantage of using electrode stimulation is that it selectively stimulates the Aδ fibers that carry nociceptive information to the brain, without stimulating touch-related mechanoreceptive fibers. In this sense the subtraction between pain and no-pain is relatively clean. However, a disadvantage is that nothing obvious happens when one is watching an electrode stimulate someone else, so Singer *et al* relied on arbitrary symbolic cues to indicate that stimulation was occurring and at what level it was occurring. The shared activation for pain here could therefore reflect any number of other, more general processes that come into play during aversive events predicted by visual signals. For example, the common activity could reflect mainly differences in anticipation or attention over the course of the whole trial. Even if the activation was as pain-specific as the interpretation implies, it is also possible that *any* objects in the visual field spatially proximal to the hand elicit pain-related responses when they are targets of potential pain stimulation (*eg* Armel & Ramachandran, 2003). Ruling this out would require a control condition featuring a noncorporeal object being "stimulated" in a position near the subject's hand.

Another recent neuroimaging study investigated pain empathy in the context of social exchange (Singer *et al*, 2006). Social cooperation may facilitate empathy, which in turn may contribute to smooth interpersonal interactions and mutually advantageous outcomes (Singer *et al*, 2005, Singer

& Fehr, 2006). Outside the scanner, subjects participated in a prisoner's dilemma game with actors whom they were told were fellow participants. The prisoner's dilemma is a turn-taking game in which money is exchanged between two players. After one player's move, the second player has the choice to cooperate (return a portion of the money) or defect (keep the money). The game works best (net gains are higher) if each player settles on a cooperative strategy. Some of the confederate actors played fair as cooperators, and others took more than their share of money in a defector role.

In the scanner, subjects subsequently underwent painful electrode pain, and watched as the fair and unfair actors underwent painful microelectrode stimulation too. The setup was similar to that of Singer *et al* 2004 with the hands of all three visible to the subject. Again, the results showed activity in ACC and anterior insula. They also found an effect of gender, with stronger ACC activations in women than in men. One gender difference was a signal change in the nucleus accumbens in men but not women when witnessing defectors receive painful stimulation. When a subjective assessment score of the "desire for revenge" was regressed with nucleus accumbens activity, the desire for revenge correlated with increased activation in men but not women. In light of this area's involvement in reward, the researchers interpret its activation for unfair players' pain as reflecting a vengeful pleasure, perhaps related to a desire to see defectors punished. This study shares features with the previous Singer *et al* study. Not only was the design similar (in particular the use of electrode and symbolic cues) but so was the

aim to link hemodynamic responses with subjective compassion (or revenge) feelings and with factors on the social level.

Pain observation without experienced pain

There are two other recent neuroimaging studies which investigate pain observation, but without the inclusion of a felt-pain condition. These studies also implicate the ACC in pain observation. Like the Singer *et al* study, the hypotheses of Jackson *et al* (Jackson, Meltzoff, & Decety, 2005; Jackson, Brunet, Meltzoff, & Decety, 2006) involve a theoretical perspective similar to the one described in the section on the "functional mechanism" section, in which visual information is transformed or mapped onto self-related representations. Jackson *et al* (2005) tested whether we assess others' pain in terms of the representation of particular body parts, namely hands and feet. In this case the translational mechanism was explicitly postulated to reside in areas involved in somatosensory mapping, unlike the Singer (2004) or Morrison *et al* (2004; chapter II) studies. In this respect it was inspired by an imaging study on action observation which showed effector-specific mappings of observed body parts onto corresponding areas on the brain's somatosensory map in SI and SII during action observation (Buccino, Binkofski, Fink, Fadiga, Fogassi, & Gallese, 2001).

While in the scanner, subjects viewed still photographs depicting painful everyday mishaps such as getting one's foot caught in the car door or cutting one's finger while slicing vegetables (Jackson, 2005). The painful events in the set of 64 photographs were balanced between mechanical, thermal, and pressure pain. The targets of the painful events also varied in gender and age

(8-56 years). Responses to these painful visual stimuli were compared to nonpainful control photographs showing the hands and feet in same settings without the painful component. After each trial, the participants' task was to rate each picture on a visual analogue scale (VAS) by moving a cursor to a position on a line indicating their rating from "no pain" to "worst possible pain."

The contrast of the pain conditions compared to the neutral conditions revealed activation in bilateral anterior cortex (8-10 mm from midline), bilateral anterior insula, right supplementary motor area (SMA) bilateral posterior parietal cortex, bilateral thalamus, and bilateral cerebellum. The authors also used the coordinates reported by Singer *et al* to define regions-of-interest in the ACC and insula. Activation in the ACC was also correlated with the degree of painfulness as rated by the subjects, but not Davis' Interpersonal Reactivity Index. Nor was there any effect of body part observed (hand or foot).

Using a similar set of stimuli, Jackson *et al* manipulated viewpoint in a second study (Jackson et al 2006). In one condition subjects were instructed to view the photographs from their own perspective as if it were their limb. In another condition they were instructed to see the events in the same photographs as happening to another individual, and in a third to imagine the depicted arm as a manikin's limb. In each trial they rated the pain for all conditions by moving a cursor on a visual analogue scale (VAS), as in the previous experiment. A second experiment in the same study repeated the same manipulation using a different, mixed (event-related block) design which involved different counterbalancing and introduced a jitter in trial

duration. Behavioral results showed that subjects rated the stimuli as more painful in the "self" perspective. Painful vs neutral stimuli produced significant signal changes in areas consistent with previous results, in particular ACC, anterior insula, and posterior parietal cortex. "Self" vs "other" perspectives revealed activations mainly in ACC, insula, and parietal operculum/SII.

Vicarious responding in other domains: touch and disgust

The other-to-self element of vicarious responding has also been explored in sensory and motivational domains other than pain. Two recent neuroimaging studies investigate the neural correlates of touch "empathy"

Table 1. Recent neuroscientific studies of empathy.

Study	Method	Proposed neural mechanism	Cortical area(s) implicated
Morrison *et al* (2004) *	fMRI	Motivational-affective vicarious response (mirror analogy)	Anterior cingulate cortex (BA 24)
Singer *et al* (2004, 2006) *	fMRI	Second-order interoceptive representation	Anterior cingulate cortex, anterior insula
Jackson *et al* (2005, 2006) *	fMRI	Shared representation (self-other) network	Anterior cingulate cortex, anterior insula
Avenanti *et al* (2005, 2006) *	MEP	Sensorimotor processing	N/A
Decety and Chaminade (2003)	fMRI	Shared representation (self-other) network	Right inferior parietal, superior frontal
Carr *et al* (2003)	fMRI	Mirror system relay to limbic system	Inferior frontal gyrus. anterior insula

* Studies involving the observation of painful stimuli

(Keysers *et al*, 2004a; Blakemore, Bristow, Bird, Frith, & Ward, 2005), and one relates disgust-related processing to the observation of others' apparently

disgusted reactions to bad odors (Wicker, Keysers, Plailly, Royet, Gallese, & Rizzolatti, 2003). These are discussed here because their cardinal design feature is to compare observation and experience within the same paradigm, like the pain studies comparing felt and seen pain.

In a series of experiments, Keysers *et al* (2004a) explored responses in SI and SII to the sensation of touch to the leg, and to video clips depicting touch to other people and to inanimate objects. Experimenters brushed the legs (left and right) of participants in various directions (up or down) with a washing glove. In the visual conditions, participants viewed the legs of other people being similarly stimulated with a metal rod, a wooden rod, or a brush. Visual control clips showed similar settings and motions but the objects did not contact the legs of the observed person. Visual and tactile stimuli were presented in separate runs.

A second experiment manipulated the target and stimulus object in one run, manually replacing the rods with airplane wings and the legs with an island in the videos. This was shown as if from an aerial perspective, but preserving the spatial arrangement and motions of the objects in the frame. In another run the legs were replaced by paper towels and office binders. A third experiment manipulated viewpoint in the original videos, showing the other perspective (feet pointing towards the observer) as well as a self perspective (feet pointing away, as if the observer were looking down on his or her own legs). No task was required.

Results showed that responses in SII overlapped between the touch experience conditions and the touch observation conditions. Other interesting outcomes from this series of experiments are that touch, and not

merely movement, is necessary for such responses to occur in SII, and that viewpoint does not modulate responses. Further, where touch is present, visual activity in SII is not limited to human body parts but also extends to inanimate objects. On the other hand, SI was not modulated by viewing the videos.

In an fMRI case study Blakemore *et al* (2005) compared responses to felt and seen touch in a synaesthetic individual to those of a group of normal, non-synaesthetic controls. The synaesthetic individual, C, experiences seen touch in terms of tactile stimulation on her own body, a variety of synasthesia which Blakemore has termed "mirrored touch synasthesia." (C spent most of her life believing that this was the usual state of affairs.) For C and the normal group of subjects, the experimenters used felt pieces mounted on a rod to stimulate participants' right or left cheek or neck in the scanner. In additional sessions, participants also viewed videos of people being touched on the face or the neck. Control videos featured objects (lamp, fan, and loudspeaker) being similarly touched.

Seeing touch to humans elicited activations in the SI head area, SII, and motor and premotor areas. STS responses were also seen when touch to humans was compared to touch to objects. This result differs from Keysers *et al's* in that SI was activated to human touch observation, and responses in SII and other areas differed between human and object touch observation. Nevertheless, a similar set of areas was activated in C: SI and SII, STS, left premotor cortex (a larger activation than in controls), and in addition, bilateral insula. The authors conclude that responses to observed touch are somatotopically organized with respect to head and neck, and that C's mirror

touch synaethesia may be an exaggerated manifestation of processes that exist to a lesser degree in normal, nonsynaesthetic individuals. Specifically, activation in somatosensory cortices during touch observation may represent subthreshold processing which in C's case becomes suprathreshold.

In a similar vein, Wicker *et al*'s (2003) fMRI investigation of disgust showed vicarious responding in the anterior insula, with overlapping activation when subjects smelled offensive odors while in the scanner and observed demonstrators' apparently disgusted reactions to the smells. In keeping with its role in visceral interoception (Craig *et al,* 2003, Augustine 1996), the insula is associated with subjective sensations of nausea and disgust (Calder, Lawrence, & Young, 2001). Phillips *et al* (1997) tested insular lesion patients with Ekman photographs depicting emotional expressions, including disgust. The patients showed a selective deficit in recognizing emotional facial expression. Calder and colleagues (Calder, Keane, Manes, Antoun, & Young, 2000) corroborated this result in healthy subjects using fMRI. In this study, the insula was active when subjects viewed faces expressing disgust. One patient with bilateral insular lesions presented a "disgust blindness" that pertained not only to the recognition of disgusted facial expressions, which in one case he spontaneously ventured to label "hungry and thirsty", but extended even to displays of retching and regurgitating food— the food was "delicious", he hazarded (Adolphs, Tranel, & Damasio, 2003). These findings have also been supported in healthy subjects using fMRI (Phillips, Young, Scott, *et al,* 1998).

Facial expressions and pain

Communicative facial expressions exist for pain, though they appear to be less reliably perceived than other emotional facial expressions (Prkachin, 1994; Williams, 2003). Contracting the orbital muscles and drawing the eyebrows together becomes more pronounced the more intense the pain (Prkachin, Berzins, & Mercer, 1994). The inaccuracy or conservatism of judgment for pain facial displays increases with longer exposure times (Prkachin *et al,* 2004). In fact, faked pain displays take longer to play out and are less coordinated than real ones (Hill & Craig, 2002). This is consistent with a model of vicarious responding at the psychological level, in which information-laden cognitive factors interact with quick— perhaps automatic— vicarious responses in empathic judgments (Eisenberg, 1991). The ability to detect pain from faces also becomes more refined as the child gets older (Deyo, Prkachin, & Mercer, 2003).

There is fMRI evidence that the dorsal ACC is also engaged when individuals view video clips featuring the painful facial expressions of chronic pain patients (Botvinick, Jha, Bylsma, Fabian, Solomon, & Prkachin, 2005). Botvinick *et al* used coordinates reported by Singer *et al* (2004) to define a region-of-interest in the ACC. Within this region, significant signal changes were observed for viewing pain faces compared to neutral controls. This result was further explored by Saarela and colleagues (Saarela, Hlushchuk, Williams, Schurmann, Kalso, & Hari, in press). They manipulated the intensity of the pain expressed in the chronic pain patients' faces by showing the same individuals' expressions while experiencing their usual chronic pain state and when pain was actively provoked when the

experimenter moved or stretched the patients' affected body parts. Subjects viewing these photographs in the scanner rated the intensity of pain. A contrast between viewing provoked vs chronic pain expressions revealed activity in the ACC, SMA, and bilateral anterior insula, among others. Further, the ACC and anterior insula activity correlated with the perceived pain intensity in the patients' expressions.

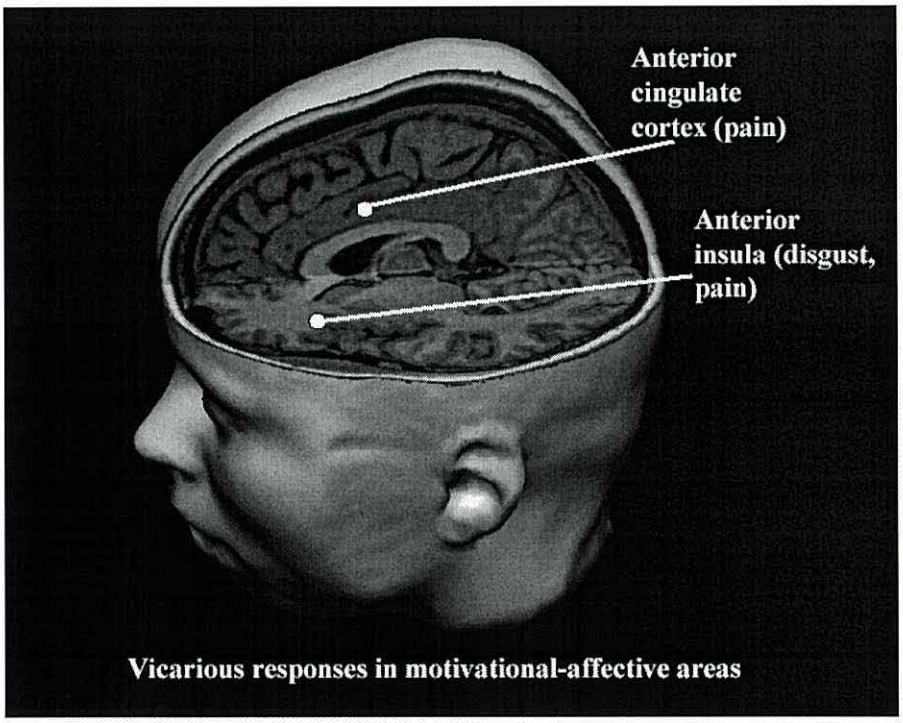


Figure 1. A cutaway view of the brain showing areas in which vicarious responses have been observed in the medial cingulate cortex (for pain) and the anterior insula (for olfactory disgust and pain). These two areas are important in relating bodily information to potential behavioral responses. (Rendered MRI image shows x = - 1 and z = 4 in Talairach space.)

IV. Overview of experimental chapters

The studies in this thesis investigate the cingulate's functional contribution to neural processing during pain observation, particularly with respect to

processing in the ACC and midcingulate. Chapters II, III, IV, and VI are neuroimaging studies, and chapter V is a behavioral study. Each chapter seeks to elucidate the role of the cingulate in pain observation, including its relevant processing dimensions, the anatomical localization of visual pain-related responses, stimulus features upon which these depend, and the relationship of pain observation to functions of the cingulate dealing with selecting, preparing, and executing motor responses.

Chapter II presents an fMRI study demonstrating the basic result that felt and seen pain give rise to common activations in the dACC/midcingulate. This area is associated with the motivational- affective rather than the sensory-discriminative dimension of pain processing. In contrast, somatosensory cortex does not show selective responses to seen pain, implying that visual information about others' potential pain does not modulate processing in sensory-discriminative, somatotopic areas. Chapter II raises the possibility that the ACC may be the locus of an "affective mirror response" which enables an immediate subjective understanding of others' pain.

Chapter III explores the nature of this conjunction further. It is possible that the conjoint activation seen in the ACC in chapter II is the outcome of neighboring but distinct activations for felt and seen pain respectively, of which bordering voxels survive the conjunction threshold due to anatomical variation and/or factors in data preprocessing, rather than true functional-anatomical overlap. Chapter III therefore examines responses to felt and seen pain, and their overlap, in single subjects on unsmoothed data. The results suggest that the BOLD signal overlap may originate from boundaries

between adjacent but distinct areas, rather than a single neural population coding equally for felt and seen pain. This has implications for the interpretation of BOLD data in addressing "mirrorlike" activations in general, whether in action-related or pain-related areas.

Chapters II and III deal with responses to others' pain observed in a perspective which situates the "victim's" hand in the space *extrapersonal* to the observer. Chapter IV extends the exploration of aversive responses to observed pain into the domain of parietal networks coding pain-related visual information in *peripersonal* space. When a rubber hand in peripersonal space is "painfully" stimulated, the visual response involves the ACC and motivational-affective areas also implicated in the previous studies. In addition, posterior parietal areas also show selectivity for pain— but only when the artificial limb is in an anatomically plausible position. This response may reflect a homology with monkey posterior parietal areas which use visual information to produce nocifensive movements. This would imply that parietal cortex plays a role in a visual network selectively processing threats to the body in the service of preparing appropriate behavioral responses.

But how might processing in such a network influence behavior? Chapter V addresses the relationship between pain observation and motor responses in a behavioral experiment. This experiment demonstrates that observing *another* person's painful stimulation has a specific influence on the *observer's* overt motor responses. It used reaction times in a go/nogo task as a measure of readiness to press or release a button. Following presentation of a video showing a hand being pricked by a needle, participants were faster to

withdraw their finger from the button, but slower to press the button. These findings indicate that merely seeing another person undergo pain facilitates motor responses appropriate to that person's situation. More generally, they also suggest that behavioral responses to observed pain are, like their counterparts in experienced pain, modulated in a complex manner suited to the current situation.

Whereas chapter V demonstrated that task-relevant pain observation influences motor responses after a variable delay, Chapter VI shows that task-relevant pain observation speeds *immediate* responses as well, when no delay is involved. This manifests as a reaction time interaction between observed noxiousness (painful, nonpainful stimulation) and type of contact (hit or miss), with fastest reponses to noxious hits. Further, the interaction occurs regardless of whether the others' hand is viewed in an egocentric or allocentric position. The neural correlates of this behavioral effect reveal that cingulate areas (likely corresponding to CMZs), but not lateral premotor areas, are sensitive to the combination of noxiousness, hits, and the requirement to execute an overt hand response. These results further reinforce the relationship between pain observation and motor processing in medial premotor areas.

CHAPTER II[1]:

VICARIOUS RESPONSES TO OTHERS' PAIN IN ANTERIOR CINGULATE CORTEX

"When once compassion is stirred within me by another's pain, then his weal and woe go straight to my heart, exactly in the same way, if not always to the same degree, as otherwise I feel only my own. Consequently the difference between myself and him is no longer an absolute one."

— Arthur Schopenhauer, *On the Basis of Morality,* 1841
(translated by Arthur Brodick Bullock)

[1] A version of this chapter has been published as Morrison, I., Lloyd, D., di Pellegrino, G., and Roberts, N. (2004). Vicarious responses to pain in anterior cingulate cortex: is empathy a multisensory issue? *Journal of Cognitive, Affective, and Behavioral Neuroscience* 4(2), 270-8.

Abstract

Using functional magnetic resonance imaging (fMRI), we show that both feeling a moderately painful pinprick stimulus to the fingertips and witnessing another person's hand undergo similar stimulation were associated with common activity in a pain-related area in the right dorsal anterior cingulate cortex (ACC). Common activity in response to noxious tactile and visual stimulation was restricted to right inferior Brodmann's area (BA) 24b. These results suggest a shared neural substrate for felt and seen pain for aversive ecological events happening to strangers, and in the absence of overt symbolic cues. In contrast to ACC 24b, primary somatosensory cortex (SI) showed significant activations in response to both noxious and innocuous tactile, but not visual, stimuli. The different response patterns in the two areas are consistent with the ACC's role in coding the motivational-affective dimension of pain, which is associated with the preparation of behavioral responses to aversive events.

Introduction

The sensation one gets upon watching *another* person get hurt has probably happened to all of us: it is something that makes us recoil, cringe, wince, say "ouch!" or experience feelings otherwise associated with pain, even if we are sitting snugly in an armchair at a safe remove from any harm. Although familiar to most people, this variety of experience is not easily described in empirical terms, and is usually called "empathy" or "sympathy" in everyday language. Here we refer to the sensations that arise with regard to the perceived physical pain of others as "vicarious pain." Vicarious pain may be a crucial predicate for more sophisticated forms of empathy, such as helping and offering comfort, and perhaps even for such complex cognitive processes as moral reasoning. In reacting to another person's predicament as if you were in that position yourself, processes are taking place in your brain that may facilitate an immediate grasp of that person's emotional state.

However, thinkers pondering the nature of empathy have noticed a tangled problem at its core, which has been referred to as the "paradox of sympathy" (Wispé, 1991). The paradox is this: if all that is available to us is third-person information about someone else's situation or emotional state, how can that produce what we readily identify as a similar first-person subjective state within ourselves? Put in other terms, this "paradox" can be broken down into two related questions. The first is a question of mechanism, that is, how does the brain accomplish this? The second is a motivational question, having to do with the behavioral relevance to an observer of another person's distress: we may understand

what is happening, but what makes us *care* about it?

Recently, neuroscience has begun to reveal mechanisms that could throw light upon the first of these questions, and thus provide insight into the second. Several neuroimaging studies have supported the view that an immediate, subjective interpretation of another individual's particular emotional state is accompanied by the activation of regions directly involved in the production of that emotion (Carr *et al,* 2003; Decety & Chaminade, 2003; Phillips *et al,* 1997; Wicker *et al,* 2003). This perspective is bolstered by an expanding body of research indicating that the observation of others' actions engages circuits involved in the preparation and planning of self-generated motor actions (di Pellegrino *et al,* 1992; Hari *et* al, 1998; Iacoboni *et al,* 1999; Rizzolatti *et al,* 1996; Rizzolatti, 1999). The existence of such action perception mechanisms has provided the foundation for a recent model of empathy which integrates emotional, behavioral, and cognitive aspects of interpersonal phenomena (Preston & de Waal, 2002).

A similar unifying basis has so far been little investigated with respect to the mechanisms of pain processing. A notable exception is a recent fMRI study showing that affective pain-related areas such as the dorsal ACC and anterior insula can be activated by a visual signal indicating that a loved one will receive a painful electric shock (Singer *et al,* 2004). In this study, female subjects viewed their own hand alongside that of their established romantic partner as electrode shocks were delivered to one or the other at either high or low levels of stimulation. Visual cues projected on a screen indicated to the subject whether the shock would occur to

herself or to her partner, as well as whether the stimulation would be low (not painful) or high (painful). This study demonstrated that affect-related regions of a pain network can be engaged in situations in which there is an imminent and ongoing threat of pain both to oneself and to a loved one.

More specific indications come from earlier single-unit data of pain-related processing in human neurological patients (Hutchison *et al*, 1999). This study investigated pain-related responses in the ACC in eleven individuals undergoing cingulotomy surgery for the treatment of obsessive-compulsive disorder or severe depression. Using microelectrodes, Hutchison *et al* (1999) recorded from ACC as several types of painful stimulus were applied to the patients' hands (painful heat, painful cold, and mechanical "pinpricks" from a sharp probe). They found stimulus-specific pain responses in area 24b of dorsal ACC (24b' of Vogt *et al*, 1995), including units that discharged preferentially to the pinprick stimulus. One of these units responded to the pinprick whether it was administered to the patient's own hand or to that of the experimenter. This particular cell appears to have been sensitive not only to pain-related input originating from the hand, but also to visual input carrying information about another person's hand.

Evidence surrounding vicarious pain mechanisms from neurological case studies is quite scant, but one unusual case that may have bearing on the pathological representation of *others'* pain was reported anecdotally in a letter (Bradshaw & Mattingley, 2001). A deceased patient's widow described to the authors an unusual symptom of her husband's allodynia (a condition in which non-noxious touch is painful). When she herself

would experience a sudden minor injury such as knocking her hand against a table, he would become very agitated, claiming that it hurt him to witness such accidents. Unfortunately, no CT scans exist of the extent of the damage in the man's brain or the areas affected. It is possible only to speculate about what might have caused this man's symptoms, but it is conceivable that the damage altering the representation of his own sensations had a corresponding impact upon his representation of others' sensations as well. However, a combined PET and fMRI investigation of another allodynia patient, in whom symptoms persisted despite a bifocal infarct in both primary somatosensory cortex (SI) and right ACC, suggests that any possible cortical substrates of allodynia are complex and not isolable to a single circumscribed region in the ACC or elsewhere (Peyron *et al,* 2000a).

Taken together, the available neuroimaging and neurophysiological evidence raises the possibility that merely observing another person in a painful situation can give rise to a pain-related response in the ACC. In the present study we used fMRI to test the hypothesis that painful stimulation increases hemodynamic responses in ACC 24b of normal individuals, not only during the firsthand experience of an ecologically-relevant mechanical stimulus ("pinprick"), but also during the observation of another individual undergoing similar stimulation. Such a common neural substrate for felt and vicarious pain would address the question of mechanism posed by the "paradox of sympathy" mentioned above.

Other studies have shown a dissociation between sensory-discriminative and motivational-affective dimensions of pain processing.

In the sensory-discriminative dimension, SI encodes sensory components of a painful stimulus, such as the bodily location and intensity of the stimulus; in the motivational-affective dimension the ACC contributes to evaluation, subjective discomfort, and response preparation in the context of painful or aversive stimuli (Craig *et al,* 2003a; Devinsky *et al,* 1995; Melzack, 1999; Rainville, Carrier, Hofbauer, Bushnell, & Duncan, 1999; Sewards and Sewards, 2002). To determine whether a similar dissociation held in our own study, hemodynamic responses to noxious and innocuous tactile and visual stimuli were compared in right ACC 24b, and in a ROI on the postcentral gyrus corresponding to primary somatosensory cortex area 3b/1 contralateral to the stimulated hand. Differences in response patterns to sensory aspects (*e.g.,* tactile) and motivational aspects (*e.g.* noxiousness) between SI and ACC would reinforce the distinctive roles for these areas in sensory-discriminative and motivational-affective dimensions of pain processing, respectively.

Methods

Participants and experimental design

Functional MRI (1.5T; 24slices; 5mm thickness; TR=3s) was used to compare the responses of fourteen healthy subjects (9 female, 5 male, mean age 23; 9 right-handed, 5 left-handed) as they experienced unpleasant pricks to the fingertips, and as they viewed video clips of others being similarly pricked. Data were also collected for control conditions involving innocuous touch presented in both the tactile and visual modalities. The stimulus for the "experienced pain" condition was

a mildly painful prick to the middle finger of the left hand using a non-ferromagnetic sharp probe (~1Hz/15sec). During scanning, the hand was placed palm-up in a relaxed position, out of the subject's sight. The tactile control stimulus was a cotton bud (Q-tip) similarly pressed onto the fingertip.

For the "observed pain" condition, a video featuring a model's left hand being pricked on the finger with a hypodermic needle was displayed. The video featured the needle coming into contact with the hand and excluded the model's face. The visual control video was identical except for the substitution of a cotton bud for the needle. Placement of the sharp probe in a plasticine-filled syringe increased the visual resemblance between it and the hypodermic needle in the video. Subjects were familiarized with the sharp probe prior to scanning, but during scanning they could neither see their hands nor the stimulus being applied. The videos were projected onto a screen at the subjects' feet as they looked into a mirror.

All visual stimuli were presented on a laptop using Presentation® software (Version 0.70, www.neurobs.com). The observed pain and visual control stimuli were presented in a trial identical in design to the tactile run. Observed and experienced pain experimental runs were conducted separately. Each run consisted of 5 blocks of 15-second presentations of both the painful and neutral stimuli interspersed with 15 seconds of baseline rest, giving a total scan time of approximately 5 minutes. For every condition there was a total of 5 stimulus presentations. After scanning, subjects were asked to rate the unpleasantness of both the experienced and the observed stimuli, respectively, on a scale of 1-5

ranging from "not at all unpleasant" to "extremely unpleasant."

Analysis

Analysis was carried out using FEAT (fMRI Expert Analysis Tool) version 5.00, part of the FMRIB software library (FSL— Oxford Centre for Functional Magnetic Resonance Imaging of the Brain; www.fmrib.ox.ac.uk/fsl). The following prestatistics processing was applied: motion correction using MCFLIRT (Jenkinson, 2002); non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 5mm; mean-based intensity normalization of all volumes by the same factor; highpass temporal filtering (Gaussian-weighted LSF straightline fitting, with sigma = 30.0s). Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich, 2001). Z (Gaussianized T/F) statistic images were thresholded using clusters determined by $Z > 1.8$ and a (corrected) cluster significance threshold of $P = 0.05$ (Forman, 1995; Friston, 1994; Worsley, 1992). Registration to high resolution and/or standard images was carried out using FLIRT (FMRIB's Linear Image Registration Tool; Jenkinson 2001, 2002).

Results

Whole brain contrasts

Feeling the sharp probe elicited significant activations in cortical areas consistently implicated in imaging investigations of pain (Table 1; Peyron *et al*, 2000). Peak clusters in group-averaged data fell in left insula, contralateral primary and secondary somatosensory cortices, and left

(ipsilateral) cerebellum. Significant peaks in these areas and the right (contralateral) medial thalamus remained after subtraction of the tactile control eliminated signal resulting from stimulation of non-nociceptive tactile receptors. The main effect of pain observation revealed activity in anterofrontal and medial frontal regions including the cingulate gyrus, whereas the neutral visual stimulus failed to produce activations above the threshold level. A conjunction analysis showing common areas of significant activation between the main effects of pain experience and observation compared to a resting baseline revealed a significant cluster in right inferior ACC area 24b (x = 6mm, y = 0mm, z = 32mm) common to the two conditions, reflecting shared activity correlated with both feeling and seeing the noxious stimulus (Fig. 1).

Table 1. Foci of pain-related activation during experience and observation

Brain regions	Coordinates of peak activation (mm)	Max Z scores
Main effect of experienced pain (Pain > rest)		
Right inferior parietal lobule	70, -24, 26	5.18
Left insula	-46, -6, 0	5.05
Right parietal postcentral gyrus	62, -16, 38	4.80
Left cerebellum	-18, -56, -30	5.18
Pain compared to neutral stimulus (Pain > neutral)		
Right parietal postcentral gyrus	62, -16, 22	5.13
ACC/SMA	0, -8, 58	5.12
Left parietal postcentral gyrus	-58, -24, 14	4.77
Right frontal precentral gyrus	32, -20, 58	4.81
Right medial thalamus	16, -14, 2	4.80
Main effect of observed pain (Pain > rest)		
Right ACC	2, 16, 42	4.72
Right medial frontal gyrus	6, 52, 2	4.40
Left ACC	-8, -2, 32	4.09
Left superior frontal gyrus	-12, 34, 50	3.94
Conjunction analysis [(pain experience-rest) + (pain observation –rest)]		
Right ACC	6, 0, 32	4.40

All values P < .05 corrected.

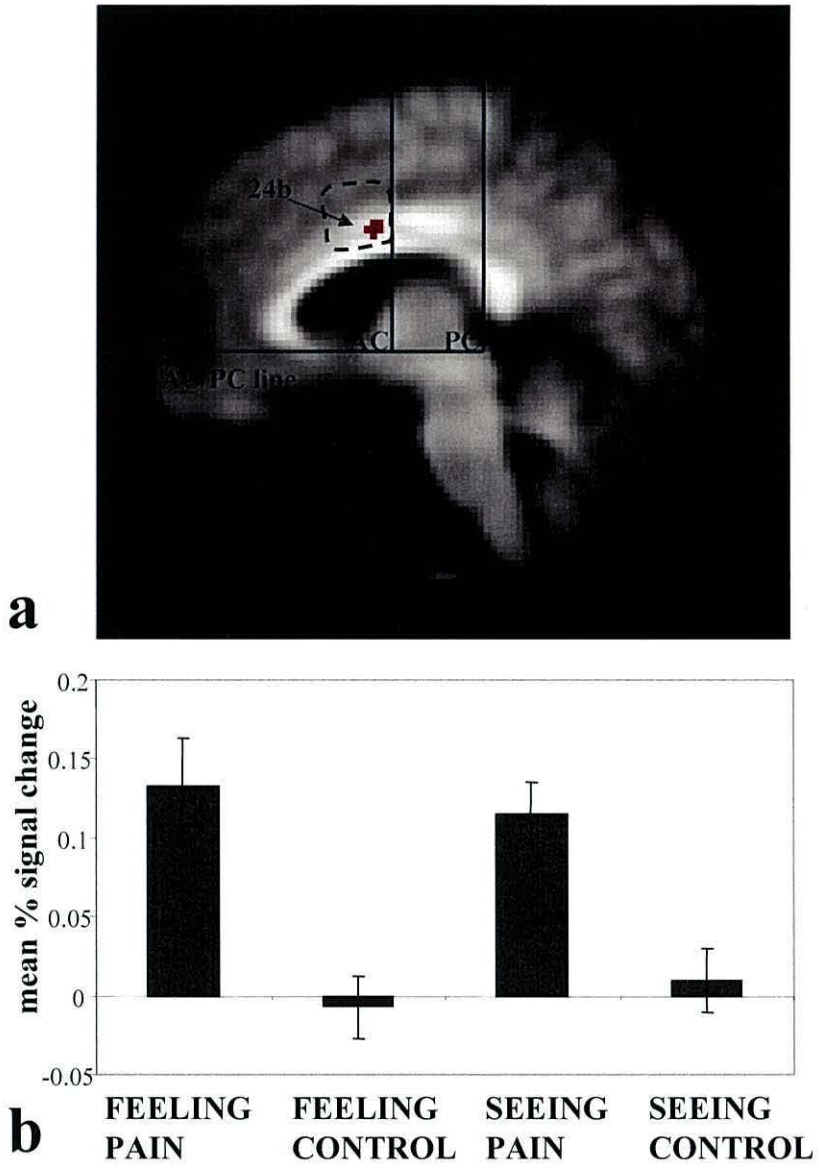


Figure 1. Activation in the ACC in response to sharp probe simulation delivered in the tactile and visual modalities. **(a)** Sagittal slice showing the common activation between the main effects of feeling the sharp probe versus seeing it applied to someone else (x = 6, y = 0, z = 32). Group functional data is superimposed upon a T1-weighted normalized anatomical image for fourteen subjects. Dashed line indicates the region–of–interest defined by the single-unit recording site reported in Hutchison *et al* (1999). *AC = anterior commissure, PC = posterior commissure.* **(b)** Signal modulation in a region–of–interest in ACC 24b defined by the coordinate range reported in Hutchison *et al* (1999) (x = 3–5 mm, y = 2–4mm, z = 32). Mean percent signal change was significantly greater in the pain conditions than the control conditions (*see Results*).

Region-of-interest (ROI) analyses

Anterior cingulate area 24b. The anatomical definition of the ROI was based on Talairach coordinates reported in Hutchison *et al*'s (1999) previous single-unit study, which also encompasses the site of overlap between the experience and observation conditions in our study (x = 3-5mm, y = 3-13mm, z = 26-36mm) (Fig. 1a). This region corresponds to right dorsal BA 24, area 24b' of Vogt *et al* (1995). Within this region, the average percent signal change was significantly greater ($p < .001$) for the pain conditions than for the control conditions, irrespective of whether the stimulus was felt or seen (Fig 1b).

Primary somatosensory 3b/1. A ROI in right (contralateral) primary somatosensory cortex (SI) was defined by the coordinates of the most significant cluster in the main effect for the innocuous tactile stimulus ($x = 64$, $y = -16$, $z = 28$) (not shown in Table 1). This activation fell on a region of postcentral gyrus most likely corresponding to hand area 3b/1. This showed significant activations to both noxious and innocuous tactile stimuli but not visual stimuli ($p < .001$) (Fig. 2). The difference between the tactile activations in SI was not significant ($p = .60$).

Comparison of ACC and SI ROIs. The SI ROI showed a significantly greater response to the innocuous tactile stimulus than ACC ($p < .001$). In contrast, the noxious visual stimulus elicited a greater response in ACC than SI ($p < .001$). Mean percent signal changes for the innocuous visual stimulus were at or below baseline for both ACC and SI (Fig. 2). The response to the sharp probe in SI was significantly greater than the tactile

pain-related response in ACC ($p < .001$), although both activations were significant in the higher-level group analysis (P = .05 corrected).

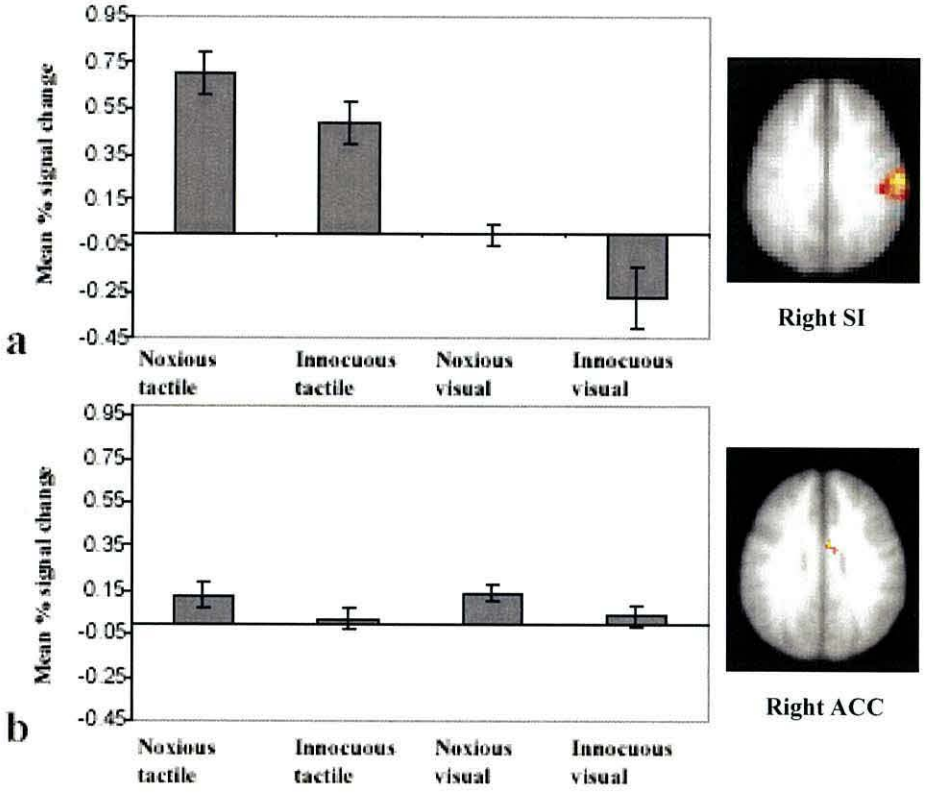


Figure 2. Differential responses in somatosensory and anterior cingulate cortices to noxious and innocuous tactile and visual stimuli. **(a)** Preferential modulation within cluster in right primary somatosensory hand area (x,y,z = 64,-16,28) to tactile noxious and innocuous stimuli. **(b)** Preferential modulation within cluster of right anterior cingulate cortex (x,y,z = 3,4,32) to noxious tactile and visual stimuli. Clusters are sample clusters representing activation within regions-of-interest. SI image: (innocuous tactile) – (rest); ACC image: (noxious tactile – rest) + (noxious visual – rest).

Unpleasantness ratings

Ratings were collected from 13 of the 14 subjects after scanning. The subjects consistently rated the observed unpleasantness ("how unpleasant did it look?") higher than the experienced unpleasantness ("how unpleasant did it feel?") of the visual and tactile conditions, respectively. On a scale of 1-5 ranging from "not at all unpleasant" to "extremely

unpleasant," the mean score for feeling the sharp probe was 2.15; for seeing the pinprick video it was 3.15. This difference was not significant ($p = .10$).

Discussion

These findings corroborate single-unit evidence (Hutchison *et al,* 1999) and point to a unique role for right ACC 24b in vicarious pain. Our results are also consistent with other studies demonstrating the participation of dorsal ACC in either experienced and observed pain, or both (Singer *et al,* 2004; Jackson *et al,* 2004), and with neuroimaging results implicating the ACC in the appraisal of one's own and others' distress (Eisenberger, Lieberman, & Williams, 2003; Peyron *et al*, 2000b; Singer *et al,* 2004). Further, a comparison of mean percent signal changes in right ACC and SI ROIs showed significant differences between responses to the innocuous tactile and noxious visual stimuli. ACC modulation was associated with noxious aspects of the stimuli regardless of whether they were presented in the tactile or visual modality, whereas SI responses corresponded to tactile but not visual elements of the stimuli, regardless of noxiousness.

A common neural substrate for felt and seen pain

The main result of this study was a focal overlap of activity in a pain-related area of ACC, right area 24b (24b' of Vogt *et al*, 1995), suggesting a common neural substrate for felt and seen pain. Such shared activity provides a potential mechanism for the rapid subjective appraisal, in pain-related terms, of tissue-damaging events happening to others. It may also serve as a springboard for further neuroscientific study of the phenomenon

of vicarious pain, as well as of more sophisticated processes or outcomes of empathy which may rely on such a mechanism. These results affirm previous neurophysiological and neuroimaging observations that nociceptive processing in the ACC, and area 24 in particular, can utilize visual information in its encoding of pain (Hutchison *et al*, 1999; Jackson *et al*, 2004; Singer *et al*, 2004).

The subjects' own hands were not visible to them and they were instructed to close their eyes during the "felt pain" condition. This allowed a dissociation between nociceptive/tactile and visual perception of the painful stimuli and an analysis of the differential contributions of each modality. This dissociation makes it possible to confirm that ACC 24b is capable of integrating pain-related information independently of visual information about one's own hand in the firsthand experience of pain, rather than being a predominantly visually-guided area.

The experiment differs from a recent neuroimaging study of empathy (Singer *et al,* 2004) in several crucial respects. Most notably, the subjects were given no overt or arbitrary cue indicating the painful stimulation of the other person, but observed the needle coming directly into contact with the fingertip, distending the skin. Also, the models whose hands featured in the videos were unknown to the subjects, implying that vicarious pain effects do not depend on a longstanding relationship with the other person. A sharp, needlelike probe rather than an electrode was used as a painful stimulus. Although electrode stimulation more effectively elicits activation of nociceptive pathways, the needle stimulus was used here partly to recreate as best as possible the conditions of Hutchison *et al*'s

(1999) study, and partly to preserve ecological validity in the stimulus videos.

It is conceivable that a function of visually-cued responses in area 24b is to apprehend potential threats whether it is oneself or someone else who stands to be hurt. Areas of the ACC that represent pain affect are also active in anticipation of painful stimuli (Hsieh *et al,* 1999; Koyama *et al,* 1998; Porro *et al,* 2003), including stimulus-specific anticipatory discharge of neurons in area 24b (Hutchison *et al,* 1999). The relationship between anticipation and empathy in visually-cued pain representations in the ACC may thus be a very close one, both functionally and subjectively. As such, it may even be fruitful to regard the representation of others' pain as a special case of anticipation.

Previous studies have shown the dorsal ACC to be implicated in attention and arousal (Downar, Crawley, Mikulis, & Davis, 2002), especially when related to response preparation (Milham, Banich, Claus, & Cohen, 2003). However, peak activations in studies of attention and emotional arousal tend to fall more anteriorly and superiorly than the focus in this study, for example in BA 32 or more rostral portions of BA 24/25 (Keightley, Winocur, Graham, Mayberg, Hevenor, & Grady, 2003; Yamasaki, LaBar, & McCarthy, 2002), which are larger in spatial extent and do not respond to painful stimulation (Davis, Taylor, Crawley, Wood, & Mikulis, 1997). In our study, common activation in ACC was restricted to 24b and did not extend into these areas.

Vicarious pain as a motivational-affective representation

We interpreted the profile of modulation in ACC 24b as indicative of a motivational, rather than a sensory, role in vicarious pain. Various studies have implicated the ACC in motivation (Bush *et al,* 2002; Devinsky *et al,* 1995; Hadland *et al,* 2003a), emotion and social behavior (Bush *et al,* 2000; Eisenberger *et al*, 2003; Hadland, Rushworth, Gaffan, & Passingham, 2003) and response selection (Hadland *et al,* 2003a; Paus *et al,* 1993; Rushworth *et al*, 2003; Walton *et al*, 2003). Motivational aspects of pain are those that pertain to desires, urges, or impulses to avoid or terminate a painful experience (Craig *et al,* 2003; Sewards & Sewards, 2002).

Motivational-affective processing is associated primarily with nociceptive pathways ascending from the dorsal horn of the spinal cord through medial thalamic nuclei, which send projections to the ACC (Devinsky *et al,* 1995; Craig *et al*, 2003; Peyron *et al*, 2000; Vogt & Sikes, 2000). In the ACC, nociceptive neurons are interspersed among cells that code for the aversive value of the stimulus (Koyama, Kato, Tanaka, & Mikami, 2001; Porro *et al,* 2003). Projections from anterior cingulate area 24b reach supplementary motor, premotor, cingulate motor, and primary motor cortices, influencing the selection of skeletomotor responses to painful stimuli (Devinsky *et al,* 1995; Matelli *et al,* 1991; Vogt *et al*, 1995). Nociceptive fields in the ACC are thus taken to represent a motivational aspect of somatic pain, contributing to the mobilization and execution of volitional movements of aversion (Schnitzler & Ploner, 2000; Sewards & Sewards, 2002). The results of the present study support this view, especially in light of the premotor

activations alongside ACC when pain experience was compared to the neutral tactile stimulus.

The motivational-affective dimension of pain processing is to a large extent functionally distinct from the sensory-discriminative dimension, which concerns somatotopic localization, intensity coding, discrimination of the type of painful sensation (*eg* burning, aching, stinging), and temporal characteristics such as its onset and offset (Hofbauer, Rainville, Duncan, & Bushnell, 2001; Ploner & Schnitzler, 1999; Ploner, Freund, & Schnitzler, 1999; Rainville, Duncan, Price, Carrier, & Bushnell 1997; Rainville *et al*,1999; Rainville, 2002). The sensory-discriminative dimension is associated with nociceptive pathways ascending through the lateral thalamic nuclei and projecting to somatosensory cortices, including hand areas 3b and 1 (Kenshalo, Iwata, Sholas, & Thomas, 2000; Schnitzler, Seitz, & Freund, 2000; Timmermann *et al,* 2001).

A relevant case study (Ploner *et al,* 1999) reports a patient with selective damage to the right postcentral gyrus and parietal operculum, the hand area of SI and secondary somatosensory cortex (SII). When stimulated with a laser on the skin of the hands and feet, the patient was unable to localize a painful stimulus on the left hand but appeared to have intact motivational processing. He identified the painful sensation as "something he wanted to avoid" although he could not discriminate its sensory characteristics (Ploner *et al*, 1999). Conversely, stimulation of anterior cingulate cortex in humans produces reports of unspecific motivation or urges, and feelings of "wanting or planning to do something" (Bancaud & Talairach, 1993). Damage to the ACC, a cortical

target for medial fiber projections, can alter pain perception without impairing localization, yet microstimulation does not produce feelings of pain (Davis, Hutchison, Lozano, & Dostrovsky, 1994; Hutchison *et al,* 1999).

To investigate any similar dimensional dissociation in our data, we compared mean percent signal changes in right ACC 24b with those in a region of the postcentral gyrus corresponding to primary somatosensory hand area 3b/1. Areas 3b and 1 are directly adjacent (Gelnar, Krauss, Szeverenyi, & Apkarian, 1998; Powell & Mountcastle 1959), and both are associated with the discrimination of passive tactile stimulation on the skin surface (Burton, MacLeod, Videen, & Raichle, 1997; Kaas and Collins 2001; McGlone, Kelly, Trulsson, Francis, Westling, & Bowtell, 2002), as well as cutaneous representation of digits of the contralateral hand (Blankenburg, Ruben, Meyer, Schwiemann, & Villringer, 2003; Francis, Kelly, Bowtell, Dunseath, Folger, & McGlone, 1999; Gelnar *et al,* 1998; Ringler, Greiner, Kohlloeffel, Handwerker, & Forster, 2003). The SI ROI was defined on the basis of its significant response to the innocuous tactile stimulus under the assumption that activation here reflects a localized sensory response to stimulation of the contralateral hand.

SI showed higher responses to both noxious and innocuous tactile but not to visual stimuli when compared to a resting baseline. ACC showed a pattern of response that was higher to noxious stimuli regardless of sensory modality, but not to innocuous tactile or visual stimuli (Fig. 2). These differences suggest that the vicarious pain effect observed in right

ACC 24b was more closely associated with the motivational than the sensory properties of the stimulus. They are also in accordance with other pain empathy studies in which a somatosensory contribution to vicarious pain was lacking (Jackson *et al*, 2004; Singer *et al,* 2004).

"Visuo-nociceptive" selectivity in the ACC: analogy with premotor mirror neurons

This study demonstrates that the mere observation of a sharp object approaching a hand, making contact with it and distending the skin, is sufficient to engage a specific pain-related area in ACC. The dorsal ACC receives indirect projections from superior temporal areas associated with higher-level, semantic visual processing (Vogt & Pandya, 1987), a region also important in associative and multisensory processing of information from different sensory modalities (Calvert, Campbell, & Brammer,. 2001; Calvert, Hansen, Iversen,. & Brammer, 2002; Hikosaka *et al,* 1997).

Pain-related areas in ACC have extensive output connections to premotor and motor areas, as noted above. In this respect, ACC 24b has several formal similarities to the properties of mirror neurons discovered in areas of macaque premotor and parietal cortex (di Pellegrino *et al*, 1992; Rizzolatti *et al,* 1996), prompting an analogy between the functional organization of action recognition and that of the motivational-affective encoding of aversive third-person events.

Neural populations in macaque premotor F5 and parietal PF transform visual shape- and space-related object information into a motor-specific vocabulary of potential actions (Rizzolatti & Luppino, 2001). These transformations are based on object features or other relevant cues, or, in the case of mirror neurons, upon the observation of others. Whereas in

these fronto-parietal circuits perception-action transformations are processed in kinesthetic-pragmatic terms, medial frontal circuits including anterior cingulate area 24b may code analogous transformations in terms of affective and motivational significance. Whether neurons in ACC 24b can be considered "affective mirror neurons" remains to be seen, but the results of this study illustrate the strong possibility that a "mirror neuron principle" is not limited to kinesthetic action-perception circuits (Gallese, 2001, 2003), but may be at work in affective-motivational circuits as well.

Summary and conclusions

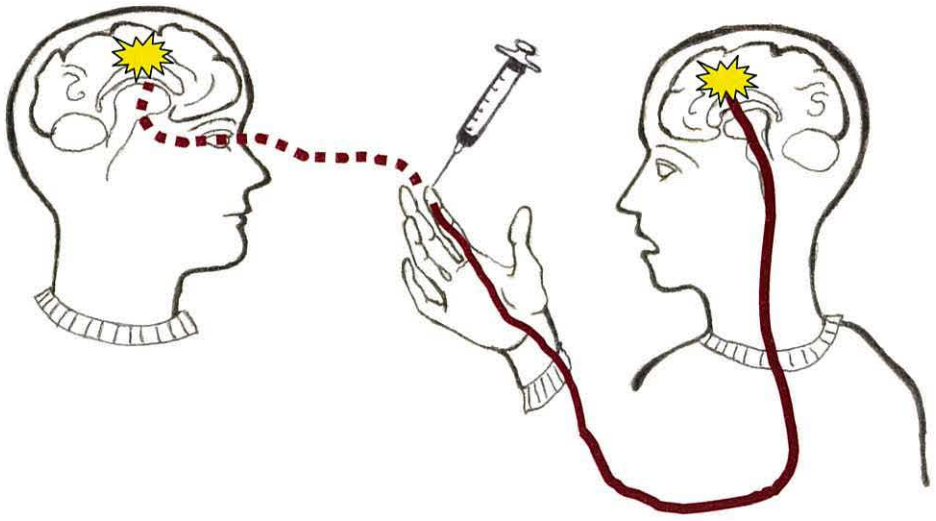
A fundamental question about empathy concerns the neural correlates of our ability to understand the emotional states of others in immediate terms. To address this issue, fMRI was used to measure brain activation in normal subjects while they either underwent moderately painful pinpricks to the fingertips or viewed a video of another person experiencing a similar stimulus. Both being pricked and observing another person being pricked was associated with focal activation of right inferior ACC 24b (24b' of Vogt *et al,* 1995). Differences in the coding of noxious and tactile properties between ACC and SI support a dissociation between the motivational-affective and sensory-discriminative dimensions of pain processing.

The organizational feature that enables the processing of visual information about painful events that befall others, even when they pose no immediate threat to the observer, admits an analogy with mirror neurons in premotor cortex. Taken together, these results encroach on the

age-old "paradox of sympathy" by providing a mechanism connecting observed painful events to an egocentric emotional and motivational network. Perhaps, although we cannot directly detect another person's tissue damage, we can still feel the suffering it causes.

CHAPTER III[1]:

ORGANIZATION OF FELT AND SEEN PAIN RESPONSES IN CINGULATE CORTEX



[1] This chapter is a draft of a manuscript currently in preparation: Morrison I., and Downing, P.E., Organization of felt and seen pain responses in cingulate cortex.

Abstract

Previous neuroimaging studies comparing pain observation with directly-experienced pain have shown conjoint activations in the cingulate cortex between felt and seen pain. However, this apparently shared neural substrate may actually reflect neighboring but distinct activations for felt and seen pain respectively, the co-localization of which is made more likely due to data processing factors such as averaging and spatial smoothing rather than the functional-anatomical overlap of a common substrate. This study explores responses to felt and seen pain, and their spatial overlap, on unsmoothed data from single subjects. All eleven subjects showed distinct felt and seen pain areas in the cingulate. But despite significant group-level activation for the statistical conjunction of felt and seen pain effects, not every individual showed a felt-seen pain conjunction. Among those that did, there was much variability in its location along the gyrus. However, the felt-seen pain conjunction always fell in a spatially intermediate location between the felt and seen pain activations. These results suggest that the BOLD signal overlap may originate from the blurring of boundaries between adjacent but distinct areas, rather than from a single neural population coding equally for felt and seen pain. This has implications for the interpretation of BOLD data in addressing "mirrorlike" activations in general, whether in action-related or pain-related areas.

Introduction

Several neuroimaging studies have shown activation of medial prefrontal areas in response to pain observation, including the anterior cingulate (ACC), supplementary motor area (SMA) and presupplementary motor area (pre-SMA) (Morrison *et al* 2004, Singer *et al* 2004, 2006; Jackson *et al* 2005; Lamm *et al,* in press). Of these, only two studies have directly compared activations of experienced pain to observed pain using conjunction analysis (Morrison *et al,* 2004; Singer *et al*, 2004). These conjunction-based studies have shown overlapping activations in the ACC. This suggests that the ACC can code both the tactile and visual aspects of a noxious stimulus, a functional property which may underlie our ability to recognize the aversive nature of others' painful situations.

This intriguing property could be due to the activity of neurons within a population which respond equivalently to both felt and seen pain. Evidence for individual neurons in the ACC exhibiting this coding feature comes from single-unit findings in a preoperative human patient (Hutchison *et al,* 1999). In this patient, a cell selective for mechanical painful stimulation also fired when the patient saw someone else being pricked by the sharp probe with which the experimenter tested for pain-related responses. The importance of this observation is that it suggests that some neurons in the ACC are capable of responding not only to physical noxious signals originating in the periphery, but also play a role in representing more psychical aspects of pain, based on visual information about others' injury. On the basis of fMRI data, however, it is

unclear whether conjunctions between felt and seen pain could reflect such an equivalent activation of underlying neuronal populations.

A major reason for this is the limitation in spatial resolution common to all imaging data: voxels are orders of magnitude larger than single cells. However, even within these limitations, there are also other reasons to examine the conjunction-based overlap further. The three main concerns motivating the present study are each to some degree related to the preparation of data for analysis. They stem from: 1) the loss of anatomical precision created by spatial smoothing and signal averaging across subjects; 2) the possibility that a felt-seen pain conjunction reflects bordering territory between functionally distinct adjacent areas; and 3) what constitutes a valid assessment of the equivalence of activation in a single region across two contrast pairs.

In particular, the two conjunction studies mentioned above (Morrison *et al,* 2004; Singer *et al,* 2004) were carried out on spatially-smoothed, group averaged data, using random effects analysis. This may have resulted in a greater degree of overlap and obscured informative sources of individual variation. Second, it is not clear whether the area of conjunction reflects a functional component common to both feeling and seeing pain (*ie*, whether the area is doing the same job in two modalities). An alternative explanation that remains to be tested is that the conjoint activation here reflects neighboring but relatively distinct activations for felt and seen pain respectively, of which bordering voxels survive the conjunction threshold as a result of signal averaging within a normalized brain space and/or spatial smoothing. The third concern is that conjunction analysis as implemented in many current analysis software packages is susceptible to a high false positive rate and, due to

assumptions about the null hypothesis when thresholding higher-order t-maps, may not warrant the inference of a logical AND (Nichols, Brett, Andersson, Wager, & Poline, 2005).

Group effects enable generalization to the population, but they can also obscure finer-grained spatial and functional aspects of BOLD responses. Analysis of selectivity below the group level is therefore important because it can have bearing on hypotheses about processing within a given area of cortex (Haxby, Gobbini, Furey, Ishai, Schouten, & Pietrini, 2001; Grill-Spector, Knouf, & Kanwisher, 2004). For example, although the fusiform gyrus responds almost equally to face and body stimuli in whole-brain group analysis, individually-defined regions-of-interest in this area revealed that the peaks were different for each of the two categories (Peelen & Downing, 2004). This suggests that dissociable foci of selectivity exist within the same population of neurons that show equivalent responses to faces and bodies on a whole-brain, group level. This issue strikes at the heart of reasoning about how shared activations between felt and seen pain support recognition of, and compassionate emotional responses to, others' pain.

Equivalent responses within the same region when pain is *seen* as when it is *felt* are thought to mediate a translation of third-person visual information about pain to first-person terms. This is a basic principle of the "common coding" hypothesis (Prinz, 1990; 1997), upon which the interpretation of much neuroimaging data on interpersonal cognition relies, either directly or indirectly. Introduced in the context of perception-action systems, the common coding concept represents an elegant computational means by which processing from different domains— for example vision and motor preparation— can be

collapsed into a single "language." Under the common coding hypothesis, information from the two domains becomes unified by virtue of the same mechanism operating in both domains, thus precluding the need for a separate "translator" substrate. When the common coding concept informs hypotheses in neuroimaging, it is often implicitly assumed that shared activations in two domains imply that an identical population of neurons is responding equivalently in each; for example, in action observation and action generation.

The common coding interpretation for pain empathy is supported by the abovementioned single unit observations from human ACC, which suggest that common coding for felt and seen pain may indeed exist on the level of the response characteristics of individual neurons (Hutchison *et al,* 1999). The inference of a common coding mechanism from fMRI conjunction results is much less direct. Primarily, the spatial resolution is so coarse that it is not possible to test whether the same neural population is equally activated in each of the two domains. The spectrum of spatial resolution that exists between single cells and clusters of voxels leaves a lot of room for spurious inference about whether the same neural population is performing the same function in both domains. Similarly, shared territory between two non-colocalized networks begs the question of what is shared functionally: it is not yet clear in the case of pain observation on what level encoding occurs (for example how abstract the representation of others' pain is in the ACC compared to directly-experienced pain), and what constitutes the common functional denominator in the two networks that gives rise to the shared response.

To what extent do cingulate areas responding both to felt and seen pain share an identical neural substrate? To address this question, we investigated the

possibilty that the conjunction-based overlap between felt and seen pain might reflect adjacent but distinct activations, which may border but not coincide with one another. We examined the features of this overlap by analysing individually defined regions-of-interest in cingulate cortex. Specifically, we identified separate felt and seen pain areas for individual subjects on spatially unsmoothed data, and defined regions of common activation on the basis of both conjunction analysis and spatial overlap for felt and seen pain. Selectivity for images of noxious objects was also tested to ensure that pain-related visual responses in the cingulate were not driven solely by the sight of potentially harmful objects outside the context of potential pain to others.

Materials and Methods

Subjects

Twelve healthy adult volunteers were recruited from the University of Wales, Bangor community (5 female, mean age 31, 1 left-handed). Participants satisfied all requirements in volunteer screening and gave informed consent approved by the School of Psychology at the University of Wales, Bangor and the North-West Wales Health Trust. Participation was compensated at £20 per session. Of the twelve, one participated only in the visual runs but not the felt-pain runs and so was included only in the visual run analysis for 'objects' (see below).

Design and Procedure

Stimuli.

As in a previous fMRI experiment (Morrison *et al,* 2004), the stimulus for the "experienced pain" condition was a mildly painful prick to the middle finger of the left hand using a sharp wooden probe (~1Hz/15sec). During scanning, the

hand was placed palm-up in a relaxed position, out of the subject's sight. The tactile control stimulus was a cotton bud (Q-tip) similarly pressed onto the fingertip. Both the sharp probe and the cotton bud were positioned in a hypodermic syringe in place of the lancet. Figure 1 shows examples of the stimuli.

For the "observed pain" condition, a video featuring a model's left hand being pricked on the finger with a hypodermic needle was displayed. The video featured the needle coming into contact with the hand and excluded the model's face. The visual control video was identical except for the substitution of a cotton bud for the needle. As before, participants were familiarized with the sharp probe prior to scanning, but during scanning they could neither see their hands nor the stimulus being applied. The videos were viewed in a mirror mounted on the head coil, projected onto a screen at the rear of the magnet bore. All visual stimuli were presented on a laptop using Presentation® software (Version 0.70, www.neurobs.com). The design was a block design, as in a previous experiment (Morrison *et al,* 2004), but differed from that experiment in two important ways. First, tactile and visual blocks were presented within the same runs. Second, a task was introduced to maintain subjects' attention to the stimuli: pressing a button when a target finger (the middle finger) was stimulated in either the tactile or visual modality.

Each run was 5 minutes, 25 seconds long and consisted of four blocks having 21 15-second trials per scan. In each block each of the four conditions was presented once, for a total of four presentations per run. Blocks 1, 6, 11, 16, and 21 were a fixation-only baseline condition. Blocks consisted of 10 15-sec stimulus presentations, in pseuso-random order with the target finger stimulated

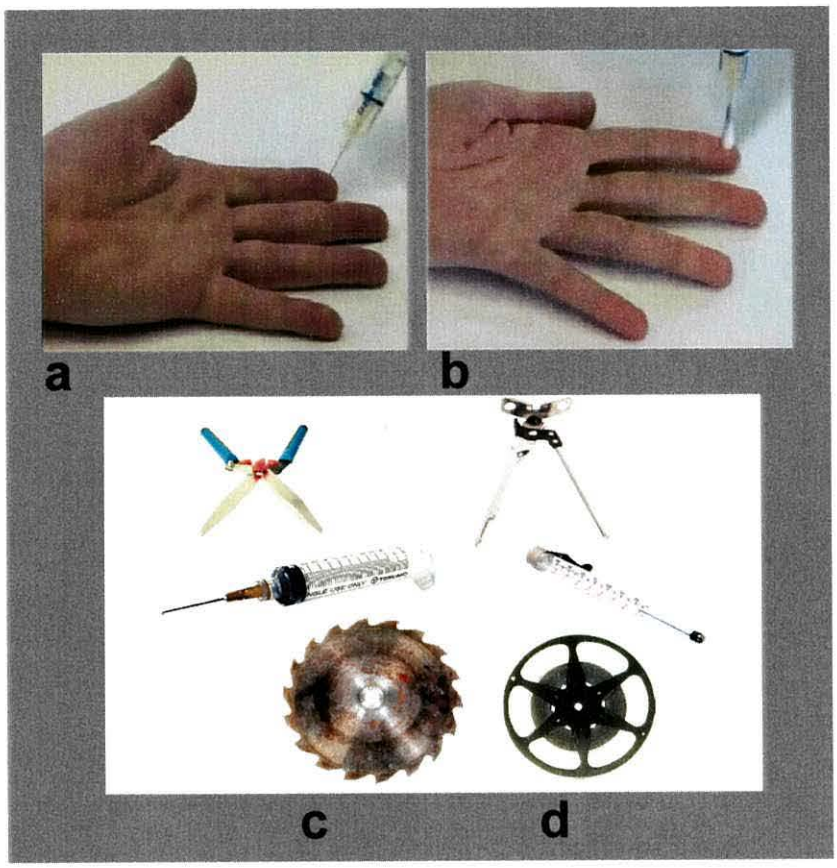


Figure 1. Example visual stimuli used in the seen pain trials (a, needle video, b, cotton bud video) and the object trials (c, noxious objects, d, innocuous objects).

at least once per block. Blocks were counterbalanced within runs using a Latin square. There were two versions of the counterbalancing design (runs 1 and 3, version 1; runs 2 and 4, version 2 for each participant). Tactile stimuli were delivered manually by the experimenter to the index, middle, ring, and little finger of the participants' left hand. The type and timing of tactile stimulation was cued for the experimenter via headphones by auditory prompts delivered by the stimulus presentation program. With their right hand, participants made button responses when they saw or felt the target finger (middle finger) being stimulated, which occurred 1-3 times out of the 15 stimulus presentations per block.

Selectivity for noxious objects

Six of the participants were also scanned during an additional run presenting still photographs of noxious and innocuous objects (Hemera PhotoObjects®). Five of these participants were also scanned during the pain runs in the same session; the sixth participated only in the objects run. The dangerous and nondangerous object sets were counterbalanced for visual similarity (Fig. 1). This was designed to test for effects of noxious-object discrimination, in order to demonstrate that pain-observation effects in ROIS showing selective responses to the sight of painful object-hand interactions were not due solely to a more general sensitivity to the sight of potentially harmful objects.

The design of the object runs was identical to that of the pain runs. Each approximately 5-minute run consisted of four blocks having 16 15-sec experimental trials and five 14-sec baseline rest intervals. In each block each of the two conditions (noxious or innocuous) was presented twice, for a total of eight presentations per run. Trials consisted of 10 15-sec stimulus presentations. Blocks were symmetrically counterbalanced within each run (*eg* 1212,2121,1212,2121). Participants were instructed to view the stimuli but no responses were required. Before the scan, subjects rated the objects as being dangerous or nondangerous (*ie* "Would the object require care in handling or not?").

Data Acquisition

A 1.5-T Philips magnetic resonance imaging (MRI) scanner with a SENSE parallel head coil was used. For functional imaging, a singleshot echo-planar imaging (EPI) sequence was used (T2*-weighted, gradient echo sequence,

repetition time (TR) = 3000, echo time (TE) = 50 ms, flip angle = 90°, field-of-view = 92 x 92 mm). The scanned area included 30 axial slices, 5 mm thick, with no gap, at 64 x 64— voxel in-plane resolution, which covered the whole cerebral cortex and the cerebellum. Reaction times were collected with a scanner-safe button box (Current Designs, Philadelphia, PA).

Data Analysis

Pre-processing and statistical analysis of MRI data was performed using BrainVoyager 4.9 (Brain Innovation, Maastricht, The Netherlands). Three dummy volumes were acquired before each scan in order to reduce possible effects of T1 saturation. Functional data were motion-corrected, low-frequency drifts were removed with a temporal high-pass filter (0.006 Hz). Spatial smoothing was not applied. Functional data were manually co-registered with 3D anatomical T1 scans (1 x 1 x 1.3 mm resolution, resampled to 3 x 3 x 3 mm voxels). The 3D anatomical scans were transformed into Talairach space (Talairach and Tournoux, 1988). The parameters for this transformation were then applied to the co-registered functional data.

Group analysis. For each participant, general linear models were created for each of the four runs. One predictor (convolved with a standard model of the HRF) modelled each of the four conditions (felt pain, seen pain, felt qtip, and seen qtip), which were submitted to a whole-brain, group average analysis. Using random effects analysis, separate t-maps were created for the contrasts (felt pain - felt cotton bud) and (seen pain - seen cotton bud), thresholded at a liberal level of $P < 0.05$ ($t = 2.22$), uncorrected for multiple comparisons, in order to avoid type II error when searching for activations among regions specified *a priori*. The central analysis for this study was a random-effects

conjunction analysis performed on the separate t-maps created for the contrasts (felt pain - felt cotton bud) and (seen pain - seen cotton bud). This creates an intersection map of both contrast pairs thresholded at significance, mapping areas in which felt and seen pain showed significantly greater increases for felt pain and seen pain compared to the innocuous controls. This method is conservative in that it excludes any voxel in which either of the paired contrasts (felt pain - felt cotton bud) and (seen pain - seen cotton bud) shows no significant effect.

Individual analyses. Similar to the group analysis, for each individual fixed-effect analysis was used to create separate t-maps for the contrasts (felt pain - felt cotton bud) and (seen pain - seen cotton bud), thresholded at $P < 0.01$ ($t = 2.5$), uncorrected. Fixed-effects conjunction maps were also created at this threshold to locate any felt pain-seen pain overlap in the dACC, where present (see *Results*).

On both the group and individual level, regions-of-interest (ROIs) were defined as the set of contiguous voxels significantly activated (at $P < 0.05$ uncorr., random effects, for group; $P < 0.01$ uncorr., fixed effects, for individuals; again, liberal thresholds were used to avoid type II error) within 10 mm^3 of the most significantly activated voxel. For individuals, the ACC felt pain, seen pain, and conjunction ROIs were defined within a limited part of the cingulate cortex including the anterior part of the gyrus and sulcus extending in the y direction from the AC plane, to cortex dorsal to the genu of the corpus callosum, Taliarach coordinates $0 < x < 10$, $0 < y < 32$, $20 < z < 45$. Only clusters > 20 mm^3 are reported for these analyses. To reinforce the conjunction analysis, a spatial intersection analysis was also performed on the ROIs defined

by each paired contrast, *i.e.* [(felt pain - felt qtip) and (seen pain - seen qtip)], for both the group and for individuals where a dACC conjunction area was present. This intersection ROI was then defined by all voxels in the spatial overlap between two independently-defined ROIs, and so represents an AND operation.

Pattern analysis was performed on these overlap ROIs by testing the correlation between the parameter estimates (beta values) between the (felt pain - felt cotton bud) and (seen pain - seen cotton bud) contrasts for each voxel. For each ROI in each subject individually, we measured the voxel-by-voxel pattern of selectivity to felt pain vs the felt cotton bud control, and seen pain versus the seen cotton bud control, respectively. This was accomplished by extracting a t value for each given contrast at each voxel in the ROI. The t value provides a useful index of selectivity, because it represents the magnitude of the difference between two conditions, relative to the within-condition variance. We then correlated, for each ROI, the pattern of selectivity for one contrast with the pattern for another. These correlations were extracted for each subject individually, and the resulting mean correlation was tested statistically against zero.

Noxious objects. For the subgroup taking part in the objects runs (n = 6), ROIs were defined for areas in which responses to noxious objects was significantly higher than those to innocuous objects. These were derived from fixed-effects activation maps for the contrast (noxious objects - innocuous objects) thresholded at $P < 0.002$ (t = 3.28), uncorrected. Within the conjunction ROI defined by the whole group analysis (n = 11), parameter estimates were also examined for responses to noxious objects for these 6 subjects.

Results

Behavioral task. Errors for detecting the target finger did not exceed 2%. For the object runs, noxious objects were rated as more dangerous than noxious objects (errors < 1%).

Group analysis. For the group, random effects analysis produced two t-maps revealing activations for felt (felt pain - felt cotton bud), seen pain (seen pain - seen cotton bud), and their conjunction respectively (all maps thresholded at $p < 0.05$ uncorrected). These are summarized in Table 1.

Felt pain. On a group level, the felt pain activation in the cingulate had two foci, one rostral focus extending into the sulcus bilaterally (*xyz* = 5, 27, 24 and -4, 24, 30), and one more caudal focus in midcingulate cortex (*xyz* = -2, 7, 34). Activations were also seen in bilateral anterior insula, right (contralateral) mid-insula, right (contralateral) putamen, and left (ipsilateral) cerebellum. Although subjects were instructed to close their eyes during tactile stimulation, this was not monitored, and visual-related activity in occipital cortex for the (felt pain - felt cotton bud) contrast is attributable to subjects having their eyes open in these conditions, resulting in common activation with the visual conditions.

Seen pain. The cingulate seen pain activation for the average of all subjects was seen anterior to the rostral felt pain focus, extending onto the crown of the gyrus bordering pre-SMA (*xyz* = -2, 23, 34). Regions of the superior frontal gyrus near the SMA and inferior frontal gyrus near BA44/45 were also activated by seeing pain (*xyz* = -13, 15, 55 and 48,29,3). Activations were also seen postcentrally in the left hemisphere, probably falling within secondary somatosensory cortex (*xyz* = -57, -13, 23 and -52, -24, 34).

Felt-seen conjunction. Consistent with previous studies, the whole-brain conjunction analysis revealed several activations in medial prefrontal cortex (dACC, MCC, and bilateral pre-SMA) and bilateral opercoinsular cortex (anterior insula/inferior frontal gyrus). On the group level, and at this threshold, the only cingulate conjunction activation that corresponded to an overlap between felt and seen pain activations identifiable on the separate felt and seen t-maps was in the left dACC (*xyz* = -2, 24, 31).

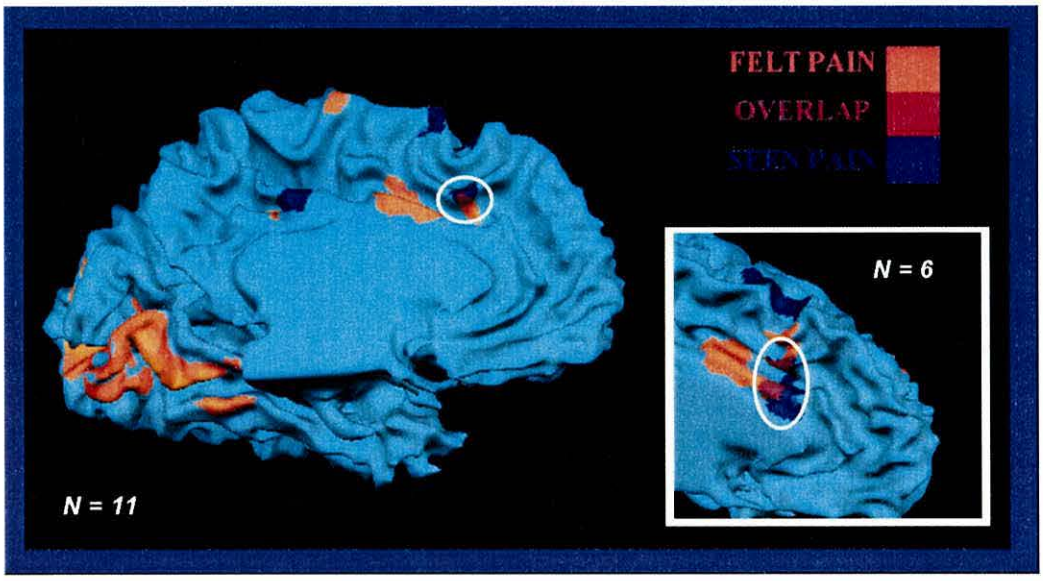


Figure 2. Activation map showing the relative locations of felt pain (orange), seen pain (blue), and their overlap (magenta) on a partly-inflated medial brain surface for the average of 11 subjects (thresholded at $P < 0.05$ uncorrected, random effects). Inset shows the same activations for the subset of six subjects that showed the felt-seen conjunction on an individual level (thresholded at $P < 0.0001$ uncorrected, fixed effects).

For the 181 shared voxels in the spatial overlap between felt and seen pain in this area, an analysis of the pattern of activation in the felt and seen pain conditions tested whether the same voxels highly activated during felt pain were also relatively more activated during seen pain in these 11 subjects. The pattern analysis revealed a significant positive correlation between the activation pattern for felt pain and that for seen pain in this overlap region, ($r = 0.20$, $p = 0.004$,

two-tailed). Figure 2 shows the relationship of the rostral cingulate felt pain, seen pain, and conjunction activations for all 11 subjects in sagittal views.

Individual analyses. For each individual, fixed effects analyses were performed to identify felt and seen pain activations in the anterior cingulate (all maps thresholded at $p < 0.01$ uncorrected, to avoid Type II error). While all 11 individuals showed distinct felt and seen pain activations along the anterior

Table 1. Felt pain, seen pain, and conjunction areas for all eleven subjects (ACC = anterior cingulate cortex, SFG = superior frontal gyrus; IFG - inferior frontal gyrus; SMA = supplementary motor area).

Region	Peak coordinates (Talairach x,y,z)	Maximum t-score	Hemisphere	Extent (voxels)
Felt pain				
Midcingulate	-2, 7, 34	6.23	L	1847
Dorsal ACC	5, 27, 24	5.45	R	345
Dorsal ACC	-4, 24, 30	3.74	L	377
Anterior insula	-33, 12, 7	4.7	L	361
Anterior insula	39, 15, -4	4.14	R	708
Mid-insula	44, -5, 8	3.68	R	325
Putamen	16, -15, 10	5.67	R	143
Cerebellum	-2, -52, -16	3.82	L	725
Visual cortex	-31, -77, 1	5.66	L	3694
Seen pain				
Rostral ACC	-2, 23, 34	4.35	L	201
SFG	-13, 15, 55	4.92	L	632
IFG	48, 29, 3	6.22	R	852
Inferior postcentral gyrus	-57, -13, 23	4.17	L	465
Postcentral gyrus	-52, -24, 34	5.2	L	712
Conjunction				
Dorsal ACC	-2, 24, 31	3.43	L	118
Superior midcingulate/SMA	2, -3, 46	4.55	R	87
Inferior midcingulate	2, -10, 31	3.77	R	51
Pre-SMA/SFG	18, 21, 55	3.92	R	69
Pre-SMA	-4, 28, 54	3.59	L	56
Anterior insula/IFG	39, 20, -1	3.64	R	71
Anterior insula/IFG	-32, 23, 7	4.09	L	93

cingulate sulcus/gyrus, a felt -seen conjunction was observed in 6 of the11 individuals. This group of 6 was designated the "overlap" subgroup and submitted to fixed-effect group-average analyses for felt and seen pain and their conjunction, thresholded at $p < .0001$ for felt and seen pain t-maps and $p < .001$ for the conjunction. These activations are summarized in Table 2. The group average activation for the overlap group (n=6) is depicted in Fig 2, and the relationships of activation foci in individuals is depicted in Fig 3.

Table 2. Conjunction areas for the six subjects showing the conjunction individually (ACC = anterior cingulate cortex, SFG = superior frontal gyrus).

Region	Peak coordinates (Talairach x,y,z)	Maximum t-score	Hemisphere	Extent (voxels)
Felt pain				
Dorsal ACC	-2, 7, 34	6.23	L	1847
Anterior insula	5, 27, 24	5.45	R	345
Anterior insula	-4, 24, 30	3.74	L	377
Cerebellum	-33, 12, 7	4.7	L	361
Seen pain				
Dorsal ACC	-2, 23, 34	4.35	L	201
Anterior insula	-13, 15, 55	4.92	L	632
SFG	48, 29, 3	6.22	R	852
Conjunction				
Dorsal ACC	-2, 24, 31	3.43	L	118
Inferior postcentral gyrus	2, -3, 46	4.55	R	87
Visual cortex	2, -10, 31	3.77	R	51

Felt pain. For individuals, peak activations for felt pain in the ACC varied in their location along the gyrus/sulcus, ranging from x = 0-3, y = 4-31, and z = 22-40. In the group average of the 6 individuals in the "overlap" group the cingulate felt-pain peak fell at *xyz* = 0, 12, 35, with further activations in

bilateral anterior insula (*xyz* = 38, 20, 6 and -40, 15, 0) and left cerebellum ipsilateral to the stimulated hand (*xyz* = -3, -68, -9).

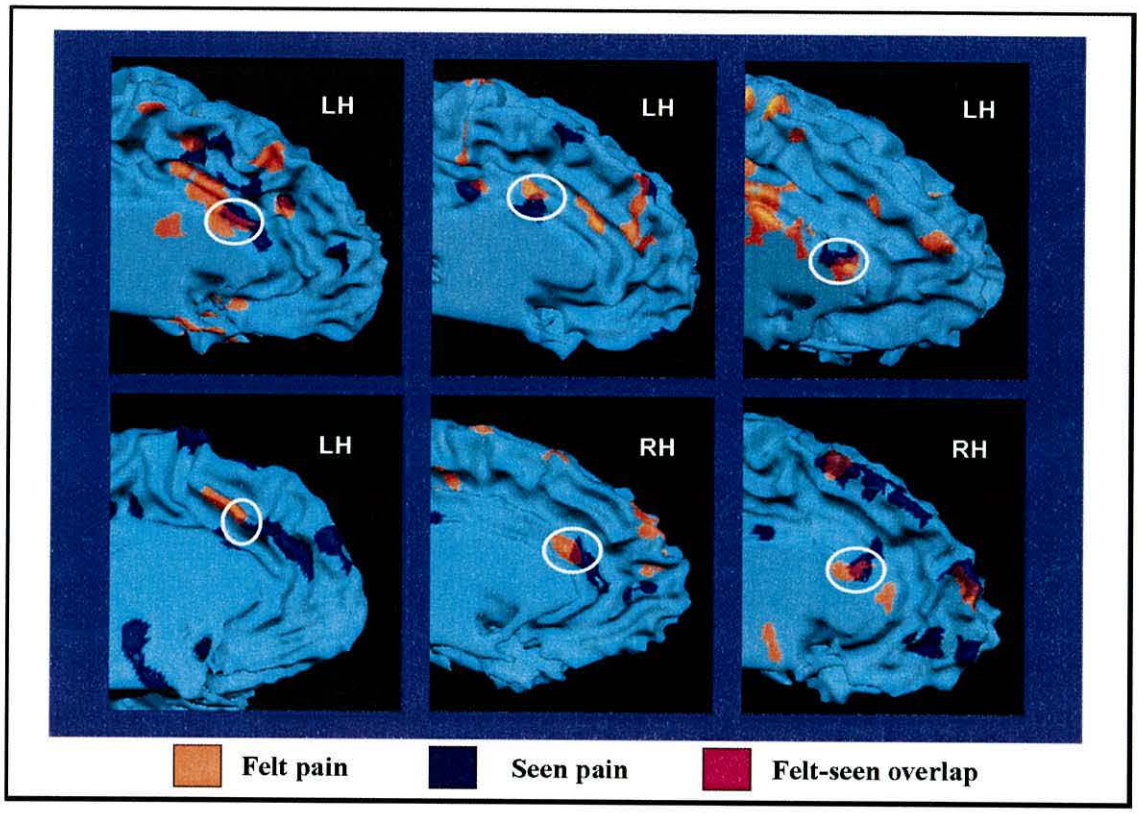


Figure 3. Activation maps showing the relative locations along the anterior cingualte gyrus of felt pain (orange), seen pain (blue), and their overlap (magenta) on a partly-inflated medial brain surface for each of the six subjects that showed the felt-seen conjunction on an individual level. Peak activations for the overlap region-of-interest along the cingulate gyrus varied from x = 0-9, y = 6-32, and z = 23-41. All activations shown fell within 2 mm of the medial surface. All surface maps show the left hemisphere except for the lower right two, which show mirror-flipped views of the right hemisphere (LH = left hemisphere, RH = right hemisphere).

Seen pain. For individuals, peak activations for felt pain in the ACC ranged from x = 0-6, y = 7-36, and z = 19-46. In the group average of the 6 individuals in the "overlap" group the cingulate seen-pain peak fell at *xyz* = 0, 23, 29, with further activations in the left superior frontal gyrus bordering pre-SMA (*xyz* = -11, 16, 57) and right inferior frontal gyrus/anterior insula (*xyz* = 46, 15, 3).

Conjunction. Within the "overlap" group of 6 individuals, peak activations for the conjunction of felt and seen pain in the ACC ranged from x = 0-9, y = 6-32, and z = 23-41. In the group average of the 6 individuals in the "overlap" group the cingulate conjunction peak fell at *xyz* = 0, 22, 29. In this group, the conjunction reflects an overlap between felt and seen pain as part of a larger pattern showing a superior-to-inferior alternation of felt and seen pain activations beginning in pre-SMA on the dorsal superior frontal gyrus and continuing medially to the cingulate gyrus (see blue and orange colored activations in Fig 2, inset). The size and distance of the overlap varied among the "overlap" subgroup of 6 subjects (mean size 83 voxels, mean felt-seen peak difference 4.1mm). Despite this intersubject variability, overlaps and conjunctions were always situated at the border between felt and seen pain activations (as opposed to, for example, one activation being nested within the extent of the other). Other activations fell in the left inferior postcentral gyrus corresponding to SII (*xyz* = -58, -14, 523), and in visual cortex (*xyz* = -3, -77, -4).

To determine whether the same voxels within the conjunction showed similar patterns to felt and seen pain, the t-values for each voxel within this region-of-interest were correlated for felt pain and seen pain for each individual in a pattern analysis. Three of the six subjects showed significant correlations, but of these two were negative ($r = -0.29$, $p = 0.01$; and $r = -0.27$, $p = 0.00006$) and one was positive ($r = 0.54$, $p < 0.00001$). This inconclusive result could reflect a number of underlying factors (*eg*, partial volume effects resulting from white matter voxels within the ROIs).

Selectivity for noxious objects. In a fixed effects analysis (thesholded at $p < 0.002$ for 6 subjects), viewing noxious objects compared to innocuous objects revealed activations in bilateral posterior middle temporal gyrus (*xyz* = 47, -60, 0 and -43, -60, 3), consistent with selectivity in this region for the sight of tools. In the cingulate, there was an activation focus in subgenual ACC (*xyz* = -3, 24, 0), and in dACC (*xyz* = -11, 32, 25). The dACC activation, however, did not overlap with any of the dACC regions-of-interest defined for seen pain or felt-seen pain conjunctions in the group as a whole. In the felt-seen pain conjunction defined by the group (n = 11), noxious objects were not discriminated from innocuous objects, $t(1,5) = 0.064$, $p = 0.95$, and responses to noxious objects were significantly lower than those to felt pain, $t(1,5) = 5.98$, p 0.002, and to seen pain, $t(1,5) = 3.27$, $p = 0.02$. These activations are depicted in Fig 3.

Discussion

These results replicate those of previous studies but also provide evidence that ACC responses to felt and seen pain are selectively organized at a finer spatial grain. Within a group of subjects showing a felt-seen pain conjunction at a whole-brain, group-average level, individually-defined regions of interest showed distinct activation peaks for felt and seen pain respectively. Although all subjects contributed to the average conjunction effect in a random effects analysis, and all showed distinct felt and seen pain areas in the cingulate, not all showed conjunctions individually. Rather than being strictly colocalized, felt and seen pain activations were bordering but distinct on both the group and individual level. Conjunctions always coincided with spatial overlaps, falling

intermediately between the felt and seen pain regions. On the group level, this is consistent with the results of Singer *et al* (2004), whose felt and seen pain activations were also distinct but overlapping.

The present findings indicate that for the some individuals, the felt-seen pain overlap occurs even without spatial smoothing. The fact that the felt and seen pain peaks were so distinct and variable, however, suggests that smoothing and averaging contribute considerably to the location and extent of the overlap observed at the group level. These findings speak against a strong interpretation that the felt-seen pain overlap reflects the activity of an identical population of neurons. Rather, the overlap may be due to the proximity in some individuals of vascular territory belonging to two adjacent areas showing distinct and selective responses to felt and seen pain, or the activity of two intertwined neural populations.

Common coding

The approach used here has bearing on the "common coding" interpretation of in much fMRI data in social cognitive neuroscience. Over the last decade, one of the central pillars of the cognitive-neuroscientific perspective on primate social cognition has been the proposal that we understand others' actions, emotions, sensations, and mental content via the same neural mechanisms contributing to similar first-person subjective states (see *eg* Gallese *et al,* 2004). This idea has proved crucial in hypothesizing about fundamental problems at the bedrock of social cognition: what makes a phenomenologically isolated individual brain able to share so intimately in the experiences of others? How

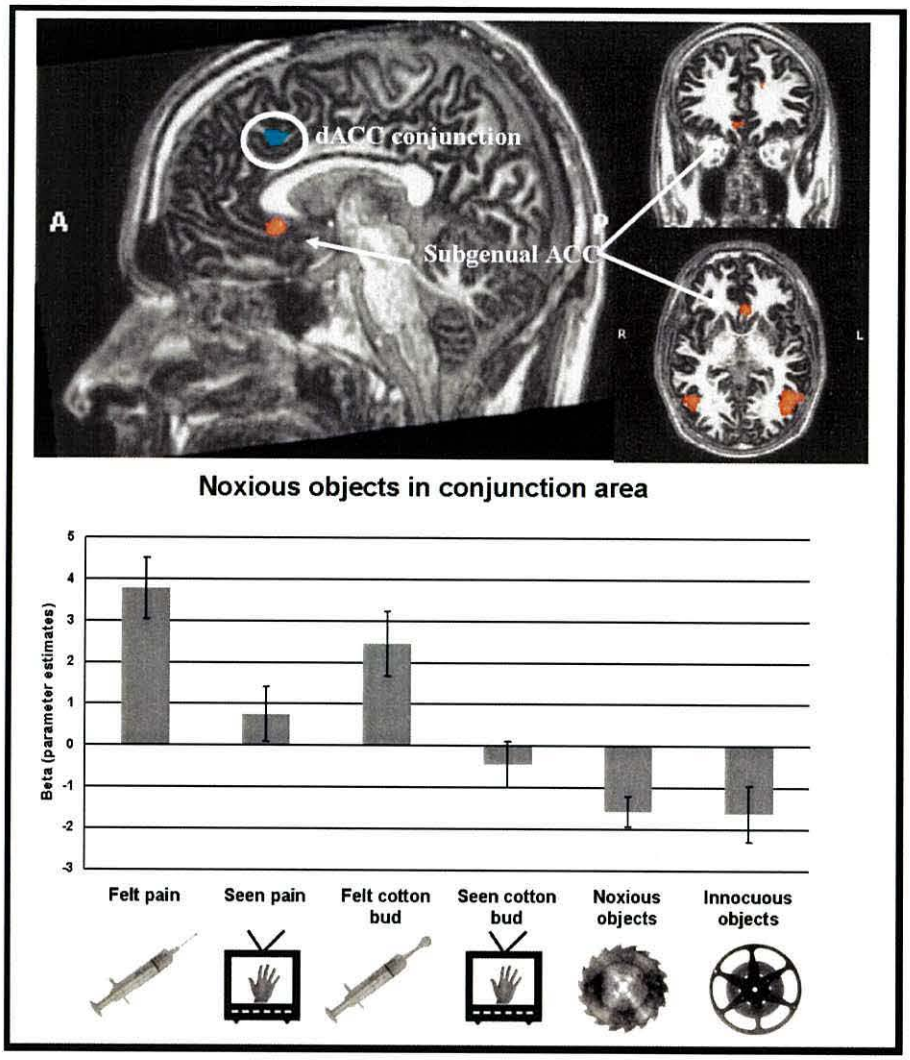


Figure 3. Activations for seeing noxious compared to innocuous objects (n = 6). Noxious objects elicited responses in subgenual ACC (-3, 24, 0), dACC (-11, 32, 25), and bilateral middle temporal gyrus (47, -60, 0 and -43, -60, 3). Map thesholded at $P < 0.002$ uncorrected, fixed effects. The focus for the felt-seen pain defined by the conjunction for all 11 subjects (-2, 24, 31) is depicted in blue, and the graph shows hemodynamic responses in that area in different conditions for the six subjects taking part in the object runs.

do we predict others' behavior on the basis of their actions? How do we so effortlessly perform complex inferences about the mental states of others?

Much evidence for common coding has accumulated over the past decade, especially from single-unit recordings in nonhuman primates. The study of similar mechanisms in multisensory processing has also been fruitful (*eg,* Calvert, 2000; Bremmer, Schlack, Shah, Zafiris, Kubischik, Hoffmann, Zilles,

& Fink, 2001; Lloyd *et al,* 2003). The now-classic example of a common coding mechanism is the mirror neuron, which responds both to observed and self-generated goal-directed actions in the monkey (Rizzolatti *et al,* 1996; Gallese *et al,* 1996; Gallese *et al,* 2004). The discovery of mirror neurons has granted important insight into these questions by identifying an empirically tractable type of neural mechanism for translating sensory representations about others into immediate, first-person terms. This has bolstered the theory that shared representations between self and other rely on shared neural substrates between first-person processing and third-person observation.

Applying the common coding hypothesis to BOLD response properties often implicitly involves three assumptions: that common activation involves an identical neural population ("substrate identity assumption"), that the responses are thus relatively spatially co-localized in extent ("colocalization assumption"), and that the strength of the response is equivalent in each domain compared to controls ("equivalence assumption"). In this study, we found that responses to felt and seen pain in the ACC challenges the first assumption (of "substrate identity"), and the second, related assumption (of "colocalization"). The responses here may still be encoding third- and first-person information in comparable terms, but what may be more important than strict substrate-identity is that the neural populations involved are commensurate in terms of their response properties (Hommel & Prinz, 2001). This may be sufficient to encode information from two domains into a common "language", for example in terms of semantic content, spatial reference frame, etc. The common coding hypothesis as set out by Prinz (1990, 1997) and Hommel & Prinz (2001) stipulates commensurate neural codes but does not necessarily imply substrate

identity; conversely, closely-related and spatially proximal responses with distinct peaks do not rule out common coding.

This caveat may especially apply in prefrontal areas such as the ACC, which are intimately involved in learning and flexible response selection, and thus alter their activation profiles sensitively in the face of changing circumstances (Iwata, Kamo, Ogawa, Tsuboi, Noma, Mitsuhashi, Taira, Koshikawa, & Kitagawa, 2005; Shima & Tanji, 1998; Bush *et al,* 2002; Williams, Bush, Rauch, Cosgrove & Eskandar, 2004;. Kennerley *et al,* 2006). In the single-unit observations indicating common coding between felt and seen pain in human ACC, the response to seen pain altered over the course of recording (Hutchison *et al,* 1999). As the patient watched the experimenter repeatedly prick someone else with the sharp probe, the pinprick-selective cell acquired an anticipatory response, firing earlier and earlier before the sharp probe struck the skin. This suggests a degree of dynamicity in the ACC's coding of seen pain, and may also reflect changing relationships among connected cells in the local network. It is therefore possible that common BOLD activations here reflect fluid, perhaps spatially-shifting nodes of similar responses within an area of cortex, rather than an invariant, classically bimodal response.

Conjunction: statistical considerations

Even if the spatial "colocalization" and "substrate identity" assumptions don't strictly hold for the present findings, does the overlapping activation in the ACC support the third implicit assumption above— namely, does it respond equivalently to felt and seen pain in a statistical sense? Conjunction analysis is often employed as a test to search for regions equivalently selective in different

domains or under different conditions. It is used to isolate areas in which voxels respond above threshold across each of two (or more) contrast pairs. For example, Morrison *et al* (2004) mapped the common activation in the ACC between feeling a pinprick compared to feeling a neutral touch of a cotton bud, and seeing a pinprick compared to seeing a cotton bud. Similarly, Singer *et al* (2004) showed common activations in the ACC and anterior insula when subjects experienced electrode pain compared to nonpainful stimulation, and when they viewed visual cues indicating that a loved one (whose hand was visible to the subject) was receiving painful compared to nonpainful electrode stimulation.

In each of these studies, the experimenters inferred that the same area activating in each of the two conditions strongly indicates that the effect of the pain variable was present in both the felt AND the seen conditions. However, the statistical procedures for excluding voxels that do *not* show equivalent activations in a conjunction analysis have a crucial impact on the kind of inference that is valid in accepting the statistical hypothesis. In turn, this affects interpretation of the activations' functional meaning. This raises a twofold issue for the use of conjunction analysis for the goal of inferring a common, equivalent effect of felt and seen pain in the ACC. The first aspect is statistical, and concerns what inferences the conjunction analysis allows about the observed activations. The second concerns the interpretation of the effects based on this statistical analysis.

The software analysis programs used by both Singer (SPM99) and Morrison (FSL) in their 2004 studies relied on the minimum statistic. That is, each of two contrast pairs was assumed to be independent, and the minimum t-value across

the contrast pairs was used to threshold the activation map for the conjunction. However, Nichols *et al* (2005) have highlighted features of the null hypothesis involved in this method which restrict both the statistical and functional inferences it warrants. Both of the conjunction-based pain empathy studies tested the "global" null hypothesis that the least significant (minimum) t-value was drawn from a random distribution. This null hypothesis states that there is *no* effect in felt pain AND *no* effect in seen pain. Thus all voxels are rejected which show no significant effect in *either* pair (*ie* both null), while those showing any activation above the minimum threshold in *either* pair (*ie* one or both) are included in the conjunction map.

The problem with this method as a test of common coding between felt and seen pain is that rejecting the global null hypothesis does not allow the inference that the effect of the pain variable is present in both the felt AND the seen conditions. This is because the false positive rate for the conjunction of two t values makes it too liberal, including activations indicating an effect of felt pain, OR seen pain, OR both. What the studies aimed to show, though, was that in certain regions there was an effect of both felt AND seen pain exclusively.

The present study implements a different, more conservative method for thresholding a conjunction map. In contrast to SPM99 and FSL, BrainVoyager (BV) uses what Nichols *et al* call the "conjunction null." (NB: no explicit, published verification of this statement exists, but is gathered from the description of the BV conjunction analysis tool in the online help guide (http://brainvoyager.com/BV2000/OnlineHelp/BrainVoyagerWebHelp/Conjunction_analysis.htm), from postings on the BV online forum (http://www.brainvoyager.com), and from personal communication with T.

Nichols, with permission.) Rather than thresholding at the minimum statistic across contrast pairs, this method first requires that each contrast pair shows an effect at a given threshold. An intersection map of significant activations of the two contrasts is then created showing only those voxels that survive the threshold in *both* analyses. It is tested against the null hypothesis that there is no effect in felt OR seen pain contrasts. Though conservative (or "overconservative", Friston, Penny, & Glaser, 2005), this is a statistically more valid route to the desired inference that the ACC responds to both felt AND seen pain.

Singer *et al*'s (2004) conjunction activation survived a more conservative masking procedure, but Morrison *et al* (2004) did not apply a similar additional test. Others have used masking procedures instead of conjunction analyses (Lamm *et al,* in press). In the present study, as a complementary method to isolate voxels shared between felt and seen pain activations, we also defined regions of interest based on the spatial overlap of the felt and seen pain regions of interest in the ACC for each subject showing the effect. While the conjunction analysis was a statistically-based AND operation for common functional activations, this intersection overlap analysis was a spatially-based AND operation for isolating the voxels included in both felt and seen pain activations, independently defined. The conjunction and the spatial overlap regions coincided, falling intermediately between the felt and seen pain activations. This was the case for both the group average and for the individual subjects that showed the conjunction.

Conjunction: interpretation considerations

Even with a statistically valid, conservative conjunction test for common coding, reinforced by spatial overlap on both the group and individual levels, interpretive issues remain. The conjunction is only as good as its constituent contrast pairs, and it is still possible that quantitatively-equivalent activations in the ACC are due to qualitatively-different processes in each modality. The contrast pairs could differ in multiple ways, owing to aspects of the task, the cognitive processes engaged (such as attention), the nature of the stimulus (such as its salience), and not least by the fact that information from two different sensory modalities (vision and nociception) were involved.

On the other hand, shared components could represent the anticipation of pain (not possible to model separately from subsequent stimulus-related signal changes in either study), top-down coping strategies, associative processing, attentional allocation, stimulus evaluation, motivational modulations (including the skeletomotor impulse to avoid the stimulus), or affective modulations (including endocrine and sympathetic changes). Discovering what the shared components are would be relevant to the common coding hypothesis, because it would indicate what the content of the common representations may be, and thus suggest what we experience on another person's behalf when we see them in pain. Considering the general response profile of the region in pain-related, attentional, and cognitive tasks, it seems most likely to us that the conjunction reflects shared activations in pain anticipation or related processes linking pain information to behavioral response, either overtly or covertly. The dorsal ACC region here is consistently activated in tasks requiring response selection and

evaluation of the relevance of stimuli in complex or context-dependent tasks (Rushworth *et al,* 2004; Shima & Tanji, 1998; Bush *et al,* 2002; Williams *et al,* 2004; Kennerley *et al,* 2006).

Yet even if a common functional denominator is present between the two contrast pairs, it is not clear that the subtraction of felt and seen pain from their "neutral" controls in each contrast pair is a clean one, free from hidden interactions. It is also problematic for the interpretation if any of the differences in each interact with the common component (Caplan & Moo, 2003). The observed effects may be qualitatively or functionally equivalent, but they may also hide one or more interacting effects. Singer *et al* ruled out interactions in which the average response to felt or seen pain was higher than the other in their 2004 study, but Morrison *et al* did not. Generally, one may still rightfully ask of this data: conjunction of what?

It is still unclear, then, whether the shared vascular response in the ACC reflects the recruitment of a population of "bimodal" or "mirrorlike" neurons sharing a function, or simply a degree of vascular "slop" because felt and seen pain areas are close together in some subjects or reflect discrete but intertwined cell populations. Analysis of the pattern of activation in the overlapping voxels in individuals failed to shed light on this question. Three of the six "overlap" subjects showed a significant correlation here between felt and seen pain, but of these only one was positive. Further experimentation is needed to rule out whether this equivocal result is due to a lack of functional correspondence in those voxels, or to other factors such as the presence of white matter voxels in these areas. On the group level, however, the correlation between felt and seen

pain responses in the overlapping voxels for those six individuals was significant and positive.

It is possible that the seen pain response in the ACC was driven mainly by the sight of a potentially dangerous object (the needle itself), rather than the interaction between others' hands and the dangerous object. This was not the case, however. Viewing noxious vs innocuous objects activated subgenual and dorsal ACC regions, but not those involved in viewing others' pain in the videos.

Summary and conclusions

These results replicate those of previous studies and reveal several compelling features of vicarious pain responses in the cingulate cortex. First, within a group which showed an overlap between felt and seen pain on average (as tested with both conjunction and intersection analyses), not all subjects showed it individually. Second, among the individuals showing an overlap, the spatial extent of the overlapping region and the distance between peak activations of felt and seen pain varied, although it was always located intermediately between the felt and seen pain activations. Third, there was no conclusive correlation between felt and seen pain activation values within the overlapping voxels in individuals, although they correlated positively in the group average. Taken together, these results qualify the proposition that areas in the cingulate cortex respond in the same manner to felt and seen pain at the voxel level. Instead, this data suggests that there are selective and organized responses to harmful stimuli in self and others within regions of the ACC, and that these respective areas an be, but are not necessarily, co-localized at a finer grain.

Far from undermining the conclusion that the dorsal ACC is associated with both experience and observation of pain, the results reinforce the idea that this region utilizes first-person pain information originating from the periphery as well as visually-based information about others' pain. However, it does not provide clear answers as to what functional process is shared. Based on the general functional properties of the area and the behavior of single cells, we believe this process is likely to be a context-dependent function related to the flexible modulation of behavioral responses, such as anticipation or covert response selection. Further, this may arise from activations among versatile, interrelated, heterogeneous cell populations. This proposal is supported by our present finding that within the ACC there are selective and organized responses to harmful stimuli in self (tactile) and others (visual), and that considerable individual variability exists. The possibility that this area responds generally to the sight of noxious implements outside the context of potential harm to body parts can be ruled out. However, the possibility that the conjunction reflects adjacent but distinct activations has not been entirely excluded. Further investigation is therefore needed before we can assert that the common BOLD activations between felt and seen pain always reflect the activity of the same population of neurons.

CHAPTER IV[1]:

VISUAL PROCESSING OF AVERSIVE OBJECTS IN PERIPERSONAL SPACE

"...Candace, howling oh-my-God-oh-my-God, holds up her hand, which is gushing blood from a deep gash that extends from her thumbnail almost to her palm. The blood is everywhere— down her arm, in the elaborate grooves she's been carving in the back of her chair...Looking at all the blood, Tick feels her own left arm begin to throb the way it always does in anticipation of hypodermic needles at the doctor's office, and at horror movies when somebody gets slashed."

— Richard Russo, *Empire Falls*

[1] A version of this chapter has been published as Lloyd, D., Morrison, I., and Roberts, N. (2006). Role for human posterior parietal cortex in visual processing of aversive objects in peripersonal space. *Journal of Neurophysiology* 95, 205-14.

Abstract

The posterior parietal cortex of both human and non-human primates is known to play a crucial role in the early integration of visual information with somatosensory, proprioceptive and vestibular signals. However, it is not known whether in humans this region is further capable of discriminating if a stimulus poses a threat to the body. In this fMRI study we tested the hypothesis that the posterior parietal cortex of humans is capable of modulating its response to the visual processing of noxious threat representation in the absence of tactile input. During fMRI, participants watched whilst we 'stimulated' a visible rubber hand, placed over their real hand with either a sharp (painful) or a blunt (non-painful) probe. We found that superior and inferior parietal regions (BA5/7 and BA40) increased their activity in response to observing a painful vs. non-painful stimulus. However, this effect was only evident when the rubber hand was in a spatially congruent (vs. incongruent) position with respect to the participants' own hand. In addition, areas involved in motivational-affective coding such as mid-cingulate (BA24) and anterior insula also showed such relevance-dependent modulation, whereas premotor areas known to receive multisensory information about limb position did not. We suggest these results reveal a human anatomical-functional homologue to monkey inferior parietal areas that respond to aversive stimuli by producing nocifensive muscle and limb movements.

Introduction

The brain is organized to support the complex spatial and sensorimotor representations required for interactions with objects in the world, such as navigation and fine manipulation. However, for objects which pose a direct threat to the body, visuo-spatial and sensorimotor mechanisms may 'flag' potentially noxious stimuli relatively early in the visual processing stream, for example, within structures of the posterior parietal cortex. Such threats are directly relevant to the body and are likely to be most imminent when they occur within the space surrounding a particular body part. In the current study we investigated whether visual processing of noxious threat-related objects in peripersonal space would activate posterior parietal cortex more than the visual response to a non-threatening object in the same space.

There is evidence that visuo-tactile receptive fields in monkey inferior parietal and intraparietal cortex are sensitive to both tactile and visual information about noxious stimuli (Dong, Chudler, Sugiyama, Roberts, & Hayashi, 1994). Cells in this region have also been associated with nocifensive movements of aversion (Cooke & Graziano, 2003). Apart from these findings, networks classically implicated in the evaluation of the behavioural relevance of aversive stimuli have not included posterior parietal cortex. Rather, in the context of pain processing, medial frontal and limbic regions (such as the anterior cingulate and anterior insula cortices) are associated with the evaluation of the motivational and behavioural relevance of the stimulus on the basis of visual or nociceptive information (Botvinick *et*

al, 2005; Jackson *et al,* 2005; Morrison, *et al,* 2004; Singer *et al,* 2004) although these studies have largely been concerned with the processing of empathy for pain.

In many situations the organism must track potential threats in terms of their spatial proximity to particular body parts, and in such circumstances it would be advantageous for underlying visuo-motor representations to be dynamically sensitive to events in the space surrounding that body part. The aim of the current study was to investigate the visual processing of aversive objects in peripersonal space, specifically that surrounding the hand. One possible way of pursuing this would be to stimulate participants' hand with an aversive (i.e., noxious) stimulus. However, because limb representation involves the multisensory integration of visual, tactile, and proprioceptive cues, this would include the contribution of nociceptive tactile input. An alternative way of isolating the visual component of noxious threat would be to present visual stimuli close to a realistic and aligned artificial limb in peripersonal space which could then be 'stimulated' in the absence of actual tactile input. This manipulation has been shown in several studies to result in shifts of the felt location of the limb/and biases in proprioception and or reaching (Armel & Ramachandran, 2003; Ehrsson, Spence, & Passingham, 2004; Farnè, Pavani, Meneghello, & Ladavas, 2000; Graziano, 1999; Holmes, Snijders, & Spence, 2005; Pavani, Spence, & Driver, 2000; Tastevin, 1937; Tsakiris & Haggard, 2005; Walton & Spence, 2004).

Artificial hands have also recently been used to investigate the *neural*

correlates of subjective limb ownership (Ehrsson *et al*, 2004). Previous behavioural research has shown that when both an artificial hand and the person's own hand (which is hidden either beneath or at the side of the person's own hand) are stroked repeatedly and synchronously by the experimenter, some participants can have the experience that the touch they feel on their own hand is located where they see the rubber hand being touched. This sensation is often accompanied by a sense of ownership of the rubber hand (Botvinick & Cohen, 1998). Using functional magnetic resonance imaging (fMRI) Ehrsson and colleagues provided evidence that the subjective experience of ownership of the rubber hand correlates significantly with premotor cortex activation. In a separate analysis this activation was observed as an interaction between the synchronicity of the stroking and the anatomical plausibility of the hand's orientation. The impression of ownership of the rubber hand can be substantially reduced or even eliminated by placing the rubber hand in an anatomically implausible position with respect to the participant's real hand, asynchronously touching the real and rubber hand and/or allowing vision of the real hand (see Maravita, Spence, & Driver, 2003 for a review).

There is also a multitude of evidence from both animal electrophysiological recordings and human brain imaging studies to suggest that activity in the premotor and posterior parietal cortex (particularly the ventral-intraparietal area; VIP) represents both the *seen* and *felt* position of the hand (for a recent review see (Graziano, Gross, Taylor, & Moore, 2004).

Multisensory cells within these regions fire both when the hand is touched or when a visual stimulus is presented near the hand (Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981) and when a fake hand is seen in place of the real hand (Ehrsson *et al*, 2004; Graziano, 1999). In the monkey area VIP has direct reciprocal connections with part of the ventral premotor cortex (F4 in PMv), the human homologue of which is the inferior frontal gyrus (BA44) (Rizzolatti, Luppino, & Matelli, 1998), forming a circuit known as the VIP-F4 circuit (Luppino, Murata, Govoni, & Matelli, 1999). Further evidence exists of a similar circuit in fronto-parietal regions of the human brain responsive to the multisensory representation of limb position (Lloyd, Shore, Spence, & Calvert, 2003).

A study by Armel & Ramachandran (2003) indicates that not only can an artificial hand be incorporated into the subject's own body representation, but that autonomic nervous system activity can occur according to the perceived threat of an object in contact with the artificial hand. They measured skin conductance responses (SCRs) whilst subjects experienced simultaneous and synchronous tactile stimulation of their own and a rubber hand. They found that if the rubber hand was suddenly and unexpectedly 'injured' following this simultaneous tactile stimulation, subjects displayed a strong SCR even though they were aware that their real hand was never in danger.

To discover whether a potentially noxious visual stimulus, perceived within peripersonal hand space would influence haemodynamic responses in the brain, especially within regions implicated in multisensory limb

representation, we biased the integration of participants' visual, tactile, and position senses by manipulating the position of the rubber hand over the participants' own hand. Noxious (sharp) or innocuous (blunt) stimulation of the rubber hand was preceded by simultaneous stroking of the real and rubber hand to facilitate participants' perception of the rubber hand as within body-part centred space (although visual capture of limb proprioception can also occur in the absence of synchronous stroking; see Farnè *et al*, 2000; Holmes *et al*, 2005; Pavani *et al*, 2000; Rorden, Heutink, Greenfield, & Robertson, 1999; Walton *et al*, 2004). Specifically, areas previously shown to play a role in coding the space surrounding the hand— such as posterior parietal and premotor cortex— are predicted to distinguish a sharp probe vs. a blunt probe striking the rubber hand.

Importantly, we expect any such discrimination to depend on the anatomical plausibility of the false limb's real position influencing the apparent position of the invisible real limb position, responding more when the rubber hand is oriented compatibly with the person's own hand (and thus proprioceptively aligned). A secondary hypothesis is that activity in anterior cingulate and anterior insula, which respond to pain-related visual information and are involved in the motivational-affective aspect of pain processing, will likewise increase for the sharp vs. the blunt probe. If these predictions are borne out, the results will provide the first neuroimaging evidence that regions supporting visuo-spatial representations of peripersonal space are capable of discriminating threatening stimuli near the hand.

Methods

Participants

Twenty-eight participants (9 males, 19 females) aged between 22 - 50 years (with a mean age of 29 years) gave fully informed written consent of their willingness to participate in this study, which had local ethics committee approval. Fourteen participants took part in Experiment 1 (rubber hand in a spatially *congruent* position with respect to the participant's own hand) and a further fourteen naïve participants took part in Experiment 2 (rubber hand in a spatially *incongruent* position with respect to the participant's own hand). All participants were strongly right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), and in good health with no past history of psychiatric or neurological disease. Participants had normal or corrected-to-normal (with contact lenses) visual acuity and normal tactile sensation.

Apparatus and materials

A realistic-looking rubber (right) hand was placed on top of the participant's own right hand (see Figure 1). A piece of semi-circular plastic piping was placed in between the rubber hand and the participant's own hand to ensure that touching the rubber hand did not inadvertently tactually stimulate the person's real hand, and was covered with a cloth to enable continuity of the perception of the fake hand and arm extending and occupying the position of the participant's real hand and arm. A cotton bud (or Q-tip) and a syringe with

a cocktail stick (also called a 'toothpick') in place of the steel lancet were used as the innocuous tactile and painful tactile probes respectively. The cocktail stick caused a moderately painful pin-prick sensation when applied to the skin (as established on all participants prior to scanning) but does not contain metal and so can be used within the MRI environment. We were able to emulate the experience of a real syringe being applied to the skin by placing it in the plastic holder of a real syringe.

Design and procedure

Prior to scanning, all participants were exposed to the effect of the rubber hand by placing their own hand underneath the plastic tubing with the rubber hand on top (in the congruent position) and a blanket covering their arm to maintain the perception of the rubber hand as an extension of their own arm. We then began simultaneous stroking of the rubber hand and the participant's own hand until they reported such statements to suggest that they could feel as if the rubber hand was their own hand or that they could feel 'touch' on the rubber hand. This typically occurred after several seconds. We then stopped the procedure and showed the participants the cotton bud/Q-tip and modified syringe (with the cocktail stick in place instead of the steel lancet) and encouraged them to feel the tactile qualities of these two objects. All participants acknowledged the Q-tip as innocuous and the cocktail stick as moderately painful.

Stimuli were presented within a modified blocked design. At the start of each block, participants experienced 30 seconds of rest followed by 15 seconds of simultaneous stroking of the rubber (right) hand and their own right hand, in a temporally synchronised and spatially compatible way. Specifically, both the rubber hand and the participant's real hand were stroked by the experimenter (using their index finger) in a unidirectional way on the middle finger of the right hand starting at the fingernail and ending at the proximal interphalangeal joint (mid-way down the finger) at an approximate rate of 1Hz. In studies where only visual cues of the fake/rubber hand were available (i.e., no simultaneous touch occurred), participants failed to incorporate the fake hand into the body image (Farnè *et al*, 2000; Pavani *et al*, 2000). We reasoned that an investigation of the visuo-nociceptive response to threatening objects in peripersonal space would benefit from including this simultaneous touch condition. However, we do not have any formal subjective measures (i.e., via questionnaires) of whether participants experienced the 'rubber hand illusion' *per se* as this was not the focus of the current study. This manipulation also ensured that, in the absence of an explicit task, participants were aware of the rubber hand throughout the 7-minute scan. After this time, either the cotton bud or the syringe was administered to the rubber hand for 15 seconds (the order of which was randomised between subjects), which the participants could see touching the rubber hand but not approaching the rubber hand given the confines of the

scanner. Three blocks of each condition (i.e., noxious touch and innocuous touch) were presented.

All stimuli were delivered at a steady rate of 1Hz (practised outside of the scanner), the duration of the stimulation was timed by a clock on the wall of the scanner, visible to the experimenter but not to the participant inside the scanner. During the pre-scan set-up and during the experiment participants were instructed to look only at the rubber hand (which they saw indirectly through a mirror positioned in the head coil of the scanner). Although we did not formally track their eye-movements during the scan, we are confident participants were looking at the stimuli throughout this novel and stimulating experiment through post-scan interviews as to their subjective impression of the effect of having the rubber hand touched with the different stimuli. Their own (right) hand was hidden from view underneath the rubber hand throughout the experiment and participants were unable to see the experimenter touching their hand as the narrow bore of the magnet restricts the field of view of the participant such that he/she can see the rubber hand (placed over his/her own right hand) and the hands of the experimenter touching the rubber hand but not the body of the experimenter which is hidden from view at the side of the magnet.

In Experiment 1, the rubber hand was in an anatomically plausible (congruent) position with respect to the participant's real arm (Figure 1). In Experiment 2, the position of the rubber hand was rotated 180 degrees such that it faced towards the participant in what was deemed by all to be an

anatomically implausible (incongruent) position. This was the optimum position for the rubber hand given the narrow confines of the scanner. Data from Experiment 2 were collected in a different scanning session from that of Experiment 1 and in a different set of participants to eliminate any familiarity or priming effects.

Scanning procedure

MR data were acquired using a 1.5 T Signa LX/Nvi neuro-optimised system (General Electric, Milwaukee, WI). FMRI was performed with a blood oxygenation level-dependent (BOLD) sensitive T_2^*-weighted multislice gradient echo EPI sequence (TE = 40 ms, TR = 3 s, flip angle = 90°, FOV = 190 mm, 64 x 64 matrix, inplane resolution 3 mm). 135 volumes were collected in a single EPI run. Twenty-four contiguous 5-mm thick axial slices were prescribed parallel to the AC-PC line and covered the whole brain. For the purpose of anatomical referencing and visualisation of brain activation, a high-resolution T_1-weighted 3D inversion recovery prepared gradient echo (IRp-GRASS) sequence was acquired (TE =5.4 ms, TR = 12.3 ms, TI = 450 ms, 1.6-mm slice thickness, FOV = 200 mm, 256 x 192 matrix), with 124 axial slices covering the whole brain (in-plane resolution 1 mm).

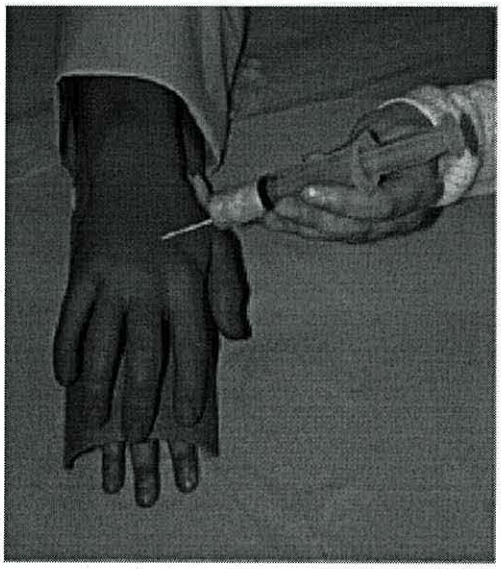


Figure 1. . Photograph of the experimental set-up. Inside the scanner, the rubber hand (representing a right hand) was placed above the participant's real right hand in either an anatomically plausible (experiment 1) or implausible (experiment 2) position. A piece of semi-circular plastic tubing was placed between the participant's real hand and the rubber hand to prevent secondary contact of the participants hand during stimulation of the rubber hand.

Data analysis was carried out using FEAT5 software (FMRI Expert Analysis Tool, Oxford Centre for Functional Magnetic Resonance Imaging Analysis of the Brain – FMRIB - University of Oxford), part of the FMRIB software library (FSL 3.2; www.fmrib.ox.ac.uk/fsl (Smith et al., 2004). The following pre-statistics processing was applied; Motion correction using MCFLIRT (Jenkinson & Smith, 2001); spatial smoothing using a Gaussian kernel of FWHM 5mm; mean-based intensity normalisation of all volumes by the same factor; non-linear highpass temporal filtering (Gaussian-weighted LSF straight line fitting, with $\sigma = 60s$). Statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation

correction of the data (non-linear spatial smoothing and prewhitening (Smith & Brady, 1997; Woolrich, Ripley, Brady, & Smith, 2001).

For each individual subject, we fitted a linear regression model (general linear model - GLM) to the data (first level analysis). Four covariates were analysed separately corresponding to the four experimental conditions: two covariates of interest; viewing the painful stimulus touching the rubber hand ('View Pain' - VP) and viewing the innocuous stimulus touching the rubber hand ('View Neutral' - VN) and two covariates of no interest; simultaneous touching of the rubber hand and real hand prior to viewing the painful stimulus ('Pain Rub' - PR) and simultaneous touching of the rubber hand and real hand prior to viewing the innocuous stimulus ('Neutral Rub' - NR). In addition, linear contrasts were also defined within the GLM framework to identify areas in which the activity relating to the painful stimulus touching the rubber hand was greater than the activity to the innocuous stimulus touching the rubber hand [i.e., (VP-VN)], both when the hand was in the congruent position [i.e., Congruent (VP-VN)] and incongruent position [i.e., Incongruent (VPVN)].

Similarly, contrasts were defined to measure activity in voxels where activity to the innocuous stimulus was greater than the painful stimulus [i.e., (VN-VP)], both when the arm was in a spatially congruent and incongruent position. The results from this analysis were contrast estimates for each condition for each of the 28 subjects (contrast images). To accommodate inter-subject variability, the contrast images from all subjects were entered

into a mixed effects group analysis (a second level analysis also known as random effects) carried out using FEAT5 software (Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Gaussian Random Field Theory Resel-based Correction, which gives the probability of a cluster, given its spatial extent and z threshold, under the null hypothesis and is therefore less conservative than the Bonferoni correction (see Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1992; Worsley, Evans, Marrett, & Neelin, 1992). Statistic images were thresholded using clusters determined by $Z = 2.3$, $P < 0.05$ (corrected for multiple comparisons across the whole brain) and transformed into the stereotaxic space of the Montreal Neurological Institute (MNI) using FLIRT (FMRIB's Linear Image Registration Tool; (Jenkinson et al., 2001).

Results

Analysis of main effects

Viewing a painful tactile probe touching the rubber hand (representing a right hand) with the hand placed in an anatomically plausible (congruent) position (vs. rest) revealed significant activation across a number of parietal and prefrontal regions as predicted. Activation contralateral to the position of the stimulated rubber hand (i.e., covering the person's own right hand) was seen in inferior parietal cortex (BA40), premotor cortex (BA6) and inferior frontal gyrus (BA44) as well as extrastriate cortex (BA18) and right superior and

middle temporal gyri. Bilateral activation was seen across middle and superior frontal gyri (BA6/8) and anterior cingulate cortex (see Table 1, Figure 2). Similar sites of activity were observed when viewing a painful tactile stimulus touching the rubber hand with the hand in a spatially *incongruent* position with respect to participants' own hands (vs. rest; see Table 1, Figure 3).

Contralateral activity was again observed in premotor and middle frontal gyrus (BA6/46), medial intraparietal sulcus and superior parietal lobe (BA7), extrastriate cortex (BA18/19) and anterior insula and posterior cingulate cortex (BA31). Ipsilateral activation was seen within parietal operculum (BA40) and precentral sulcus with bilateral activation occurring within superior temporal and inferior frontal gyri (BA45/46) and anterior cingulate cortex.

Viewing an innocuous tactile probe touching the rubber hand with the hand placed in an anatomically plausible (congruent) position (vs. rest) revealed contralateral activation of premotor cortex (BA6), superior parietal and temporal lobes and extrastriate visual cortex. Ipsilateral activation was seen in inferior and middle frontal gyrus (BA44), and bilateral activation in inferior parietal lobe (BA40; see Table 2, Figure 4). With the rubber hand in a spatially incongruent position with respect to participants' own right hand (vs. rest) significant activation was seen in the contralateral hemisphere in inferior

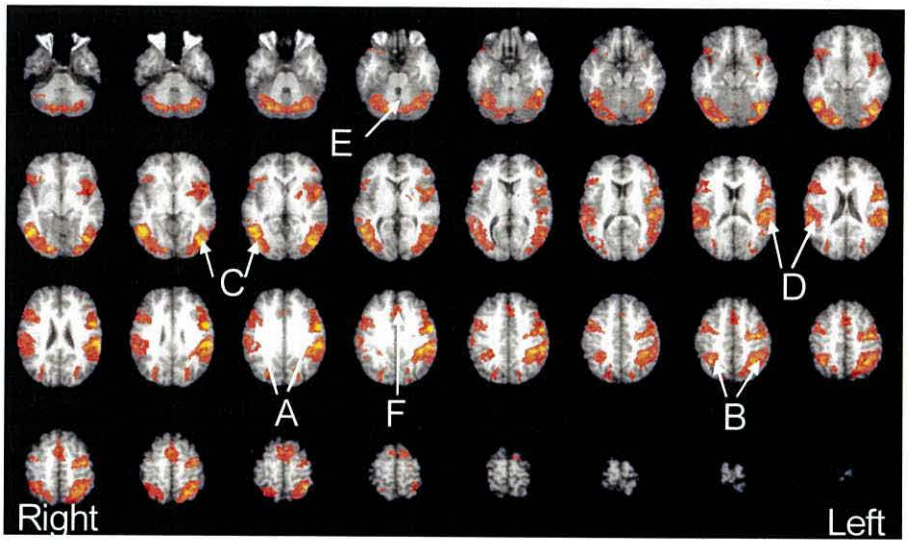


Figure 2. Activation map illustrating a significantly greater response to viewing the painful tactile probe applied to the rubber hand when the hand was in an anatomically plausible position (with respect to the participants' real hand) vs. rest (no stimulation). Maps were cluster-based thresholded at $z < 2.3$, $P < 0.05$ (corrected for multiple comparisons) and are shown in axial sections across the whole brain starting at the level of the brain stem (moving from left to right across the page in 4-mm slices) in radiological convention (right side of the brain on the left side of the picture). A = premotor cortex; B = superior parietal lobe; C = temporal-occipital cortex; D = inferior parietal lobe; E =cerebellum;F = anterior cingulate cortex.

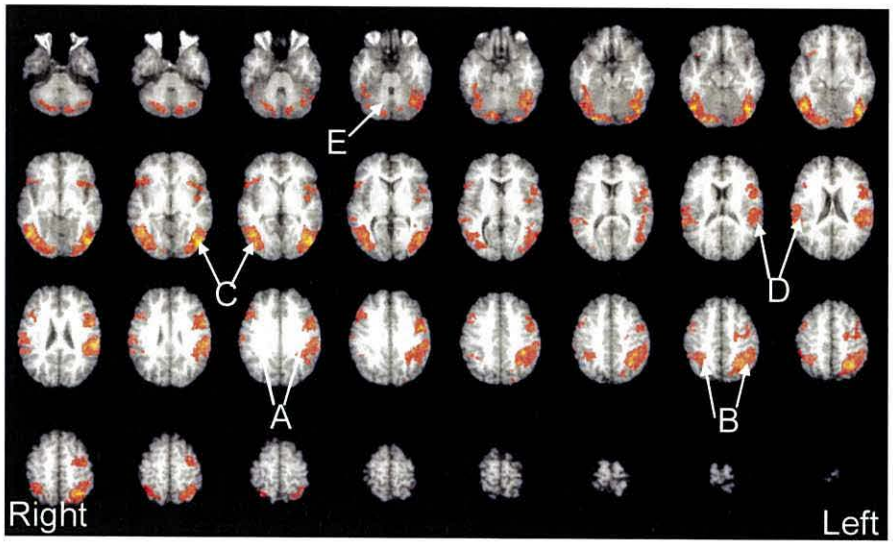


Figure 3. Activation map illustrating a significantly greater response to viewing the painful tactile probe applied to the rubber hand when the hand was in an anatomically implausible position (with respect to the participants' real hand) vs. rest (no stimulation). Maps were cluster-based thresholded at $z < 2.3$, $P < 0.05$ (corrected for multiple comparisons) and are shown in axial sections across the whole brain starting at the level of the brain stem (moving from left to right across the page in 4-mm slices) in radiological convention (right side of the brain on the left side of the picture).

Table 1. Activation in response to a painful tactile stimulus touching the rubber hand (representing a right hand) when the hand is in a spatially congruent and incongruent position with respect to the participant's own right hand (activations determined by clusters greater than $z < 2.3$, $P < 0.05$). MNI coordinate and peak z score of the maximum activating voxel in each cluster are shown.

Region	MNI Coordinates (*x,y,z mm*)			Maximum *z* score	R/L
Congruent Arm Position					
Premotor cortex (BA6)	−54	2	34	5.70	L
Inferior parietal lobe (BA40)	−56	−28	26	5.48	L
Extrastriate cortex (BA18)	−44	−80	−2	5.44	L
Middle temporal gyrus	56	−56	0	5.40	R
Middle frontal gyrus (BA6/8)	50	10	44	4.40	R
Superior frontal gyrus (BA6)	2	12	60	4.18	R
Middle frontal gyrus (BA9)	58	18	32	4.11	R
Inferior frontal gyrus (BA44)	44	18	24	3.99	R
Superior temporal gyrus	48	24	−22	3.81	R
Medial frontal gyrus (BA6)	−4	0	58	3.45	L
Anterior cingulate cortex (BA32)	0	24	38	3.41	—
Incongruent Arm Position					
Extrastriate cortex (BA18)	−42	−74	−6	6.54	L
Medial intraparietal sulcus	−38	−48	52	5.94	L
Parietal operculum (BA40)	60	−20	22	5.93	R
Superior parietal cortex (BA7)	−22	−60	62	5.82	L
Premotor cortex (BA6)	−50	0	30	5.28	L
Middle frontal gyrus (BA6)	−26	−8	56	5.07	L
Superior temporal gyrus	−40	−8	−6	4.90	L
	40	−2	−14	4.85	R
Precentral sulcus	34	−2	50	4.86	R
Inferior frontal gyrus (BA45/46)	48	28	12	4.57	R
	−40	32	4	4.28	L
Anterior cingulate cortex (BA24)	2	−4	34	4.38	R
Posterior cingulate gyrus (BA31)	−14	−32	34	4.17	L
Anterior insula	−36	22	8	3.55	L
Middle frontal gyrus (BA46)	−34	42	16	3.12	L

frontal gyrus (BA44/45) and inferior and superior parietal lobes, extrastriate visual cortex (BA18), temporal lobes including the hippocampus and parahippocampal gyrus whilst premotor cortex activated bilaterally extending into the precentral sulcus, sylvian fissure and inferior frontal gyrus (BA47; see Table 2, Figure 5). Ipsilateral activation was seen within middle frontal gyrus (BA6/9/10/11).

Table 2. Activation in response to an innocuous tactile stimulus touching the rubber hand (representing a right hand) when the hand is in a spatially congruent and incongruent position with respect to the participants own right hand (activations determined by clusters greater than $z < 2.3$, $P < 0.05$). MNI coordinate and peak z score of the maximum activating voxel in each cluster are shown with the laterality of response.

Region	MNI Co-ordinates (*x,y,z mm*)			Maximum *z* Score	R/L
Congruent Arm Position					
Extrastriate cortex (BA18)	−46	−76	−2	5.91	L
Inferior parietal lobe (BA40)	−56	−30	24	5.07	L
	68	−22	26	3.71	R
Superior parietal lobe (BA7)	−32	−56	54	5.02	L
Premotor cortex (BA6)	−50	2	36	4.87	L
Middle frontal gyrus (BA6/8/9)	48	8	50	4.66	R
Superior temporal gyrus	−54	8	2	4.17	L
Inferior frontal gyrus (BA44)	58	16	32	3.93	R
Incongruent Arm Position					
Extrastriate cortex (BA18)	−42	−76	−2	6.26	L
Inferior parietal lobe (BA40)	−60	−26	28	5.74	L
Superior parietal lobe (BA7)	−28	−54	50	5.71	L
Premotor cortex (BA6)	−54	2	34	5.13	L
	42	−6	42	3.78	R
Precentral sulcus	−50	0	40	4.90	L
	40	0	42	3.96	R
Sylvian fissure	−54	4	4	4.70	L
	40	−4	−8	3.67	R
Middle frontal gyrus (BA6)	36	−4	48	4.33	R
Inferior frontal gyrus (BA44/45)	−44	40	2	4.22	L
Superior temporal gyrus	−40	−12	−8	4.04	L
Middle frontal gyrus (BA9/10/11)	32	64	−8	3.94	R
Hippocampus	−16	−22	−10	3.89	L
Inferior frontal gyrus (BA47)	26	32	−18	3.83	R
	−44	42	−4	3.41	L
Inferior temporal gyrus	−34	−8	−28	3.67	L
Parahippocampal gyrus	−24	−32	−10	3.61	L

Contrast of main effects

A contrast of the main effects revealed those regions which activated significantly more in response to a painful tactile probe touching the rubber hand vs. an innocuous tactile probe (and *vice versa*) either with the rubber hand in a spatially compatible (Experiment 1) or incompatible (Experiment 2) position with respect to participants' own right hands. Viewing a painful vs. innocuous tactile stimulus touching the rubber hand with the hand in a spatially congruent position [i.e., Congruent (VP – VN)] revealed significant contralateral activation of superior and inferior parietal cortices, superior

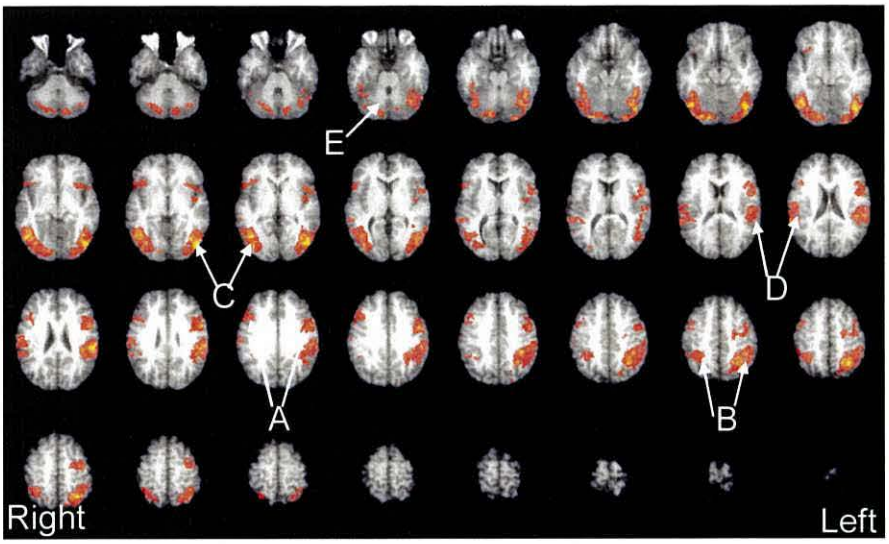


Figure 4. Activation map illustrating a significantly greater response to viewing the innocuous tactile probe applied to the rubber hand when the hand was in an anatomically plausible position (with respect to the participants' real hand) versus rest (no stimulation). Maps were cluster-based thresholded at z ,2.3, $P < 0.05$ (corrected for multiple comparisons) and are shown in axial sections across the whole brain starting at the level of the brain stem (moving from left to right across the page in 4 mm slices) in radiological convention (right side of the brain on the left side of the picture). A = Premotor cortex; B = Superior parietal lobe; C = Temporal-occipital cortex; D = Inferior parietal lobe; E= Cerebellum.

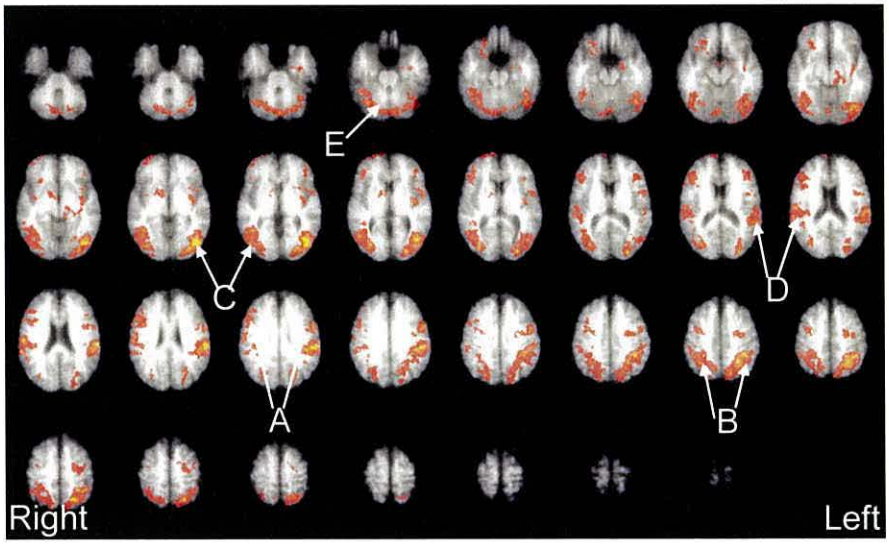


Figure 5. Activation map illustrating a significantly greater response to viewing the innocuous tactile probe applied to the rubber hand when the hand was in an anatomically implausible position (with respect to the participants' real hand) versus rest (no stimulation). Maps were cluster-based thresholded at $z < 2.3$, $P < 0.05$ (corrected for multiple comparisons) and are shown *(Figure 5 caption continued)* in axial sections across the whole brain starting at the level of the brain stem (moving from left to right across the page in 4 mm slices) in radiological convention (right side of the brain on the left side of the picture). A = Premotor cortex; B = Superior parietal lobe; C = Temporal-occipital cortex; D = Inferior parietal lobe; E = Cerebellum.

temporal gyrus and sulcus and fusiform gyrus (BA19). Bilateral activation was observed in the VI lobe of the cerebellum,anterior cingulate cortex (BA24) and medial and superior frontal gyri (BA6) (Table 3; Figure 6). With the rubber hand in a spatially incongruent position with respect to participants' own hands [i.e., Incongruent (VP – VN)] significantly greater activation was seen in response to the painful tactile stimulus vs. the innocuous stimulus ipsilaterally in right putamen, superior temporal gyrus and anterior insula (Table 3).

At the cluster-based threshold tested ($Z = 2.3$, $P < 0.05$) no regions demonstrated significantly more activation to the innocuous tactile stimulus vs. the painful stimulus applied to the rubber hand in either a spatially congruent or incongruent position.

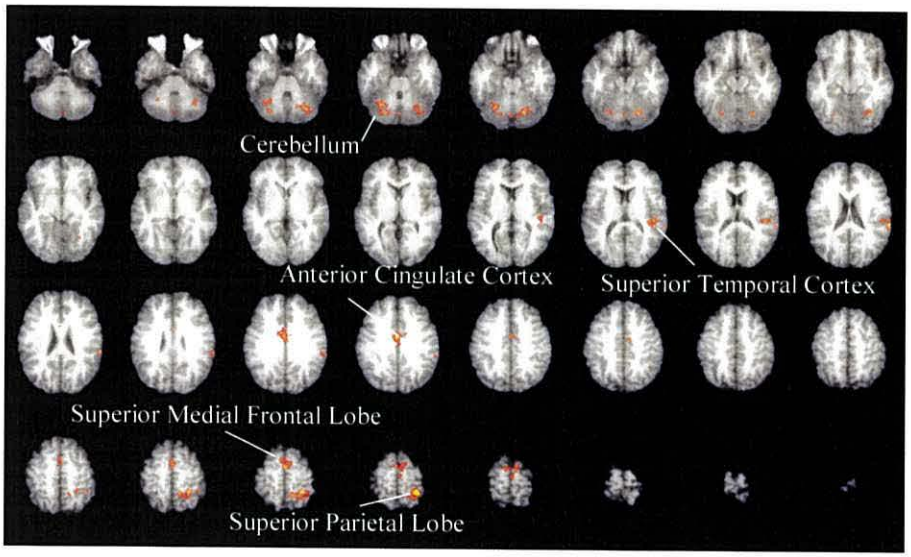


Figure 6. Activation map illustrating a significantly greater response to viewing the painful tactile probe applied to the rubber hand when the hand was in an anatomically plausible position (with respect to the participants' real hand) versus the *innocuous* tactile probe. Maps were cluster-based thresholded at $Z < 2.3$, $P < 0.05$ (corrected for multiple comparisons) and are shown in axial sections across the whole brain starting at the level of the brain stem (moving from left to right across the page in 4 mm slices) in radiological convention right side of the brain on the left side of the picture).

Discussion

The major outcome of the current study was that regions of the contralateral posterior parietal cortex (surrounding the intraparietal sulcus) discriminated between painful and non-painful stimulation of a rubber hand in participants' peripersonal hand space. Preferential activation in response to viewing the sharp (painful) stimulus compared to the blunt (non-painful) stimulus contacting the fingers of the rubber hand (in the absence of actual tactile input to the real hand and with the rubber hand in an anatomically plausible position) was seen in superior parietal (BA5/7) and inferior parietal (BA40) cortices. Other areas showing similar BOLD signal modulation included mid-cingulate and superior-medial frontal lobe, the cerebellum, and the fusiform and superior temporal gyri. On the basis of these results, we propose that the response of the posterior parietal cortex points to its role in the visuo-spatial encoding of noxious threats, operating alongside other motivational, proprioceptive, and movement-related areas in representing motivationally-significant aversive events.

The posterior parietal cortex and noxious threat representation

A primary function of posterior parietal cortex is the integration of visuospatial and somatosensory information to shape an appropriate motor response (for a recent account see Grefkes & Fink, 2005). In the monkey, the inferior and superior posterior parietal areas chiefly receive visual inputs from striate cortex, but are also the first regions along the dorsal visual stream to

integrate these retinally-derived signals with other sensory signals (such as somatosensory and proprioceptive afferents) to form a higher-order representation of visual space (Driver & Mattingley, 1998). Rizzolatti (Rizzolatti & Matelli, 2003) has proposed a separation of the dorsal stream parietal areas into two distinct 'sub-streams', ventral and dorsal. In particular, the ventral part of the dorsal stream is comprised of inferior parietal regions (PF and PG) and supports visual representations of space for the purposes of organizing action. These regions have also been associated with action intention (Andersen & Buneo, 2002) and are extensively connected with frontal premotor areas (Rizzolatti, Fogassi, & Gallese, 2002; Rizzolatti et al., 2003; Shipp, Blanton, & Zeki, 1998).

The inferior parietal area observed in our study is in the region of the human homologue of monkey areas PF and PG, which play just such a role in the organization of action with respect to objects in space. Although posterior parietal processing is mainly insulated from semantic information about objects from the ventral visual stream, studies of human neglect patients have indicated that inferior parietal cortex is itself involved in implicit visual awareness of objects in the context of movement planning (Marshall & Halligan, 1988; Rizzolatti & Berti, 1990). We therefore suggest a role for the inferior parietal area in the motivational response to threatening stimuli visually encoded in peripersonal space.

Besides its role in integrating visual responses to objects in peripersonal

space, in humans, posterior parietal damage can alter pain sensation, sometimes resulting in hypoalgesia and asymbolia for pain (Berthier, Starkstein, & Leiguarda, 1988; Greenspan & Winfield, 1992). Microstimulation in an epilepsy patient has been observed to evoke a painful somatosensory aura (Salanova, Andermann, Rasmussen, Olivier, & Quesney, 1995). So far, however, very little is known about the role of the human posterior parietal cortex in processing *visual* information about pain yet there is evidence that visuo-tactile receptive fields in monkey inferior parietal and intraparietal cortex are sensitive to both tactile and visual information about noxious stimuli (Dong et al., 1994). In these areas, the visual receptive field is bound to the space surrounding the tactile receptive field, *e.g.* the hand or face. In the macaque, one study showed that a proportion of cells in inferior parietal area PF fired both when skin on the face was stimulated with noxious heat, and when the monkey viewed a threatening stimulus coming towards or hovering near that part of the skin (Dong, Hayashi, Roberts, Fusco, & Chudler, 1996). Furthermore, the responses of these cells closely matched the behavioural response curves for a tolerance-escape task the monkeys performed. Similarly, cells in nearby ventral intraparietal area (VIP) have also shown specifically nocifensive properties. Microstimulation here has produced eye, lip, and arm movements comparable to those elicited by an aversive airpuff into the eyes (Cooke et al., 2003).

A possible visuo-spatial network for motivational relevance

Here we postulate a possible network for the visuo-spatial encoding of aversive stimuli. The overarching feature of this network is the encoding of visuospatial information in body-part-centred terms, for the ultimate purpose of organizing effective action away from the aversive stimulus. The main functional components of this network are: 1) body-part-centred encoding of the space surrounding the hand (in our study, the interpretation of 'rubber hand space' as peripersonal hand space) 2) discriminating the motivational relevance of objects in that space (here, whether the probe was noxious or innocuous); and 3) elaborating the motivational-affective sensorimotor representation of the stimulus in terms of appropriate motor responses.

The object in hand space becomes incorporated into the body schema in the sense that the space surrounding the rubber hand is interpreted as that surrounding the real hand. Under normal circumstances, proprioceptive and tactile input from one's real hand would be in register with the visual information about hand position. In this study, we highlighted the visual, not the tactile, component of the representation of hand space by using a rubber hand that occluded the real hand from view. Because vision often dominates touch in cases of multisensory spatial conflict it is very likely that objects within this surrogate hand space were interpreted by posterior parietal visual areas as being near the real, proprioceptively-sensed hand and thus processed in hand-centred terms. Studies in monkeys and humans have shown this peripersonal space around the hand to be dynamic, extending a virtual body envelope around not only the hand but also non-body objects within it, such

as tools (Maravita, Husain, Clarke, & Driver, 2001; Maravita, Spence, Kennett, & Driver, 2002; for an alternative view see Holmes, Calvert, & Spence, 2004), artificial limbs (Botvinick et al., 1998; Graziano, Cooke, & Taylor, 2000; Pavani et al., 2000), and even the adjacent tabletop (Armel et al., 2003).

An element of this body-schema incorporation depends merely on there being an object within peripersonal hand space. The main effects (Tables 1 and 2) revealed a contralateral parietal opercular cluster (BA40) and an ipsilateral superior parietal area (BA7) which did not differentiate between a hand that was oriented in an anatomically plausible way and one that was rotated 180 degrees. However, other pain-preferring posterior parietal areas were sensitive to the orientation of the hand. This is consistent with monkey studies in which individual neurons' responses to a plausible artificial limb decreased when the anatomical plausibility was violated or when the object did not resemble a hand (Graziano, 1999; Graziano et al., 2000). The parietal opercular area also showed a significant response to viewing the non-painful tactile stimulus, but both posterior parietal areas showed significantly higher responses to the painful as compared to the non-painful stimulus (Table 3).

Another such posture-sensitive activation was seen in the cerebellum, which is, amongst other things, heavily implicated in position sense as well as in nociception (for a recent review see (Saab & Willis, 2003). Major afferents to the cerebellum come from inferior parietal cortex and cingulate gyrus. It also receives visual projections from two ventral-stream areas that

differentiated between painful and nonpainful stimuli: extrastriate area 19, and the suprasylvian fissure (Saab et al., 2003).

According to Blakemore and colleagues (Blakemore, Frith, & Wolpert, 2001), the cerebellum uses a forward model to compare the predicted consequences of an action to the actual result of an action and updates the prediction accordingly. In order to do this they suggest that activity in the cerebellum depends on the sensory-specific consequences of movement and signalling the sensory discrepancy between predicted and actual sensory feedback. For example, the cerebellum may be involved in signalling the discrepancy of seeing a painful probe touch the rubber hand, which the participant has incorporated into his/her own body representation, but not feeling any painful tactile sensation resulting from the probe touching the skin.

Relationship with classical motivational-affective networks

Beyond its initial visuo-spatial representation, the relevance of the object in hand space is evaluated in motivational terms. Our results suggest that posterior parietal regions are capable of discriminating between painful and non-painful stimuli. Other areas conventionally associated with the motivational and affective evaluation of aversive stimuli were also preferentially active to the painful stimulus. It is interesting that two of these, the putamen and right anterior insula, preferred the implausible orientation. The putamen and anterior insula have often been reported in neuroimaging

studies of pain (Bingel, Glascher, Weiller, & Buchel, 2004; Bowsher, Brooks, & Enevoldson, 2004; Brooks, Nurmikko, Bimson, Singh, & Roberts, 2002; Brooks, Zambreanu, Godinez, Craig, & Tracey, 2005) and the insula may have a unique role in empathy for pain (Decety & Jackson, 2004; Morrison *et al*, 2004; Singer *et al*, 2004). If the representation of aversive events in the anterior insula and putamen is not strictly bound to visuo-spatial and visuo-tactile coherence, it may not be 'tricked' by seeing the rubber hand receiving noxious stimulation in this context.

Alongside the posterior parietal areas, the anterior cingulate activations revealed by the contrast between painful and non-painful stimuli (Figure 6) are of particular interest. The anterior cingulate cortex focus seen in this study is well-positioned to correspond to cingulate motor zones (CMZs) as determined by human functional and cytoarchitectonic studies (Vogt, Berger, & Derbyshire, 2003; Vogt & Sikes, 2000). The CMZs receive dense projections from inferior parietal lobe in monkeys and humans (Isomura & Takada, 2004; Matelli, Luppino, & Rizzolatti, 1991; Strick, Dum, & Picard, 1998). The nociceptive function of these mid-cingulate areas is well established (Sewards & Sewards, 2002; Vogt *et al*, 2000). The focus seen in this study was in a posterior mid-cingulate region that is thought to play a role in short-latency sensorimotor orienting to painful stimuli, perhaps utilizing spatial information from its parietal inputs (Vogt *et al*, 2003). In the monkey, CMAs send fibres to premotor and primary motor cortices, as well as having direct projections to dorsal horn motorneurons in the spinal cord (Isomura *et*

al, 2004; Matelli *et al*, 1991; Paus, 2002). The motor areas show moderate somatotopic organization for trunk and distal and proximal limbs, and representations of cutaneous as well as skeletal muscles have been observed here in the macaque (Akazawa *et al*, 2000).

CMZs in posterior mid-cingulate are considerably more interconnected with rostral mid-cingulate regions, which also fall within the cluster significantly activated for the painful stimulus. Whereas CMZs have predominantly premotor properties, these nearby mid-cingulate areas are also associated with the motivational-affective dimension of pain processing (Price, 2000; Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Sewards *et al*, 2002) and response selection (Hoshi, Sawamura, & Tanji, 2005; Isomura *et al*, 2004). In that context their role is tied to the ability to link events with outcomes, allowing the prediction and avoidance of noxious stimuli. Both CMZs and adjacent rostral mid-cingulate are characterized by dense fast excitatory (NMDA) and inhibitory (AMPA) receptor types (Bozkurt *et al*, 2005). It is therefore possible that the activity observed in the BOLD signal change in this region is due to the facilitation of an appropriate response to a threat in hand space, but by the same token it may reflect inhibition related to sensorimotor response potentiation.

In summary, we propose that posterior parietal areas play a role in immediate, reactive nocifensive responses. These responses are tied to specific effectors and are coded in an egocentric spatial reference frame. Via direct cortical connections they provide initial information to cingulate motor

and frontal premotor areas about the relevance of the stimulus. The mid-cingulate in particular may be involved in elaborating the representation of stimulus valence and is involved in more flexible motor response selection, learning, and regulation. Both mid-cingulate and prefrontal regions use contextual information and past experience to produce appropriate responses (Hadland, Rushworth, Gaffan, & Passingham, 2003; MacDonald, III, Cohen, Stenger, & Carter, 2000; Matsumoto, Suzuki, & Tanaka, 2003). The representation of pain in these areas is more flexible in the sense that they support a 'generative' (Haggard, 2001) representation of the noxious stimulus; that is, they incorporate factors such as current task constraints, motivational values, and past experience to produce behavioural outcomes that are not predictable from the nature of the stimulus alone. This representation is predictive, labile, and probably less immediately dependent on specific effectors or spatial information (Mesulam, 1999).

The role of premotor cortex

Contrary to our initial hypothesis premotor cortex did not significantly change its response to viewing a painful tactile stimulus touching the rubber hand despite the fact that this region was activated consistently in all conditions (see Tables 1 and 2 of main effects). Posterior parietal and frontal premotor areas of the primate brain share dense inter-projections forming well-studied functional circuits for the planning and control of action (*e.g.* Rizzolatti & Luppino, 2001). Despite several methodological differences,

there is good correspondence between the sites of premotor cortex activation in the current study and those found by Ehrsson et al., (Ehrsson *et al*, 2004). Ehrsson and colleagues used fMRI to explore the neural correlates of the rubber hand illusion with respect to the subjective sensation of limb ownership. The illusion was associated with activation along the left inferior precentral sulcus (BA44/6), the posterior bank of which corresponds to ventral premotor area 6 and the anterior bank to the posterior part of area 44. When the rubber hand was both plausibly oriented and synchronously stroked, the response in premotor cortex was superadditive, and correlated positively with subjective ratings about the strength of the illusion.

This region is well suited to the multisensory representation of one's own body as it is anatomically connected to visual and somatosensory areas in the posterior parietal cortex and to frontal motor areas (Rizzolatti *et al*, 1998). Cells in the parietal and premotor cortex have been shown to represent both the seen and felt position of the hand in both humans and non-human primates, discharging when the hand is touched or when a visual stimulus is presented near the hand (Lloyd *et al*,2003) (for a recent review see (Graziano *et al*, 2004). However, despite its sensitivity to multisensory proprioceptive and tactile input, we did not see any evidence for a differential response to painful and non-painful tactile probes touching the rubber hand using fMRI. However, the population response of cells in this region may have been too small to detect with fMRI and it would be premature to say that the premotor

cortex does not directly encode the biological relevance of stimuli touching or approaching the hand.

Conclusions

This study provides the first neuroimaging evidence of a role for human posterior parietal cortex in the visuo-spatial coding of the motivational relevance of events in hand space. We observed a significant increase in activation in this region in response to viewing painful (vs. innocuous) stimulation of the rubber hand (when in an anatomically plausible position) in the absence of tactile stimulation of the real hand. This is consistent with primate research which has shown similar preferential spatial encoding of noxious stimuli in posterior parietal areas, suggesting that homologous regions in the human brain may share similar functions in this regard. In our study, however, premotor areas associated with the subjective feeling of limb ownership did not discriminate between painful and non-painful stimuli. These results provide compelling hints of an integrative network supporting visuo-spatial and sensorimotor aspects of aversive events in the primate brain, which future research can explore.

CHAPTER V[1]:

RESPONSE-SPECIFIC EFFECTS OF PAIN OBSERVATION ON MOTOR BEHAVIOR

"Now someone tells me that *he* knows what pain is only from his own case!"

— Ludwig Wittgenstein, *Philosophical Investigations,* section 293 (2nd Ed., Blackwell, 1958)

[1] A version of this chapter is currently in press at *Cognition* as Morrison, I., Poliakoff, E., Gordon, L., and Downing, P.E., Response-specific effects of pain observation on motor behavior.

Chapter V: Response-specific effects of pain observation on behavior

Abstract

How does seeing a painful event happening to someone else influence the observer's own motor system? To address this question, we measured simple reaction times following videos showing noxious or innocuous implements contacting corporeal or noncorporeal objects. Key releases in a go/nogo task were speeded, and key presses slowed, after subjects saw a video of a needle pricking a fingertip. No such effect was seen when the observed hand was replaced by a sponge, nor when the needle was replaced by a cotton bud. These findings demonstrate that pain observation modulates the motor system by speeding withdrawal movements and slowing approach movements of the finger. This illustrates a basic mechanism by which visual information about pain is used to facilitate appropriate behavioral responses.

Chapter V: Response-specific effects of pain observation on behavior

Introduction

We wince when a doctor's needle breaks the skin, and even the mere prospect of a needle thrust into one's flesh is enough to make many people cringe. Evidence from clinical and experimental research indicates that experiencing pain indeed influences the motor system, at levels ranging from reflex action in the spinal cord to modulation in pain-related areas of neocortex. Motor responses to pain are thought to serve a protective function, whether it is to withdraw from an immediately offensive noxious stimulus or to restrict the movement of an injured body part (Farina, Tinazzi, Le Pera., & Valeriani, 2003; Le Pera, Graven-Nielsen, Valeriani, Oliviero, Di Lazzaro, Tonali, & Arendt-Nielsen, 2001; Millan, 2002).

But what happens to our motor system when we see a doctor brandishing a needle at someone else? It is possible that pain observation, like pain itself, modulates motor behavior. These effects may even specifically enable appropriate movements, for example the readiness to withdraw the hand or to avoid touching an object. Such an influence of pain observation on motor responses would suggest that our representation of others' pain is at least partly motoric. It would also support a perspective in which vicarious pain responses carry "selfish" heuristic advantages: motor representations accompanying pain observation could affect the observer's responses to potentially harmful situations (Avenanti, *et al,* 2005; Morrison, in press).

Despite accumulating evidence that experienced painful stimuli influence cortical motor systems, the nature of a similar influence during pain observation is currently unclear. Some research shows that pain

observation *inhibits* hand muscles via the cortical motor system (Avenanti *et al,* 2005). This is proposed to reflect diminished cortical-level excitatory interference in favor of spinal reflexes (Valeriani *et al,* 2001), possibly by massively "switching off" motoneuron pools in the affected limb in order to reduce the range of potential motor responses (Leis, Stokic, Fuhr, Kofler, Kronenberg, Wissel, Glocker, Seifert, & Stetkarova, 2000). Another proposition is that motor readiness is *facilitated* by pain observation. Some evidence supporting this perspective comes from research showing that experiencing pain can reduce withdrawal reflex latencies via mechanisms of descending facilitation (Calejesan, Kim, & Zhuo, 2000), originating in cortical areas such as the anterior cingulate cortex which also utilize pain-related visual cues in a context-dependent manner (*e.g.* Tang, Ko, Ding, Qiu, Calejesan, & Zhuo, 2005). A third possibility is that pain observation gives rise to complex patterns of facilitation and inhibition that vary according to the situation. Indeed, thus far research across species and methods has failed to demonstrate an invariant relationship between noxious stimulation and facilitation or inhibition of nociceptive or skeletomotor responses (Millan, 2002).

One approach to clarifying this in the case of pain observation is to measure the effect of pain observation on reaction times. No study to date has required participants to make overt movements following pain observation. In this experiment, we used a go/nogo reaction-time paradigm to explore how visual pain-related information contributes to the execution of motor responses at the behavioral level (Fig. 1). Reaction times were recorded after an interval (ISI) of 100 or 500 ms, following 1-

second video clips depicting needles pricking fingertips. Control clips depicted fingertips being touched by innocuous cotton buds, or sponges being touched with either needles or cotton buds. Button presses (approach movements) were compared to button releases (withdrawal movements; Wentura, Rothermund, & Bak, 2000). We predicted that pain observation would not only influence reaction times, but would do so in a context-specific manner. That is, reaction times should decrease for withdrawal movements relative to approach movements, in response to viewing noxious compared to innocuous stimuli. This would support the hypothesis that pain observation influences the motor system in a response-specific manner.

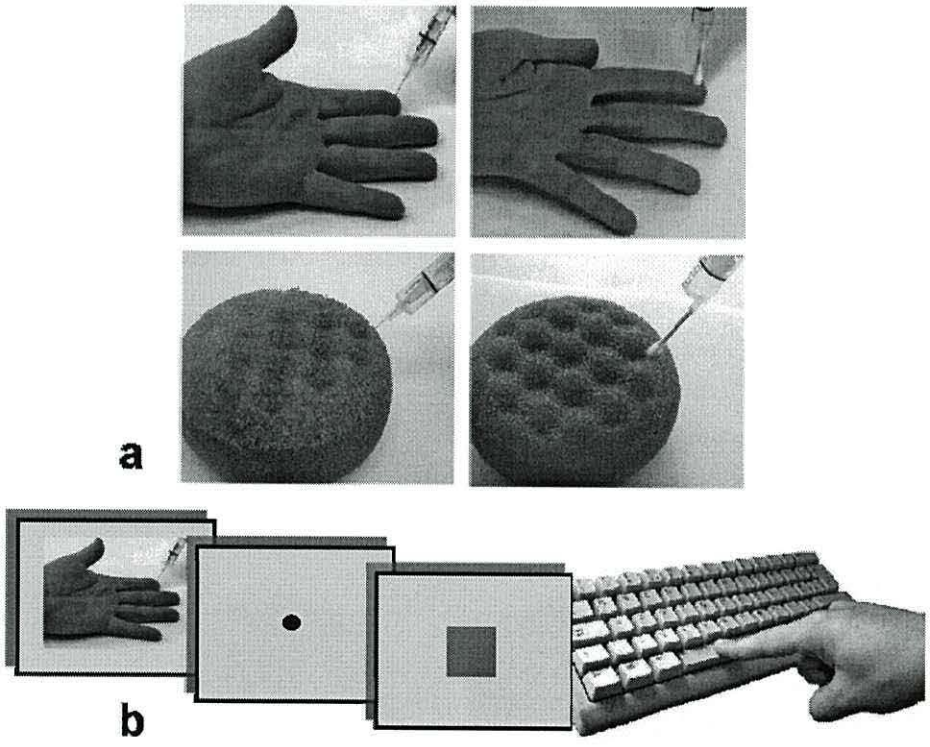


Figure 1. Stimuli and trials. *a)* Clockwise from top left: example still frames from hand and needle video; hand and cotton bud; sponge and cotton bud; sponge and needle. *b)* Sequence of events in trial: 1000 ms video clip depicting one of four target-implement combinations, 100 or 500 ms ISI, signal indicating go or nogo response, and participant's response by either pressing or releasing a button.

Methods

Participants

Twenty-four right-handed female undergraduate volunteers (mean age 19) from the University of Manchester (N=17) and University of Wales Bangor (N=7), with normal or corrected-to-normal vision, participated in this study. Female students were recruited in order to reduce well-established gender variability that exists among pain, empathy, and fear measures. One subject's data were excluded due to exceeding a limit of 20% errors.

Materials

There were 20 different hand movie clips, 10 of which depicted hypodermic needles pricking the fingertips and 10 in which the lancet was replaced by a cotton bud (see Fig. 1). The perspective on the hand, the implement's angle of approach, and the finger stimulated (index, middle, ring, pinky) were varied. In each clip the participants' view of the hand was allocentric, *i.e.* as if it were another person's hand, at angles from +90° to -90° relative to the viewer's position. The 20 sponge clips (10 needle, 10 cotton bud) similarly varied the angle at which the sponge was seen. The moment of contact between the implement and the target came at approximately 600 ms into each 1-second clip. Stimuli were presented using Presentation 9.10® software on a 43-cm PC screen at a viewing distance of 61 cm.

Chapter V: Response-specific effects of pain observation on behavior

Design

The experiment was a 2x2x2x2 factorial within-subjects design. The four factors were: a) target (hand or sponge), b) implement (noxious or innocuous), c) interstimulus interval (100 or 500 ms), and d) response type (press or release).

Procedure

During each trial, subjects saw a 1-second video depicting either a hand or a sponge, which was shown being either punctured by a needle or touched by a cotton bud (see Fig. 1). After each video, participants fixated centrally for either 100ms or 500ms awaiting a go or nogo signal (a blue square for go, an orange square for nogo). Participants were instructed to alternate between press and release responses from go trial to go trial (*eg*, if they had pressed the button in the previous go trial they left it pressed down and then released it to respond in the next go trial).

The percentage of go trials was 80% (320/400 trials). There were eight blocks, each consisting of 50 trials. The conditions were presented in pseudorandom order within blocks and counterbalanced across blocks to ensure equal representation of each stimulus type among go and nogo trials.

Prior to testing, each participant also completed Balanced Emotional Empathy Score questionnaire (BEES; Mehrabian & Epstein, 1972). An example question is: *"I get a strong urge to help when I see someone in distress."*

Results

Mean errors did not exceed 3% in any of the eight conditions. The mean correct response times were submitted to a 2x2x2x2 repeated measures ANOVA with four within-subject factors: target, implement, ISI, and response type. There was a significant four-way interaction among these factors, $F(1,23) = 6.3$, $p = .02$ (Fig. 2).

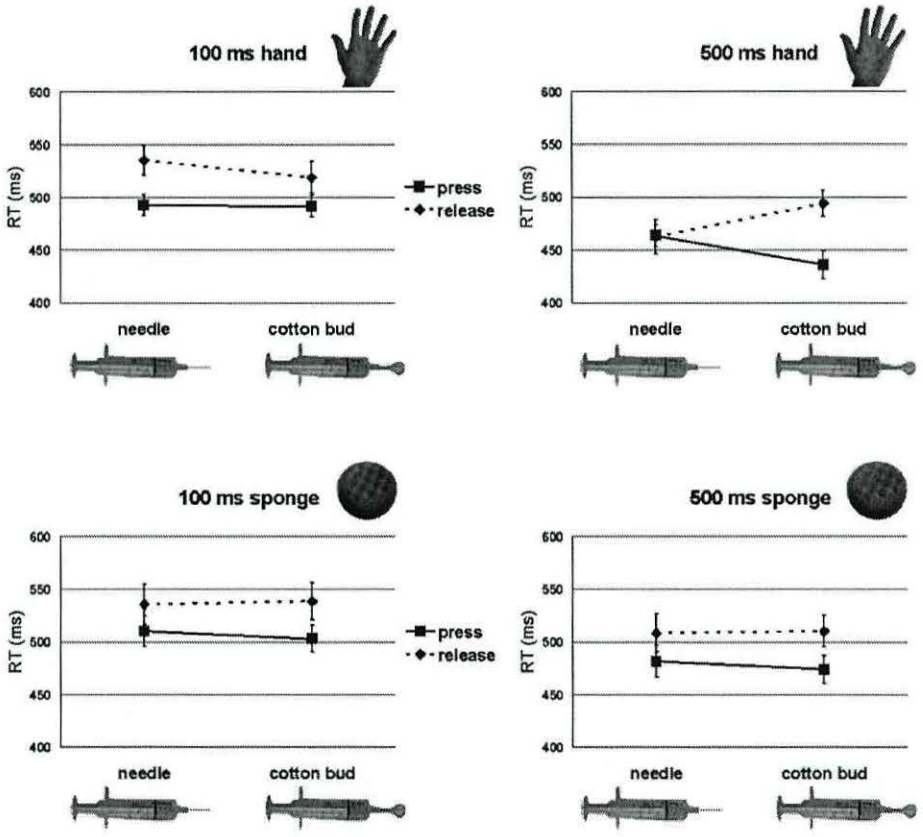


Figure 2. Mean reaction times across ISI (100 or 500 ms), target (hand or sponge), implement (needle or cotton bud), and response (press or release). A significant main effect of response driven by generally faster presses was present in all conditions, except when needles punctured a fingertip at 500 ms (upper right panel). Here, responses following pain observation resulted in an interaction between implement and response for hands, $F(1,23) = 7.84$, $p = .01$. In the 500 ms hand conditions only, releases were faster for needles and slower for cotton buds, with presses showing the opposite pattern (see *Results*).

To investigate this interaction further, three-way ANOVAs were performed for the 100 and 500 ms ISI conditions separately. These analyses revealed a significant three-way interaction in the 500 ms conditions (F (1,23) = 5.14, p = 0.033), but not in the 100 ms conditions (F (1,23) = 1.46, p = 0.23), in which there was only a significant main effect of response type (press or release), F (1,23) = 12.19, p = .002. Two separate two-way ANOVAs were then carried out for each target type (hand or sponge) at 500 ms ISI (see Fig. 2). In both analyses, there was a significant main effect of response type (press or release), all Fs (1,23) > 10.15, all ps < 0.004, with press responses overall faster than release responses. However, the only significant two-way interaction between implement and response was found in the hand condition at 500 ms ISI, F(1,23) = 7.84, p = 0.01. There was no corresponding significant two-way interaction in the sponge condition, F (1,23) = 1.101, p = 0.305. The interaction between implement and response for hands at 500 ms reflects the fact that the RT advantage for presses over releases found in all other conditions was absent when a needle was seen contacting a hand at 500 ms ISI, t(23) = -0.156, p = 0.87. This effect was driven by a significant speeding of releases (t (23) = -2.26, p = 0.034, mean effect 31.5 ms) and a significant slowing of presses (t (23) = 2.52, p = 0.019, mean effect 27.7 ms), for needles relative to cotton buds.

To test for an effect of viewed finger compatibility in the critical 500 ms needle and hand conditions, response times for trials in which the stimulated finger in the video was the same as, or different from, the response finger (index) were submitted to a three-way ANOVA with

finger, implement, and response as factors. The viewed finger did not interact with the response and implement factors, $F(1,23) = 0.093$, $p = 0.763$, suggesting the effect of observing a needle piercing a finger is not specific to actions made with the same finger.

A reaction time measure of participants' readiness to press the button in the critical 500 ms needle and hand conditions was calculated as the difference between presses and releases. This measure showed a significant positive correlation with scores on the BEES empathy questionnaire (Mehrabian & Epstein, 1972), $r = 0.43$, $p = 0.03$, two-tailed. This correlation was not seen in the other conditions (all ps > 0.05).

Discussion

This experiment demonstrates a specific influence of pain observation on overt motor responses. After viewing a video in which a needle pricked a finger, participants' withdrawal movements were speeded and approach movements were slowed. However, this interaction between implement and response was only seen when the target of the needle was a hand, and not a non-body object (sponge). It was also seen only after a 500 ms interstimulus delay, but not after a shorter delay of 100 ms. In all other conditions, the press response was faster than the release response (Fig. 2). These results suggest that visual social information about potential injury influences situation-appropriate behavioral responses.

The outcome of this study raises several intriguing questions about the nature of pain observation's influence on the motor system, and its implications for social cognition. First, are such responses immediate and automatic, or are they more likely to be context-dependent and mediated

by other cognitive factors? Second, are there generalizations that can be made about whether pain observation facilitates or inhibits the motor system? Finally, could there be a relationship between the motor effects seen here and empathy?

The sensitivity of reaction time patterns to the presence of a body part and to whether the required movement brought the finger towards or away from the visual stimulus suggests some degree of context-dependence in the processing of the response. This is consistent with an ecological interpretation in which the sight of a sharp implement interacting with a hand could present the observer with information about the potentially harmful outcome of touching the noxious object. This may involve facilitation of motor responses that would be appropriate for avoiding or withdrawing from the object. In this sense, observation of others' injury may bear a similarity to action affordances, in which the visual features of a perceived object (for example, a mug with its handle turned towards the subject) facilitate specific, compatible motor acts (for example, grasping the handle; Tucker & Ellis, 1998; Phillips & Ward, 2002). By the same token, pain observation may elicit "aversive affordances", visuomotor mappings that could play an important role in the guidance of behavior (see also De Houwer, Crombez, Baeyens, & Hermans, 2001).

The lack of an interaction in the 100 ms ISI conditions raises the question of whether any such affordance-like visuomotor mappings would occur as an immediate, direct route for action during pain observation, or whether other time- or task-dependent factors can influence the response. The present experiment cannot address this directly, because the video

clips were task-irrelevant and reaction times were measured only with respect to the go signal. It is possible, though, that any initial response may be suppressed, attenuated, or even elaborated by top-down processes that depend on task factors and the length of the interval by which the video clip is followed by the go signal. Comparable timecourse effects have been observed for action affordances (see Phillips & Ward, 2002).

Yet regardless of the temporal development of the underlying processing, would pain observation always be expected to *facilitate* movement? Recent TMS studies have shown that pain observation selectively *inhibits* the relevant muscles of the hand (Avenanti *et al,* 2005, Avenanti *et al,* in press). After watching a needle inserted deep into either a hand's first dorsal interosseus muscle (between index finger and thumb) or abductor digiti minimi muscle (on the side of the hand adjacent to the little finger), significant motor evoked potential (MEP) amplitude decreases were specific not only for the body part observed but for the particular muscle observed, compared to a non-body object (tomato) or an innocuous cotton bud control. In both direction and magnitude, the decrease in MEP amplitude during pain observation resembles the response to directly-experienced painful stimuli (Farina *et al*, 2003; Le Pera *et al,* 2001). This widely-observed MEP decrease has been interpreted as indicative of motor cortex inhibition of the distal muscles, possibly reflecting a freezing response.

Whereas studies using MEP measures with TMS show motor cortex inhibition during pain and pain observation, our behavioral study shows that approach-type button presses and withdrawal-type button releases are

differentially affected rather than being uniformly inhibited. This underscores the potential importance of context and task requirements on such responses. Unlike the TMS study discussed above and those in which pain is directly experienced on the hand, the experiment described here explicitly required motor responses and the stimuli were viewed in the context of producing a finger movement. In these circumstances inhibitory and facilitory influences of pain observation may be tailored to particular responses.

This is consistent with findings showing that complex interactions between arm and hand muscles can be instigated by cortical motor systems during pain itself (Urban, Solinski, Best, Rolke, Hopf, & Dieterich, 2004), and that distal motor responses to pain are under constant influence of descending mechanisms of facilitation and inhibition (Millan, 2002). Such considerations notwithstanding, both the behavioral and TMS results can be interpreted in terms of a broad defensive/protective role of motor responses to real or potential pain. For example, in the presence of actual or potential pain in distal effectors such as the hand, an interruption of prehension would be adaptive (Farina *et al*, 2003).

The response-specific effect of pain observation on overt movements helps to delineate further related hypotheses about aspects of the processing underlying the perception-response link. In particular, this finding now paves the way for exploring levels of goal, effector, and fine somatotopic specificity. For example, at what level is the perception-response link encoded? The overt movement may be influenced more by

the "goal" of avoiding the visual stimulus location regardless of effector used (*eg* foot or hand) or finger position (*eg* moving the finger away *vs* towards it). Alternatively, it may be the case that pain observation is effector-specific, or consistently "freezes" only the extensor muscles, even in circumstances where flexion would be more appropriate to avoid the stimulus.

Taken together, the differentiation between press and release responses shown in the present study, alongside the muscle specificity in that of Avenanti *et al,* implies that the influence of pain observation on motor processing is more complex than an unmediated, muscle-general retraction reflex. For overt responses, though, the degree of refinement of any somatotopic mapping awaits further investigation. Press and release responses in this study were made with the index finger, while the videos featured stimulation to a variety of fingers. However, we found no interaction between the finger viewed (index or other) and the factors of implement (needle or cotton bud) and response (press or release). An experimental design explicitly designed to address the behavioral impact of observing specific effectors or fingers being painfully stimulated (for example, in an interference paradigm) may effectively capture any somatotopic effects in pain observation.

The response-specific effects of pain observation could reflect the motoric output of a process evaluating the motivational significance of the stimulus. These results are not sufficient to establish any relationships of antecedence between affective-evaluative and motor processes. Yet they do indicate that such affective-motor processing may not be limited to

circumstances in which the observer could be harmed directly. Visual information about potential harm to others may also be sufficient to modulate appropriate motor responses on the part of the observer.

This could be interpreted as a basic mechanism contributing to an ability to empathize. Recent neuroimaging research has suggested that some of the same brain areas underlying motivational-affective components of pain processing are also active during pain observation (Morrison *et al,* 2004; Singer, *et al,* 2004; Jackson, *et al,* 2005; Lloyd *et al,* 2006; Chapter IV). These include medial areas associated with motor response preparation, notably dorsal anterior and midcingulate cortices and adjacent supplementary and pre-supplementary motor areas. It is possible that empathy relies in an important way on mechanisms that couple affective visual information with appropriate behavioral output, either covertly or overtly. Indeed, the positive correlation between reaction times (press-release differences for needles and hands at 500 ms) and scores on the BEES empathy questionnaire supports this possibility.

However, we wish to make a distinction between *pain empathy* and *pain recognition.* We regard pain empathy as a compassionate affective state which the observer experiences on behalf of the sufferer, and which may result in prosocial actions. The results of the present study do not address this subjective feeling of empathy. Rather, we believe that the influence of pain observation on motor responses seen here reflects *pain recognition*, a basic appraisal of the pain-related nature of the sufferer's situation. Although pain recognition may be necessary for empathy, it is not sufficient for it, and may occur independently of empathy in day-to-

day contexts. Nevertheless, pain recognition may involve affective evaluation and motor response modulation, as our results suggest (see also Gallese, 2003, and Preston & de Waal, 2002, for related neuroscientific and ethological perspectives on empathy).

In conclusion, this experiment demonstrates for the first time that pain observation influences behavior in a response-specific manner. By using reaction times as a measure of readiness to press or release a button, this study adds to evidence that pain observation, like pain itself, affects motor processing. So although the doctor's needle sinks into someone else's arm, not yours, modulation of your motor system by pain-relevant visual information could contribute to the way you evaluate the risk of potential harm in that situation— perhaps influencing your own behavioral response to the object.

CHAPTER VI[1]:

SEEING OTHERS' PAIN MODULATES MOTOR PROCESSING IN CINGULATE CORTEX

"...may pain and pleasure, success and failure, shift as they will—
It's only action that can make a man."

— Goethe, *Faust,* Part I, chapter iv (Faust's Study— "The Contract")
translated by Randall Jarrell

[1] This chapter is a draft of a manuscript currently in preparation: Morrison I., Peelen, M.V., and Downing, P.E., The sight of others' pain modulates motor processing in human cingulate cortex.

Abstract

Neuroimaging evidence has shown that dorsal anterior cingulate and midcingulate areas respond to both felt and seen pain. These regions are involved in preparing context-appropriate motor responses to painful situations, but it is unclear whether the same holds for observed pain. Participants in this fMRI study viewed short animations depicting contact between a noxious implement (*eg* sharp knives, hammers) or an innocuous implement (*eg* butter knives, wooden spoons) and a hand. Participants were required to execute or suppress button-press responses depending on whether the implements hit or missed the other person's hand. The combination of the implement's noxiousness and whether it contacted the hand strongly affected reaction times, with the fastest responses to noxious-hit trials. BOLD signal changes mirrored this behavioral interaction with increased activation during noxious-hit trials in midcingulate, dorsal anterior, and dorsal posterior cingulate regions. The potentially harmful content of noxious-hit animations influenced hemodynamic responses in these regions despite its task-irrelevance and the fact that participants did not themselves stand to experience pain during the experiment. Crucially, the activations also depended on whether the subject made an overt motor response to the event, linking these cingulate regions' role in pain observation to their role in motor processing.

Introduction

When we see someone cut their finger, bump their knee against a coffee table, or get their hand caught in a closing door, we often flinch as if we ourselves were reacting to the pain. Shared neural processes between feeling and seeing pain may underlie our ability to empathize with others' distress. Cognitive neuroscience has recently begun to explore empirical and theoretical aspects of this possibility (Preston & de Waal, 2002; Gallese, 2003; Decety & Jackson, 2004, Avenanti *et al,* 2005, 2006; Blair, 2005; Lawrence, 2006; Singer & de Vignemont, in press; Lamm, Batson, & Decety, in press). In particular, neuroimaging investigations have shown that pain-related motivational-affective regions, notably the anterior and mid-cingulate cortex (ACC and MCC) and anterior insula, are activated by pain observation (Morrison *et al,* 2004; Singer *et al,* 2004; Jackson *et al,* 2005 2006; Botvinick *et al,* 2005; Saarela *et al,* in press, Lamm *et al,* in press). This research suggests that areas coding the unpleasant aspects of pain might also contribute to a "secondhand" understanding of others' pain.

However, the precise functional role of these areas during pain observation remains unclear. The implicated areas include medial frontal regions such as the MCC and supplementary and pre-supplementary motor areas (SMA and pre-SMA), which are of especial interest not only because they are involved in the processing of acute pain (eg, Peyron 2000), but also because of their established roles in premotor processing and the selection and organization of movements (Matelli *et al,* 1991; Rushworth *et al,* 2004; Russo *et al,* 1998; Morecraft & van Hoesen, 1997).

Since skeletomotor movement representation is a crucial component of the motivational-affective representation of pain itself (Seward & Seward 2002; Vogt *et al,* 2003; Ruehle, Handwerker, Lennerz, Ringler, & Forster, 2006), it may also be central to pain observation. An intriguing possibility is that these medial areas may contribute to the recognition of others' distress partly through engaging appropriate movements of aversion during pain observation (Morrison *et al* 2004; Morrison, in press, Morrison *et al,* in press; Amodio & Frith, 2006).

The premotor properties of midcingulate areas, then, may be quite crucial in this regard for several reasons. First, the neural mechanisms underlying pain recognition may be functionally similar to those supporting action recognition in lateral premotor areas, with observation eliciting "mirror" responses in regions of the brain closely co-localized and functionally-allied with those involved in first-person action representation (Rizzolatti *et al,* 1996; Hutchison *et al,* 1999; Gallese *et al,* 2004). It has been proposed that pain recognition and empathy similarly rely on such other-to-self translations in the emotional or motivational-affective dimension of pain processing (Gallese, 2003; Morrison *et al,* 2004; Singer *et al,* 2004). Second, in everyday life, we are able to recognize others' injuries as being of a painful nature, even if our emotional reaction is minimal or nonexistent. This implies that mechanisms exist which support recognition of others' pain without necessarily instigating a full-blown compassionate response. Such mechanisms may predict the probable aversive consequences to the

observed event in a manner comparable to mirror-system involvement in predicting action outcomes.

Midcingulate areas therefore provide the focus of this fMRI study not only because they are involved in the motivational-affective dimension of pain and pain observation, but also because they have been characterized as medial premotor areas on the basis of functional and anatomical criteria in human and nonhuman primates (Matelli *et al,* 1991; Koski & Paus, 2000). This region contains the cingulate motor zones (Paus *et al,* 1993; Picard & Strick, 1996) which have reciprocal connections with one another as well as with other premotor areas. It also has direct and indirect outputs to primary motor areas and to the spinal cord (Morecraft & van Hoesen, 1997). The midcingulate responds to noxious stimulation of the skin and muscle (Akazawa *et al*, 2000). It has also been associated with skeletomuscular movements of aversion, with intracortical microstimulation producing distal and proximal limb movements (Isomura & Takada, 2004).

That pain observation systematically influences motor processing is suggested by evidence from motor-evoked potential (MEP) and behavioral studies. The stimuli used in these studies involved noxious implements hitting another person's hand, so the motor-specific responses seen in them are also associated with the convergence of noxiousness and contact. Avenanti *et al* demonstrated effector-specific, muscle-specific (Avenanti *et al*, 2005) and intensity-dependent (Avenanti *et al*, in press) MEP amplitude decreases in cortical motor excitablity, resembling the effects of directly-experienced pain on MEP measures (Farina *et al,* 2003; Le Pera *et*

al, 2001). Similarly, behavioral data show a specific influence of pain observation on *overt* motor responses (Morrison *et al*, in press; chapter V). Following task-irrelevant videos in which a needle pierced a finger, participants' withdrawal-type key-release movements were speeded and approach-type key-press movements were slowed, after an interval in a go-nogo task. Taken together, this evidence indicates that visual information about another person's potential injury influences one's own situation-appropriate overt behavioral responses in a movement-specific manner, and motor cortex excitablity in a somatotopically-organized manner.

In this fMRI study, we examine the relationship between pain observation and movement-related processing in cingulate areas. No study to date has attempted to explore the movement-related properties of these motivational-affective areas during pain observation. To do this, we scanned people as they observed pain during a task requiring them to execute or suppress overt motor responses. Participants viewed short 2-frame sequences in which a potentially harmful object (like a knife or hammer) comes into contact with, or nearly misses, a hand. Visually-similar innocuous objects were presented as control events (Fig. 1). In order to test any modulatory effect of pain observation on motor response selection, in separate blocks subjects responded with a button press either to object-hand contact events (hits) or to miss events (misses), with the noxiousness of the object always remaining a task-irrelevant factor.

We hypothesized that in order to encode a visual event as painful, the brain must track a combination of key factors: the noxiousness of the

object and the contact it makes with the body part. We predicted that cingulate areas that are modulated by both these factors in combination are also modulated when motor responses are overtly executed. Because midcingulate and related medial areas are associated with both pain-related and premotor properties, the three factors of motor response, contact, and noxiousness were expected to interact only in these medial areas. Further, we expected a behavioral interaction between the factors noxiousness and contact, based on pilot data (Morrison & Peelen, unpublished data). Finally, we predicted that cingulate activity would correlate with reaction time measures of this interaction, demonstrating a link between pain observation and the processing underlying production of hand movements in the midcingulate.

Materials and methods

Participants. Sixteen right-handed healthy adult volunteers were recruited from the University of Wales, Bangor community (8 female, 8 male, mean age 27). Participants satisfied all requirements in volunteer screening and gave informed consent approved by the School of Psychology at the University of Wales, Bangor and the North-West Wales Health Trust. Participation was compensated at £20 per session.

Stimuli and procedure. The experimental design was a 2x2x2 factorial. The three factors were: a) response (button-press or non-button-press), b) contact (hit or miss), and c) noxiousness (noxious vs innocuous). During each trial, subjects saw a 1500ms two-frame sequence of still photographs depicting a hand palm-down on a table top. The first frame of each

sequence showed a noxious or innocuous implement poised in the same position in the upper-right corner of the frame. The final frame showed the implement either contacting or falling slightly short of the hand's middle finger.

Participants were instructed to respond by pressing a key with their right middle finger at the onset of the second frame, when the nature of the contact was discerned. Response times were thus time-locked to the start of the second frame. For half the blocks participants responded only to hits, regardless of implement. In the other half, they responded only to misses. Instructions at the start of each block indicated to the participants whether they should respond to hits or misses during that block. Participants were familiarized with the task through a five-minute training session before scanning.

Stimuli and trial structure are depicted in Fig. 1. Three different noxious implements were used (hammer, hatpin, paring knife) alongside visually-matched innocuous controls (wooden spoon, blunt end of hatpin, butter knife). The factors of contact and noxiousness were counterbalanced, and the type of implement was randomized, within four 8-minute runs. Each run consisted of four 100-second task blocks containing 24 trials (96 total) and six trials per condition. The task blocks alternated between the "respond to hits" and the "respond to misses" instructions by block (counterbalanced across subjects). Five 16-second fixation blocks were interleaved between task blocks. Each 4-second trial began with 500 ms fixation, followed by the 1500-ms 2-frame sequence, and ended with 2000ms fixation.

Data acquisition. A 1.5-T Philips magnetic resonance imaging (MRI) scanner with a SENSE head coil was used. For functional imaging, a singleshot echo-planar imaging (EPI) sequence was used (T2*-weighted, gradient echo sequence, repetition time (TR) = 3000, echo time (TE) = 50 ms, flip angle = 90°). The scanned area included 30 axial slices, 5 mm thick, with no gap, at 64 x 64— voxel in-plane resolution, which covered the whole cerebral cortex and the cerebellum. Field-of-view was 192 x 192 mm. Reaction times were collected with a scanner-safe fiber-optic response pad system (fORP, Current Designs).

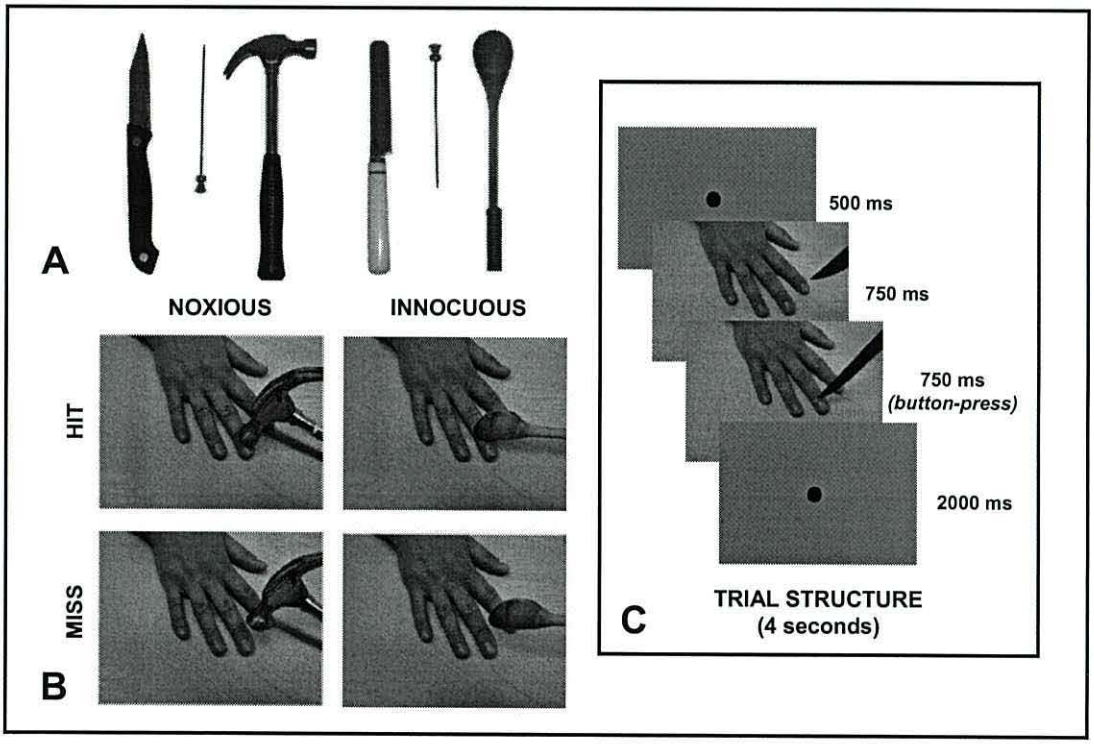


Figure 1. Stimuli and trial structure. (A) depicts the noxious and innocuous sharp knife/butter knife, hatpin point/hatpin head, and hammer/spoon stimuli. (B) shows the photographs used in the second frame in the 2x2 design between the factors noxiousness (noxious/innocuous) and contact (hit/miss). (C) shows the sequence of events in a 4-second trial: 500ms fixation, followed by the 1500-ms 2-frame sequence (button presses occurred at the onset of the second frame), and a further 2000ms fixation.

Data analysis. Pre-processing and statistical analysis of MRI data was performed using BrainVoyager 4.9 (Brain Innovation, Maastricht, The Netherlands). Three dummy volumes were acquired before each scan in order to reduce possible effects of T1 saturation. Functional data were motion-corrected, low-frequency drifts were removed with a temporal high-pass filter (0.006 Hz). Spatial smoothing was applied with a 6mm full width at half maximum filter. Functional data (3 x 3 x 5 mm voxels) were manually coregistered with three-dimensional (3D) anatomical T1 scans (1.3 x 1.3 x 1.3-mm resolution). The 3D anatomical scans were transformed into Talairach space (Talairach and Tournoux 1988) and the parameters for this transformation were subsequently applied to the coregistered functional data.

For each participant, general linear models were created for each of the two runs. One predictor (convolved with a standard model of the HRF) modelled each of the eight conditions (button-press noxious hit, button-press innocuous hit, button-press noxious miss, button-press innocuous miss, non-button-press noxious hit, non-button-press innocuous hit, non-button-press noxious miss, non-button-press innocuous miss). Each predictor modelled a 1-second interval beginning with the onset of the second frame (the moment of hitting or missing) in each trial. Active trials were excluded for which the behavioral response was incorrect, exceeded an interval of 1000 ms, or occurred 150 ms or less after the onset of the second frame. These predictors were submitted to a whole-brain, group average analysis. Random effect contrasts were performed at an

uncorrected threshold of $p < 0.0005$ ($t = 4.415$) and a cluster size threshold of > 50 mm^3.

Contrasts. To discover areas in which BOLD signal changes were modulated by the combination of the factors response (button-press or non-button-press), noxiousness (noxious or innocuous), and contact (hit or miss), we performed a whole-brain search for a three-way interaction between these factors. We therefore used the contrast (noxious hit - innocuous hit) - (noxious miss - innocuous miss) for the button-press trials vs (noxious hit - innocuous hit) - (noxious miss - innocuous miss) for the non-button-press trials, to define regions-of-interest (ROIs).

To reveal which premotor and motor areas were involved in trials in which participants made a button-press, the main effect of button-pressing was tested by comparing all button-press conditions to all non-button-press conditions. To identify midcingulate regions which responded to noxious hits generally, we also applied a contrast reflecting the simple effect of all noxious hit trials regardless of whether an overt movement was made: [(noxious hits - innocuous hits) for button press trials] and [(noxious hits - innocuous hits) for non-button-press trials].

Results

Behavioral results.

Mean errors did not exceed 2%. The mean correct response times were submitted to a 2x2 repeated measures ANOVA with two within-subject factors: implement (noxious or innocuous) and contact (hit or miss). There was a significant interaction between the noxiousness of the

implement (noxiousness) and whether it hit or missed the observed hand (contact), F (1,15) = 22.09, p = 0.0002. The behavioral reaction times were sensitive to the combination of noxiousness and contact, with fastest responses to noxious hits compared to innocuous hits and noxious misses, t (1,15) = -3.69, $p = 0.002$; , t (1,15) = -6.21, p = 0.00001, respectively. A significant main effect of contact was also seen, F(1,15) = 22.02, $p = 0.0002$.

fMRI results

Three-way interaction. As predicted, under conditions in which overt motor response selection was required, cingulate regions alone responded to the combination of noxiousness (noxious/innocuous) and contact (hit/miss) in combination with the motor response factor (button-press/non-button-press). The three activation foci revealed by the whole-brain three-way interaction contrast were in dorsal ACC (dACC; *xyz* = 0,26,31, max t value 6.29), MCC (*xyz* = 3, -12, 38, max t value 5.74), and dorsal posterior cingulate cortex (PCC; *xyz* = 0,-25,35, max t value 5.25). No other regions were activated in the whole brain.

The dACC activation fell within the region encompassed by activations in previous pain observation neuroimaging studies (Morrison *et al,* 2004; Singer *et al,* 2004, 2006; Jackson *et al,* 2005, 2006; Lloyd *et al,* 2006; Lamm *et al,* in press), in BA32 bordering pre-SMA and the middle frontal gyrus. The MCC activation fell on the cingulate gyrus in the region of Vogt *et al*'s area 24b (Vogt *et al,* 1995, 2003) and extended into the sulcus bordering SMA, likely corresponding to the caudal cingulate motor zone (cCMZ) of Dum & Strick (2001), homologue to the

dorsal/ventral cingulate motor area in the monkey (Matelli *et al*, 1991; Paus *et al,* 1993, 2002; Matsumoto *et al* 2004; Henderson, Bandler, Gandevia, & Macefield, 2006). The PCC activation fell on the cingulate gyrus inferior to the boundary between SMA and MI in the region of Vogt's area 23d (Vogt *et al,* 2006).

By definition, the 3-way interaction between reponse (button-press or non-button-press), noxiousness (noxious or innocuous), and contact (hit or miss) was significant within these ROIs, as they were identified by the three-way interaction contrast in the whole brain. To determine further the degree of significance of the BOLD interaction pattern within these ROIs, BOLD parameter estimates (beta values) from the fMRI data for correct trials were analyzed using 2x2x2 repeated-measures ANOVAs for the factors response (button-press or non-button-press), noxiousness (noxious or innocuous), and contact (hit or miss). The interaction of these three factors was significant at the $p < 0.05$ level in each ROI, dACC: $F(1,15) = 29.09$, $p = 0.00007$; MCC: $F(1,15) = 24.92$, $p = 0.001$; and PCC: $F(1,15) = 21.02$, $p = 0.003$ (Fig. 2).

Correlation with reaction times. In order to correlate BOLD parameter estimates with reaction times, an interaction effect value was used to capture the differences among noxious and innocuous hits and misses in button-press trials for both fMRI and behavioral data: (noxious - innocuous hits) - (noxious - innocuous misses). This difference of differences produces a single value encapsulating the interaction effect. The MCC activation was the only ROI to show a significant correlation with reaction time measures of the behavioral noxiousness-contact

interaction effect (r = -.48, p = 0.03, one-tailed; Fig. 2). A one-tailed test was used because a negative correlation was specifically predicted in which faster reaction times show an inverse relationship with increased BOLD responses, on the basis of evidence that ACC neurons increase firing during pain-related escape movements (Iwata, Kamo, Ogawa, *et al,* 2005).

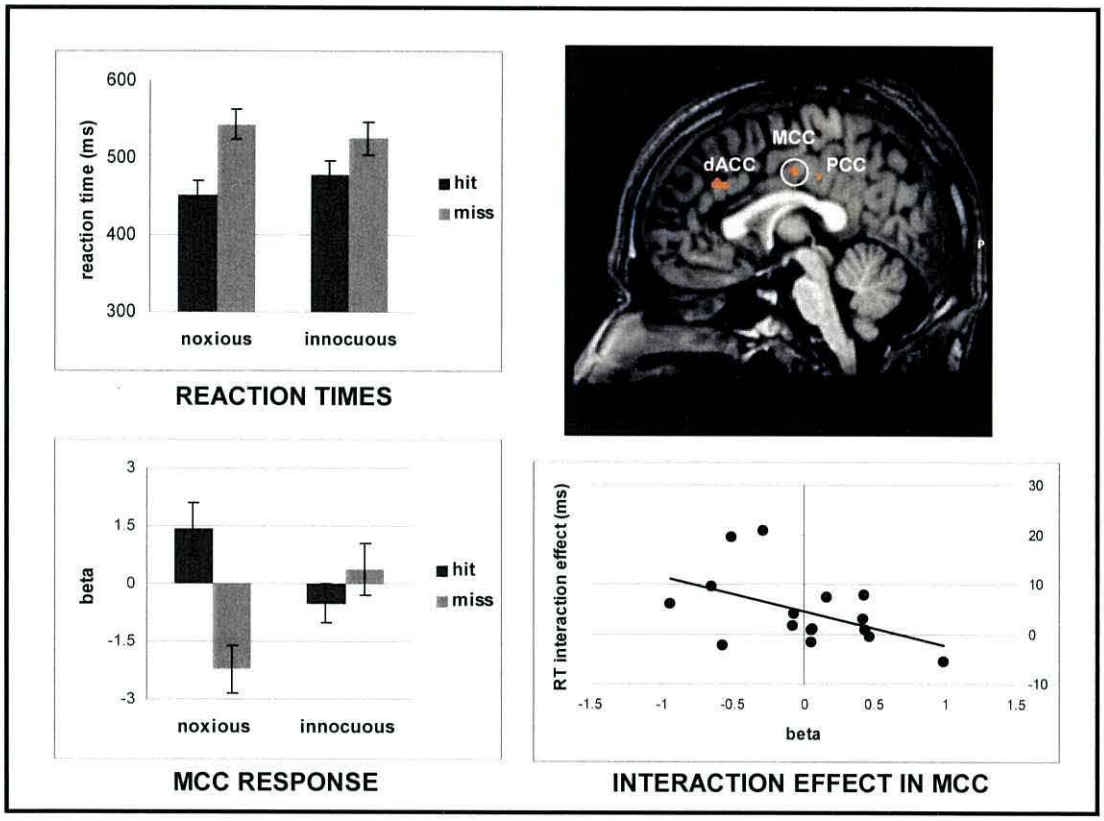


Figure 2. Cingulate regions-of-interest activated in sixteen subjects by the three-way interaction contrast between response (button-press/non-button-press), noxiousness (noxious/innocuous), and contact (hit/miss), at P < 0.0005 uncorrected. The upper left panel shows the reaction time interaction between noxiousness and contact, F(1,15) = 22.09, p = 0.0002. The lower left panel shows the BOLD responses mirroring the behavioral interaction pattern in button-press trials, with higher hemodynamic responses corresponding to faster reaction times, in the MCC activation (white circle in the sagittal view in the upper right panel). The lower right panel shows a correlation (*r* = -48, p = 0.03, one-tailed), between the interaction effect values of BOLD responses in MCC and reaction times, based on the behavioral interaction pattern and calculated as (noxious-innocuous hits) - (noxious - innocuous misses). dACC = dorsal anterior cingulate cortex, MCC = midcingulate cortex, PCC = posterior cingulate cortex.

BOLD patterns in non-button-press trials. Since the 3-way interaction contrast used to define the cingulate ROIs explicitly stipulated a pattern for non-button-press conditions inverse to that of the button-press conditions, we expected to find that pattern in these ROIs when an overt movement was not required. But we were further interested in the degree of these differences for non-button-press trials. Thus to investigate the degree of significance for the 3-way interaction in each ROI, we performed two 2-way ANOVAs separately for the interaction of noxiousness (noxious or innocuous) and contact (hit or miss) separately for button-press trials and non-button-press trials.

2-way ANOVA, dACC. In the dACC, this interaction was significant for button-press-trials, $F(1,15) = 7.53$, $p = 0.01$. It was also significant for the non-button-press trials, $F(1,15) = 10.26$, $p = 0.005$. This noxiousness-contact interaction in the button-press trials was driven by higher BOLD responses to innocuous misses compared to noxious misses as stipulated by the behaviorally-based 3-way interaction contrast, $t(15) = -2.31$, $p = 0.03$. In non-button-press trials, it was driven by higher responses to noxious misses than innocuous misses, $t(15) = 3.67$, $p = 0.002$, alongside trends for higher responses for noxious misses than noxious hits, $t(15) = -2.34$, $p = 0.033$, and innocuous hits than innocuous misses, $t(15) = -2.31$, $p = 0.035$. These trends reached borderline significance at the corrected alpha level of $p = 0.03$, and indicate that the dACC distinguishes hits and misses with the highest responses to noxious misses during hit-instruction blocks and to innocuous misses during miss-instruction blocks (there was no significant difference between these responses, $t(15) = -.185$, $p = .85$).

2-way ANOVA, MCC. In the MCC, the 2-way ANOVA between noxiousness and contact showed a significant interaction for button-press trials, $F(1,15) = 6.11$, $p = 0.02$. The interaction was also significant for non-button-press trials, $F(1,15) = 15.71$, $p = 0.001$, alongside a main effect of noxiousness, $t(15) = 5.79$, $p = 0.029$. Differences among these conditions in button-press trials were not significant apart from a trend for greater noxious than innocuous hits as stipulated by the behavioral 3-way interaction contrast, $t(15) = 2.25$, $p = 0.039$, and for greater noxious hits than misses, $t(15) = 1.93$, $p = 0.07$ (all other ps > 0.1). The interaction in the non-button-press trials was driven by higher BOLD responses to noxious misses than noxious hits, $t(15) = -3.36$, $p = 0.004$ (as stipulated by the 3-way interaction contrast), and higher responses to noxious than innocuous misses, $t(15) = 4.47$, $p = 0.0004$. The response profile in the non-button-press trials in MCC shows a preference for noxious miss stimuli during hit-instruction blocks.

2-way ANOVA, PCC. The PCC showed a significant noxiousness-contact interaction for button-press trials, $F(1,15) = 13$, $p = 0.002$, but not non-button-press trials, $F(1,15) = 3.05$, $p = 0.1$. For button-press trials, the interaction was driven by higher responses to noxious hits than innocuous hits, $t(15) = 2.65$, $p = 0.018$, or noxious misses, $t(15) = 2.51$, $p = 0.023$. The difference between noxious and innocuous misses was borderline, $t(15) = -2.3$, $p = 0.036$, with noxious misses being higher. This indicates that when button-presses were required, the PCC showed a preference for noxiousness, with the highest activation to noxious hits. The lack of a

noxiousness-contact interaction in non-button-press trials implies that this area is more closely linked to active motor responses.

Fig. 3 shows the different activation profiles in these three ROIs for noxious hits and misses during button-press and non-button-press trials. Note that many of the activations graphed in Fig. 3 lie below the fixation baseline; however, this experiment was designed to compare signal changes relative to control conditions rather than absolute changes from a resting baseline. Reductions from baseline are commonly reported in the ACC, possibly due to high "default mode" levels of activity here during rest (Gusnard *et al*, 2001).

Main effect of button-press trials. Contrasting all button-press conditions to all non-button-press conditions revealed activation in contralateral primary motor cortex (-39, -28, 51, max t value 10.02), as well as SMA (-1, 14, 57, max t value 5.23; 0, -15, 46, max t value 4.65), MCC (-2, -5, 44, max t value 4.99), posterior insula (-46, -21, 17, max t value 5.66; -37, -14, 14, max t value 5.56), putamen (-9, -18, 9, max t value 5.78), hypothalamus (-10, -3, -6, max t value 6.41), and ipsilateral cerebellum (28, -42, -23, max t value 8.84). No activations were present in lateral prefrontal cortex (Fig. 4).

Simple effect of noxious hits. A rostral midcingulate region selective for noxious hits regardless of whether a response was made was identified by another whole-brain contrast between noxious vs innocuous hits over button-press and non-button-press trials (0, 7, 35, max t value 4.18, $p < 0.005$; Fig. 4). The main effect of noxiousness was significant here, $F(1,15) = 13.19$, $p = 0.002$. This region of midcingulate cortex is

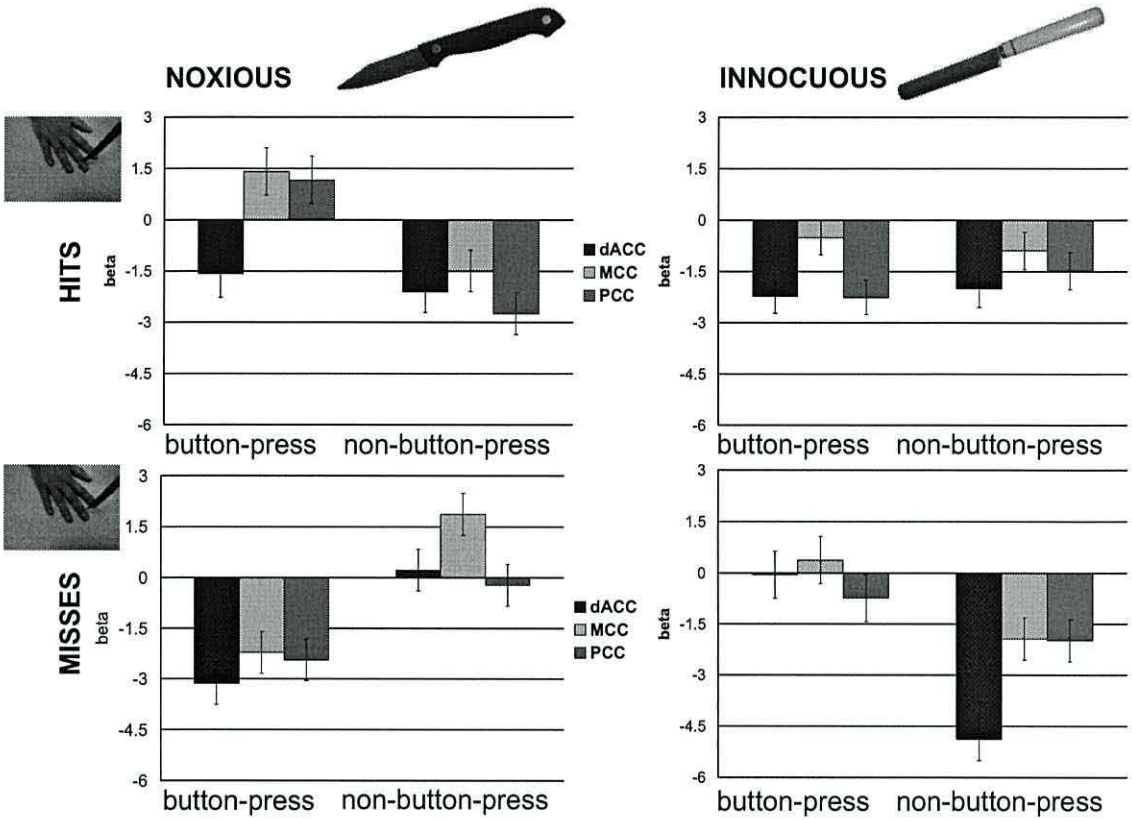


Figure 3. Hemodynamic responses to all conditions across the three cingulate regions-of-interest. The upper two graphs show parameter estimates (beta values) for trials in which the implement hit the hand, the lower two for when it missed; the left two graphs are for conditions in which the implement was noxious, the right two for when it was innocuous. In each graph, the left bar cluster shows BOLD responses for those trials in which the participants pressed the button, and the right bar cluster for those in which no button-press was required. The fixation baseline is plotted as zero in these graphs, but note that this experiment was designed to compare signal changes relative to control conditions rather than absolute changes from a resting baseline. Reductions from baseline are commonly reported in the ACC, possibly due to high "default mode" levels of activity here during rest (Gusnard *et al*, 2001). dACC = dorsal anterior cingulate cortex, MCC = midcingulate cortex, PCC = posterior cingulate cortex.

implicated in much previous pain observation neuroimaging research (Morrison *et al,* 2004; Singer *et al,* 2004, 2006; Jackson *et al,* 2005, 2006; Lamm *et al,* in press). The MCC ROI defined by the 3-way interaction contrast did not overlap with this area, indicating that the peak activation in an area generally responsive to noxious hits in the midcingulate is not identical with that of the midcingulate area more closely linked with the production of an overt response.

Discussion

The behavioral interaction between noxiousness (noxious or innocuous) and contact (hit or miss) reinforces previous behavioral results indicating that pain observation influences motor responses (Morrison *et al,* in press), as well as MEP findings that it affects motor cortex excitability (Avenanti *et al,* 2005, in press). Hemodynamic activity in the midcingulate and dorsal anterior and posterior cingulate cortices— but in no other premotor areas— mirrored these reaction time relationships in a three-way interaction between response (button-press or non-button-press), noxiousness (noxious or innocuous) and contact (hit or miss). Further, the noxiousness of the implements influenced both behavioral and hemodynamic responses despite being irrelevant to the task. These results indicate that these cingulate areas track the combination of noxiousness and contact between harmful implements and others' body parts, and link this functional sensitivity to response selection processes. This is consistent with the cingulate's premotor properties (Vogt *et al,* 1995; Vogt & Sikes, 2000) and its role in response selection on the basis of motivationally-relevant information (Rushworth *et al,* 2004; Shima & Tanji 1998; Bush *et al,* 2002; Williams *et al,* 2004; Kennerley *et al,* 2006).

Pain observation and reward-guided response selection

Previous neuroimaging studies have demonstrated a common neural substrate in the cingulate cortex for feeling and seeing pain, whether ecological or symbolically-cued (Morrison *et al,* 2004; Singer *et al,* 2004, 2006) and during observation of ecological painful stimuli (Jackson *et al*

2005, 2006). The cingulate also responds when seeing painful expressions of others (Botvinick *et al,* 2005; Saarela *et al,* in press) and shows overlapping activation between seeing painful expressions and hearing aversive tones (Lamm, Batson, and Decety, in press). These results suggest that pain and pain observation engage similar functional processes in the cingulate.

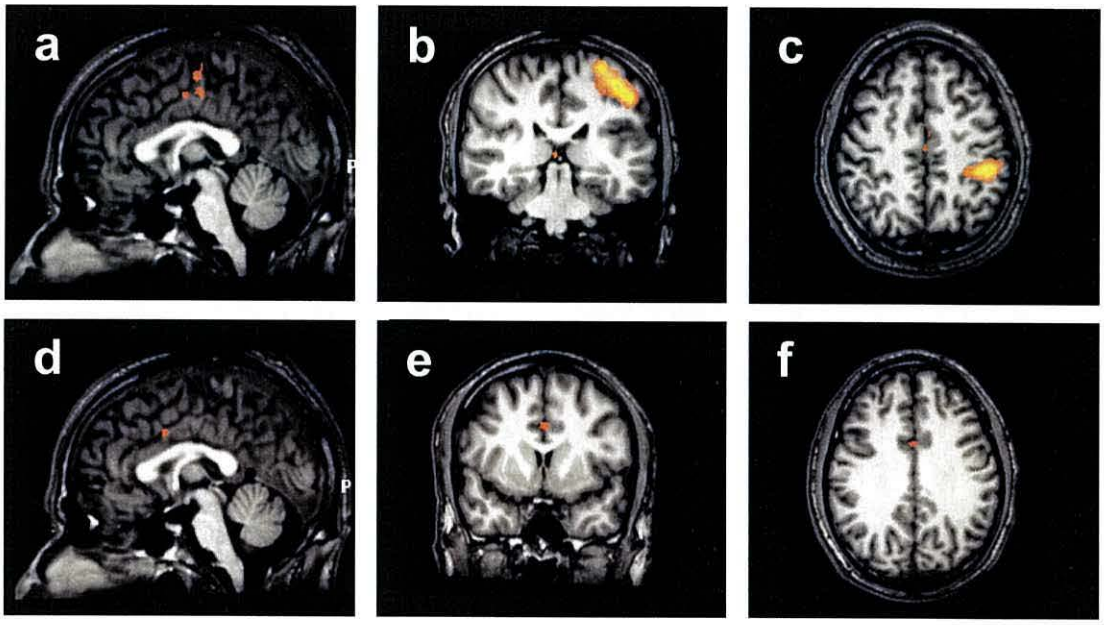


Figure 4. BOLD activation maps for sixteen subjects showing medial premotor and primary motor foci for the main effect of button-pressing on sagitttal, coronal, and axial slices (a-c: slices shown are *xyz* = -2, -28, 51); and a midcingulate focus for the simple effect of noxious hits regardless of whether a button-press was made (d-f: slices shown are *xyz* = -1, 7, 35), thresholded at $P < 0.0005$ and $P < 0.005$ uncorrected, respectively. Structural slices are shown in radiological convention with the right-hand side of the image corresponding to the left hemisphere (contralateral to the hand pressing the button).

However, so far there has been no neuroimaging evidence providing a more refined picture of what those shared functional processes might be. The available evidence suggests that they are likely to be related to the motivational-affective dimension of pain processing, supporting the representation of pain's aversiveness (Morrison *et al,* 2004; Singer *et al,*

2004). The present findings elucidate the motor-related nature of this function by demonstrating that different cingulate subregions modulate their responses depending on whether an overt movement is made, rather than operating as a reflexive, automatic affective mechanism responding in a uniform manner to others' pain. This also implies that seeing others' pain engages covert processing in medial premotor-related areas, and that this processing is modulated according to the situation. This proposition is in keeping with the cingulate's postulated context-sensitive, motor-related function in pain processing (Vogt *et al,* 2005; Sewards & Sewards, 2002).

Even outside the domain of pain-related processing, the cingulate's wider role in context-sensitive response selection has led it to be described as an "interface" between motor control, motivational drive, and cognition (Paus, 2002). An emerging hypothesis of cingulate function postulates that the dACC and MCC are chiefly involved in the reward-guided selection of actions (Rushworth *et al,* 2004, Shidara & Richmond, 2002). For example, cells in the rostral and caudal cingulate motor areas of monkeys showed changes in firing when a reduction in the amount of juice reward delivered to the monkeys led to the selection of an alternative response and the initiation of a new movement (Shima & Tanji, 1998).

This is in keeping with neuroimaging studies implicating homologous regions in human ACC (Bush *et al,* 2002) and in human single-unit recording studies in which the magnitude of dACC cell responses to instructions to change movement types depended on monetary reward value (Williams *et al,* 2004). Similarly, following selective dACC lesions,

monkeys are impaired on reward-guided and foraging tasks that require decision-making based on cost-benefit assessments (Kennerley *et al*, 2006, see also Rushworth *et al,* 2003). Rats too have difficulty adapting their behavior in choosing among varying cost-benefit alternatives after cingulate lesions, which ablate pre-lesion tendencies to assess larger rewards as worth the additional effort necessary to obtain them (Walton, Bannerman, Alterescu, & Rushworth, 2003; see also Akkal, Bioulac, Audin, & Burbaud, 2002). In particular, these areas are thought to process reinforcer associations specifically related to outcomes of self-generated actions, as opposed to those associated with perceptual discrimination of a particular stimulus (Hadland *et al,* 2003a, Turken & Swick, 1999).

There is little doubt that the experience of pain can be a powerful source of motivational information by which behavior is guided. However, it is an open question whether the observation of others' pain can also convey motivationally-relevant information in the absence of direct experience. The present findings suggest that it can: the implement's noxiousness affected both behavioral and hemodynamic responses despite being task-irrelevant. The sight of another person's hand as vulnerable to damage from sharp knives, heavy hammers, and poky pins may thus be inherently aversive, engaging regions in the cingulate cortex involved in the selection and execution of hand movements.

To press or not to press

The cingulate has also been consistently engaged during tasks that involve monitoring the processing of incoming information for potential

conflict between competing responses (Botvinick *et al,* 2004). This conflict typically takes the form of overcoming overlearned or prepotent actions in classical cognitive tasks such as Stroop interference (Carter *et al* 2000), go/nogo (Rubia *et al,* 2001, Menon *et al,* 2001, Braver *et al,* 2001, Garavan *et al,* 2003), flanker (Casey *et al,* 2000), oddball (Ullsperger *et al* 2001), and verb generation (Barch *et al* 2000) tasks. It also manifests when the task requires choosing actions voluntarily or choosing among underdetermined alternatives (Botvinick *et al,* 1999; Walton *et al,* 2003). Conflict monitoring and similar functions can be considered varieties of outcome evaluation, embedded in the more general function of coordinating response selection and execution depending on the motivational value of the action's consequences (Botvinick *et al*, 2004).

Because our paradigm involved the viewing of others' hands as the target of potentially harmful stimulation during a cognitive task, the results of the present study place the cingulate's role in pain observation into the broader perspective of its more general functional properties. These dispositions of the dACC and MCC in particular may have partially contributed to the pattern of results seen in this study. Namely, noxious misses may have introduced a degree of conflict between ecological/learned prepotent motor reactions to the noxiousness of the implement, and the task-related requirements to execute or suppress a button-press depending on the instructions in a given block (*ie,* in non-button-press trials). Alternatively, the conflict could take the form of uncertainty about whether the implement would strike, with some conditions and not others requiring additional processing before making or

withholding a motor response (for example, for misses generally, and noxious misses in particular).

For button-press trials this may have given rise to the reaction time cost for noxious misses compared to innocuous misses. The need to suppress prepotent movement tendencies in the face of uncertainty or a mismatch with an anticipated outcome would slow reaction times to noxious misses, resulting in the comparatively faster reaction times for *innocuous* misses seen in the behavioral interaction pattern, as well as the comparatively higher hemodynamic responses. A degree of conflict may also give rise to higher hemodynamic responses especially in non-button-press trials, in which the implement itself (seen in the first frame) betokens harm, but the nature of the contact (seen later, in the second frame) implies no *actual* hit risk while looming a bit too close to the person's hand to eliminate entirely the implication of a *potential* hit risk.

Our hypothesis about the BOLD responses in the cingulate centered primarily on the effects of noxious hits during button-press trials and the neural correlates of the behavioral interaction pattern, because these are the responses that could be tied most directly to behavior in this paradigm. We had no specific predictions about the behavior of the cingulate ROIs during non-button-press tasks beyond showing a complementary activation pattern to that in trials in which overt movements were made. The fact that these areas did show complementary patterns in non-button-press trials— that is, for misses in hit-instruction blocks and hits in miss-instruction blocks— indicates that there is covert modulation of these areas during pain observation even in the absence of an overt response.

Covert processing can conceivably take several forms. The form of noxiousness-selectivity seen in the ROIs revealed by the present paradigm hinges on the hypothesis that pain observation prompts motoric reactions and thus heightens the need for motor control. The response profiles of these areas may resemble ACC responses to noxious stimuli in the macaque monkey which *increase* firing during pain-related escape movements, but *decrease* firing to the same stimulation during illumination and temperature change-detection tasks which call for suppression of any immediate motor responses to the pain (Iwata, Kamo, Ogawa, *et al,* 2005). Similarly, whereas the generally higher responses to noxious hits in button-press trials may reflect facilatory processing manifesting in faster reaction times, their lower responses to noxious hits in miss-instruction blocks and noxious misses in miss-instruction blocks may exhibit the same tendency as the neurons in monkey ACC in suppressing motor responses.

Since there is no behavioral data to assist in the interpretation of the non-button-press activations, further experimentation is needed to disentangle the possible component processes covertly involved in pain observation's effects on overt response production. These functions may involve processes of motor facilitation and inhibition which have clear behavioral outcomes but indistinguishable or ambiguous BOLD counterparts. Although it is clear that the factors of noxiousness and contact modulate the selection and execution of motor responses when another person's hand is seen in interaction with a potentially harmful object, it is not possible to distinguish between facilitation and inhibition

on the basis of BOLD data. It is extremely plausible that motor-related response modulation in the ACC/MCC involves both (*eg,* Krams, Rushworth, Deiber, Frackowiak, & Passingham, 1998).

Functional relationships among cingulate areas

Pain observation may enhance a readiness to move to the extent that noxious hit conditions gain a reaction time advantage when participants are vigilant for hits. That means that seeing someone else's injury could poise the medial premotor areas on a knife-edge, so to speak, between the execution and suppression of a motor response. In this regard the present findings have bearing on how the different subregions of dACC, MCC, and PCC contribute to the neural processing of others' pain.

The MCC ROI emerges as the area most directly related to the behavioral interaction pattern and to reaction times. This activation fell in a caudal area likely to be the hand area of the caudal cingulate motor zone (cCMZ; Niki & Wantabe, 1976; Paus *et al*, 1993; Picard & Strick, 1996; Dum & Strick, 1998; Paus, 2002). It is associated with the production of quick hand responses, especially in simple tasks (Deiber *et al,* 1999), and has a relatively low threshold compared to other cingulate motor areas (Deiber *et al,* 1999, Picard & Strick, 1996), consistent with its generally higher BOLD responses across conditions in this study. Aside from its strong association with manual motor output (Paus *et al,* 1993, 2002), it has also been associated with pain (Koyama *et al,* 1998, Henderson *et al,* 2006) and pain avoidance (Koyama *et al,* 2001) in human and nonhuman primates, and contains proprioceptive and cutaneous receptive fields in the

monkey (Cadoret & Smith,1995). This is in keeping with its characteristics in the present study: it was closely related to motor output in its activation pattern and correlation with reaction times, but showed a main effect of noxiousness even in non-button-press conditions— and, critically, it was sensitive to the combination of noxiousness and hits (especially during hit-instruction blocks).

If the MCC ROI is modulated by the need to make or withhold a movement, it may do so on the basis of signals from interconnected areas that respond in a more uniform manner to noxious hits regardless of whether the button is pressed. The activation for the simple effect of noxious hits in a nearby region of midcingulate could be such an area. This activation focus showed BOLD increases to noxious hits across button-press and non-button press trials. Interestingly, this area does not overlap with the putative cCMZ hand area in the MCC ROI, but falls more closely within an area of MCC consistently activated in the growing body of neuroimaging research on pain observation and pain empathy (Botvinick *et al,* 2005; Jackson *et al,* 2005, 2006; Lamm *et al,* in press; Morrison *et al,* 2004; Singer *et al* 2004, 2006;).

The dACC focus, on the other hand, shows a more complex activation profile consistent with its versatility among cue-, preparation-, and response-related discharges in the monkey. This area contains functionally heterogeneous populations of cells which respond in different proportion to different phases of pain- and reward-guided movement preparation in several paradigms (Shima & Tanji, 1998; Isomura & Takada, 2004; Hoshi *et al,* 2005; Kennerley *et al,* 2006). If comparable

heterogeneity exists in human dACC, it may have given rise to the often-counterintuitive pattern of activation here, especially during trials that could not be related to reaction times.

The exact nature of this region's involvement in relating pain observation to motor processing is unclear, but whereas the MCC is more directly related to the behavioral interaction pattern and to reaction times, the dACC may be performing background operations resulting in the production of correct responses while "ignoring" salient but task-irrelevant noxious features of the stimuli. Its activity may even reflect components of an emerging intention for action (Hoshi *et al,* 2005). A patient with a rostral ACC lesion (covering the dACC activation seen in this study) was impaired on the Stroop task, whereas a patient with a more caudal lesion (covering the cCMZ) showed normal Stroop interference effects despite being slower than normal controls (Swick & Jovanovic, 2002). This indicates that these ACC/MCC subregions work together to integrate stimulus content and current task demands to produce appropriate and timely responses.

Such functional relationships between dACC and MCC may also come into play during pain observation. As in the present study, the dACC peak for the conjunction of "self" and "other" pain in Singer *et al* (2004) co-occurred with a more caudal and superior MCC peak. In another study, the conjunction between feeling and seeing a pinprick stimulus also produced a dACC-MCC pair (Morrison & Downing, in prep; chapter III). These areas are directly implicated in reward-guided action selection in the monkey (Shima & Tanji, 1998). When monkeys performed voluntary

switches of movement type (manipulating a lever) on the basis of reductions in the juice reward, rostral ACC recording sites were found to contain mixed populations of neurons both selective and nonselective for movement types. In contrast, caudal populations were more associated with the movement preparation and initiation phases. Within these areas themselves, there is also evidence that pain-related and finger-opposition-related responses produce distinct activations (Kwan, Crawley, Mikulis, & Davis, 2000), though the finger movements were not in response to painful stimulation.

Little is known about the anatomical connectivity in this region of human cortex (but see Johansen-Berg, Behrens, Robson, Drobnjak, Rushworth, Brady, Smith, Higham, & Matthews, 2005). Connectivity and functional profiles here are complex in human and nonhuman primates (Tanji, 1996; Wang, Shima, Sawamura, & Tanji, 2001) and gyral and sulcal patterns vary considerably among human individuals (Vogt *et al,* 1995, 2003; Paus *et al,* 1996). Despite this, connectivity patterns may partially account for co-activation patterns among these regions. In the monkey, caudal cingulate motor areas (CMAs) on the dorsal and ventral banks within the sulcus project massively to other medial and lateral premotor areas as well as primary motor cortex, thalamus, and spinal cord (Matelli *et al,* 1991; Vogt *et al,* 1995). SMA and the dorsal caudal CMA each receive input from primary somatosensory cortex and share similar signal, set, and movement response properties (Russo, Backus, Ye, & Crutcher, 2002; Isomura & Takada, 2004). In humans, the co-activation between caudal ACC (*eg* MCC) and medial frontal gyrus (*eg* pre-

SMA/dACC) tends to increase when the task involves a manual response (Koski & Paus, 2000).

Considering what is known of the connectivity of this region with parietal cortex and dorsal PCC in humans, it is possible that response-relevant visual information about others' pain follows a ventromedial visual pathway via dorsal projections through parietal cortex. Posterior parietal cortex has visuomotor properties (Anderson & Buneo, 2002; Fogassi & Luppino, 2005), is associated with nocifensive movements to aversive stimuli (Dong *et al,* 1994; Cooke *et al,* 2003; Cooke & Graziano, 2004), and has also been reported in pain observation in human neuroimaging studies (Jackson *et al* 2005, 2006; Lloyd *et al,* 2006; Lamm *et al,* in press), as well as in hypnotically induced pain (Derbyshire *et al,* 2004). Alongside midcingulate cortex, it also responds to noxious events in peripersonal hand space in humans (Lloyd *et al* 2006). The dPCC (23d) activation is especially interesting in this light, as this area receives inputs from dorsal-stream parietal areas (Vogt *et al,* 2006), and is also involved in orienting to and organizing motor responses to pain (Vogt *et al* 2005, 2006). Overall, this dorsomedial cingulate network may constitute a pathway integrating visual object information from the dorsal stream for the purposes of selecting or suppressing an overt response during pain observation.

Conclusions

Hemodynamic responses in the cingulate during pain observation track the combination of noxiousness and contact and are linked to motor

response selection. This suggests that, like our responses to pain itself, our reactions to others' pain are not wholly reflexive. The cingulate may rank stimulus features and prioritize responses on the basis of both motivational and contextual relevance. Consistent with the cingulate's role in reward- or pain-guided response selection, the noxiousness of implements in interaction with others' hands influences processing in a manner that affects reaction times. And consistent with the cingulate's wider role in flexibly relating the current situation to potential behavioral responses, motor responses during pain observation may be selected and executed or suppressed according to the constraints of the prevailing circumstances.

CHAPTER VII[1]:

DISCUSSION

"It is needless to push our researches so far as to ask, why we have humanity or fellow-feeling with others. It is sufficient, that this is experienced to be a principle in human nature. We must stop somewhere in our examination of causes; and there are, in every science, some general principles, beyond which we cannot hope to find any principle more general. No man is absolutely indifferent to the happiness and misery of others. The first has a tendency to give pleasure; the second pain. This every one may find in himself. It is not probable, that these principles can be resolved into principles more simple and universal..."

— David Hume, *Enquiry Concerning the Principles of Morals,* 219-200 (footnote).

[1] Portions of this chapter are adapted from a book chapter in press: Morrison, I., Motivational-affective processing and the neural foundations of empathy. In T. Farrow and P. Woodruff, Eds., *Empathy in Mental Illness and Health.* Cambridge: Cambridge University Press.

I. Summary: the ACC and pain observation

The findings presented in the foregoing chapters point to a role for the dorsal anterior cingulate (dACC) and midcingulate cortex (MCC) in both experienced pain and pain observation (chapters I, II, and VI). These events are presented in a spatial reference frame external to the observer's peripersonal space. When potenially painful events occur in peripersonal space, the cingulate also modulates its response, alongside posterior parietal areas which may contribute to the preparation of nocifensive movements (chapter IV). Moreover, pain observation was shown to have specific influences on motor processing (chapters V and VI). The relationship to behavioral responses was also associated with cingulate activation (chapter VI).

Anatomical localization and ACC function

These findings add to our emerging picture of which areas of the brain respond to visual information about pain in others and relate it to behavioral outcomes. A meta-analysis of the cingulate activations revealed in these and other "pain empathy" neuroimaging studies suggests a segregation of midline cingulate activations (+/- 1 cm from midline) into two main clusters (Fig. 1). One cluster centers in the dACC and pre-SMA, and the other more caudally in MCC inferior to SMA and MI. This may imply that distinct but interconnected cingulate areas contribute to vicarious pain processing and the preparation of potential motor responses. The dACC areas may play more of a cognitive role, integrating perceptual information with contextual factors. The MCC activations, on the other hand, may be more directly related to motor output and the tracking of specific motivationally-relevant action outcomes. The boundary

between them may correspond to the cytoarchetectonic and connectivity division between MCC and more rostral areas of the dACC (Vogt 1995, 2003). This apparent segregation requires further investigation in future studies.

It is not immediately clear what the activations in the dACC (black dots on Fig. 1) may have in common. Insofar as it is possible to assign shared elements to these activations, it may be the case that they each have to do with some aspect of changing context, whether this involves switching between input modalities (*ie* touch and vision), incongruities among these modalities, shifting task constraints, or the interpretation of abstract symbolic cues. Where evidence is available, they also show a high degree of individual and gender variation.

Activations (2) and (3) come from chapters III and VI respectively. Activation (2) is the site of the overlap between distinct felt and seen pain areas for needle-pricks, and shows individual variation in its location from a caudalmost focus of y =6 to a rostralmost focus of y = 32. Activation (3) is a rostral ACC activation that showed a task-related sensitivity to noxious hits (chapter VI), and it is the only dACC activation in this meta-analysis that is directly related to response selection. It also showed a trend for greater activation for noxious misses than hits when button-presses to hits were required, perhaps reflecting the incongruity or expectancy violation of a dangerous object *not* making contact with the hand in the context of hits. Similarly, activation (1) might result from a comparable incongruence or expectancy violation, when the sight of an anatomically-plausibly-positioned limb being painfully stimulated in peripersonal space does not give rise to a concomitant painful sensation from the actual hand (chapter IV).

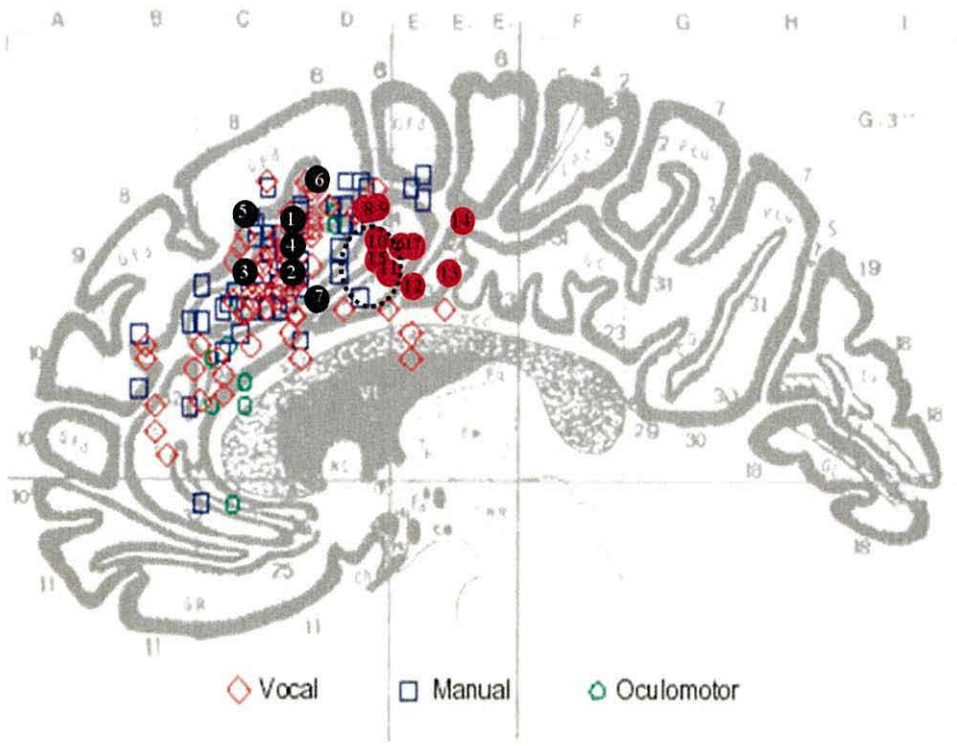


Figure 1. Meta-analysis of pain observation activations within 10 mm of midline bilaterally. Black dots = dACC activations; red dots = MCC activations. Dotted line indicates recording site of Hutchison *et al* (1999). Activations are superimposed on map of activations associated with response conflict and error monitoring for vocal, manual, and oculomotor responses (Botvinick *et al,* 2004). Numbered activations are explained in the text and in Table 1.

Activation (4) is a peak for the conjunction of felt and seen pain when seen pain consisted of a colored arrow cue indicating that the other person's hand would undergo painful electrode stimulation (Singer *et al,* 2004). This may require an abstract level of processing *per se*, as well as in linking the meaning of the symbolic cue to the equivalent pain sensation in oneself. It should be noted that activations (5) and (6) are not independent of activations (4) and (8),

Table 1. Activations implicated in pain observation across existing neuroimaging studies. Numbers refer to activation labels in Fig. 1.

Study	Contrast	Coordinates
dACC		
1. Lloyd *et al,* 2006 (chapter IV)	Seen needle prick to rubber hand (plausible position)	0, 24, 38*
2. Chapter III	Conjunction: felt and seen needle prick	-2, 24, 31
3. Chapter VI	Interaction: seeing noxious implement hits during overt button-presses	0, 26, 31
4. Singer *et al,* 2004	Conjunction: felt and symbolically-cued electrode pain	0, 24, 33
5. Jackson *et al,* 2005	Seeing still photographs of ecological pain	6, 26, 40
6. Jackson *et al,* 2005	Seeing still photographs of ecological pain	-10, 18, 44
7. Singer *et al,* 2006	Conjunction: felt and symbolically-cued electrode pain to fair players	9, 18, 27*
MCC		
8. Singer *et al,* 2004	Conjunction: felt and symbolically-cued electrode pain	6, 26, 40
9. Singer *et al,* 2004	Interaction: electrode pain in self and others	6, 6, 42
10. Jackson *et al,* 2006	Seeing ecological pain in self perspective	0, 0, 36
11. Morrison *et al,* 2004 (chapter II)	Conjunction: felt and seen needle prick	6, 0, 32*
12. Lloyd *et al,* 2006 (chapter IV)	Seen needle prick to rubber hand (implausible position)	2, -4, 34*
13. Chapter III	Conjunction: felt and seen needle prick	2, -10, 31
14. Chapter VI	Interaction: seeing noxious implements during overt button-presses	3, -12, 38
15. Chapter VI	Noxious hits with and without button-presses	-3, 7, 35
16. Chapter III	Main effect: felt and seen needle prick	-3, 5, 37
17. Chapter VI	Conjunction: noxious hits during button-presses and without button-presses	0, 2, 37

* = MNI coordinates

because Jackson *et al* (2004) defined their cingulate ROIs as 10-mm spheres based on the latter coordinates (reported in Singer *et al,* 2004). These activations were for still photographs of ecological pain-related stimuli (mechanical and thermal: slicing, crushing, burning, etc) of hands and feet while subjects assessed and rated the painfulness. Activation (7) was only found in

women, in a conjunction between feeling electrode pain and witnessing symbolically-cued pain to fair and unfair players in a game (Singer *et al,* 2006).

Activations in the MCC (red dots in Fig. 1) generally occurred when there was a more direct relationship to overt motor responses in the presence of a task, a closer match between felt and seen pain stimuli, or to "self"-related processing of visual pain-related stimuli. Like activation (4), activation (8) is a peak for the conjunction of felt and seen pain when seen pain consisted of a colored arrow cue indicating that the other's hand would undergo painful electrode stimulation (Singer *et al,* 2004). Unlike activation (4), this activation was relatively far from the midline at x = -9 contralateral to the stimulated hand, bordering the SMA/pre-SMA. It may reflect a need to repress movement of the simulated hand, a motor-based representation that may also have been engaged by the sight of another's hand being similarly stimulated. Activation (9) fell within the left hemisphere (Singer *et al,* 2004). Although it showed a visual sensitivity to the pain cue, its response in "other" conditions dropped off while remaining high in the "self" pain conditions (this is discussed more in the following section). Consistent with this putative role in self-relevant processing, another midline MCC activation (10) resulted from an instruction to imagine the seen limb as one's own in still photographs (Jackson *et al* 2005).

Activations (10), (11), (12), (15), (16), and (17) all fell within or near the region from which Hutchison *et al* (1999) recorded when they observed human single cells responsive to both felt and seen pain (dotted line on Fig. 1). Activation (11) was the site of a conjunction between felt and seen needle-prick pain (Morrison *et al,* 2004; chapter II). In this study there was a close visual match between the felt and seen pain stimuli, a hypodermic syringe with a

wooden probe in place of the lancet. Although the subjects did not see the probe when they were undergoing direct painful stimulation, they had been familiarized with it before entering the scanner. Activation (12) was seen in chapter IV (Lloyd *et al,* 2006) when an implausibly-oriented rubber hand was struck with a sharp probe in a hypodermic syringe. This can be contrasted with dACC activation (1) which responded to "painful" stimulation of the limb in a plausible orientation. Although the artificial limb was situated within peripersonal hand space for (12), its anatomically implausible orientation at a 180° rotation to the subject's real hand may have provided cues reducing the expectation of a tactile signal from the real hand. The rubber hand's status may thus have been equivalent to that of another person's hand despite being in peripersonal space, making this activation consistent with those in the MCC showing sensitivity to others' injury.

Activations (15), (16), and (17) coincide quite closely although they come from different studies (chapters III and VI). Activation (15) represents the BOLD response to noxious hits regardless of whether an overt button-press was made (chapter VI). Like (15), activation (16) fell -3 mm from the midline and reflects the main effect of felt and seen pain activations (chapter III). Activation (17) is the conjunction of seen noxious hits with and without a button-press response (chapter VI). Activation (14) was sensitive to the combination of noxiousness and contact when an overt button-press was required, mirrored behavioral interaction patterns, and correlated with reaction times (chapter VI). The relative locations of these MCC activations within the same brain space for the overlap and hit/miss studies are depicted in Fig 2.

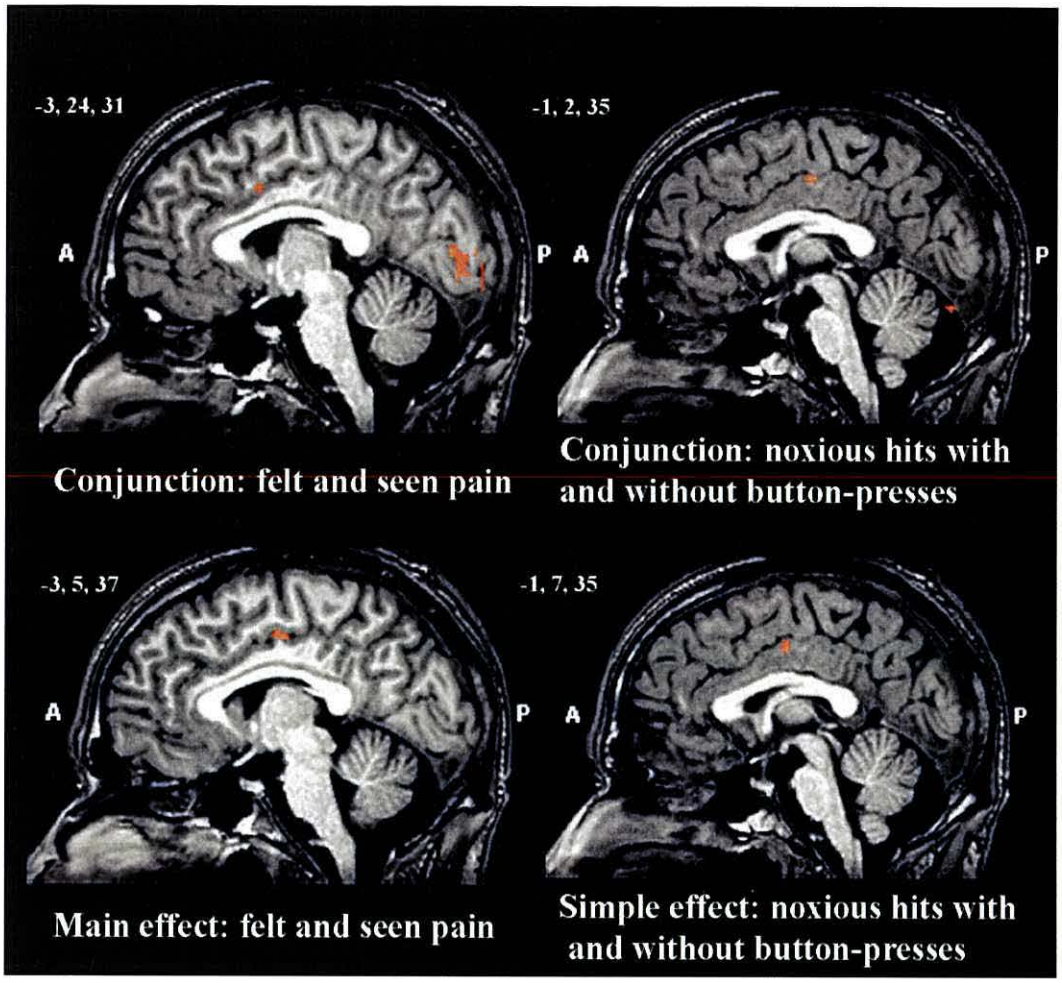


Figure 2. Comparison of pain observation activation loci in chapters III, and VI. All activations are superimposed on the same anatomical image, at x = -3 for the images on the left-hand side of the figure (from chapter III) and at x = -1 for those on the right (from chapter VI).

As noted in the previous chapter, there may also be functional relationships between dACC and MCC during pain observation. The dACC conjunction peak in Singer *et al* (2004) co-occurred with the more caudal and superior MCC peak (activations 4 and 8). The conjunction between feeling and seeing an ecological pain stimulus also produced a dACC-MCC pair (2 and 13; chapter III). Likewise, two peaks were seen for the response, noxiousness, and contact interaction in chapter VI (activations 3 and 14). Activations (1) and (12) may also have had a functional relationship, perhaps depending on whether the

rubber hand was unambiguously non-self (12) or self-like but "numb" within peripersonal space (1).

When viewed as belonging to a distinct cluster, the dACC activations in particular require interpretation in terms of this region's engagement in tasks involving conflict and error detection (*eg,* Menon *et al,* 2001). The activations in Fig. 1 are plotted upon a meta-analysis of neuroimaging activations for studies involving response conflict and/or error monitoring for vocal, manual, and oculomotor responses (Botvinick *et al,* 2004). It has been postulated that a primary function of this region of the ACC is to monitor the processing of incoming information for potential conflict between competing responses. As noted in chapter VI, this conflict typically takes the form of overcoming overlearned or prepotent actions in classical cognitive tasks such as Stroop interference (Carter *et al* 2000), go/nogo (Rubia *et al* 2001, Menon *et al* 2001, Braver *et al* 2001, Garavan *et al* 2003), flanker (Casey *et al,* 2000), oddball (Ullsperger *et al* 2001), and verb generation (Barch *et al* 2000) tasks. It also manifests when the task requires choosing actions voluntarily or choosing among underdetermined alternatives, or involving error commisssion (Botvinick 1999, Walton *et al,* 2003).

However, as the body of relevant research grows for human and nonhuman primates, and the characterization of the ACC's functional neuroanatomy becomes more refined, there is a correspondingly growing need to reassess the anatomical localization of conflict and error-related functions in the cingulate. Such a reassessment may lead to a reassessment of its functional characterization too, as more data become available. For example, human lesion data has yielded equivocal results with some patients but not others showing

impairment on traditional cognitive tasks such as Stroop (Swick & Jovanovic, 2002; Baird, Dewar, Critchley, Gilbert, Dolan, & Cipolotti, 2006). Rushworth *et al* (2004) have pointed out that many of the activation foci assigned to ACC for conflict monitoring and error detection actually center on the caudal superior frontal gyrus (pre-SMA). These may, however, share functional/cortical territory with response-conflict-associated regions of ACC proper. These activations fall roughly within the coordinates $y = 18\text{-}21$ and $z < 35$ in medial cortex (Rushworth *et al*, 2004; Botvinick *et al*, 2004). They tend to lie about 24 mm (+/- 7 mm) anterior to the AC plane (Picard & Strick, 2001). Most response-conflict-related activations, though, also tend to be more dorsal than ACC proper, at $z = 45$ or higher (Rushworth *et al*, 2004).

This area of the medial prefrontal cortex has also been associated with the voluntary control of action. Nachev *et al* (2002) demonstrated that conflict monitoring and voluntary action selection activate anterior and posterior portions of pre-SMA, respectively. This implies that whatever this area's role in response conflict is, it does not simply boil down to its role in making voluntary responses that override prepotent, overlearned, or otherwise standard responses. Further, activity in dACC was found not to depend on error feedback or response conflict when subjects switched response sets on the basis of feedback after making an action (Walton *et al*, 2004). Similarly, following selective dACC lesions, monkeys are impaired on reward-guided and foraging tasks that require decision-making based on cost-benefit assessments, without having an effect on error correction (Kennerley *et al*, 2006, see also Rushworth *et al* 2003). Rats too have difficulty adapting their behavior in choosing among varying cost-benefit alternatives after cingulate lesions, which ablate pre-lesion

tendencies to assess larger rewards as worth the additional effort necessary to obtain them (Walton, Bannerman, Alterescu, & Rushworth, 2003; see also Akkal, Bioulac, Audin, & Burbaud, 2002).

On an anatomical level, little is known about connectivity in this region of human cortex (but see Johansen-Berg *et al,* 2005). Connectivity and functional profiles are complex in human and nonhuman primates (Tanji, 1996) and gyral and sulcal patterns vary considerably among human individuals (Vogt *et al,* 1995, 2003; Paus *et al,* 1996). Despite this, connectivity patterns may partially account for co-activation patterns among these regions, as noted in chapter VI. Precentral gyrus peaks (*eg* in SMA) co-occur with caudal ACC peaks, but this relationship shows no influence of response rates or the presence of manual responses (Koski & Paus, 2000). The co-activation between caudal ACC (*eg* MCC) and medial frontal gyrus (*eg* pre-SMA), however, increases when the task involves a manual response (Koski & Paus, 2000). The evaluative functions of dACC/pre-SMA and the response-related functions of MCC/SMA may unite views of the medial prefrontal cortex which emphasize conflict monitoring (evaluation) and those that emphasize selection for action (selecting a motor response). Yet it is often difficult to disentangle responses in motor-response related cingulate areas from task factors, because the determination of output-specific activity in noninvasive neuroimaging techniques necessarily involves a task of some sort (*eg* in localizing the CMZs; Paus *et al,* 1993).

But is it possible to reconcile these possible accounts to assign a general function to the medial prefrontal cortex, which includes the dACC, MCC, pre-SMA, and SMA? Chapter VI discussed another, emerging hypothesis of cingulate function which postulates that the dACC and MCC are chiefly

involved in the reward-guided selection of actions (Rushworth *et al,* 2004, Shidara & Richmond, 2002). Cells in the rostral and caudal cingulate motor areas of monkeys showed changes in firing when reduced rewards led to the selection of an alternative response and the initiation of a new movement (Shima and Tanji, 1998). This is in keeping with neuroimaging studies which implicate homologous regions in human ACC (Bush *et al,* 2002) and in human single-unit recording studies in which the magnitude of dACC cell responses to instructions to change movement types depended on monetary reward value (Williams *et al,* 2004).

In particular, these areas are thought to process *action* (not perceptual/stimulus) reinforcer associations (Hadland *et al,* 2003a). Rather than standing as an alternative to conflict-monitoring and error-detection accounts of the ACC, then, these functions may be embedded in the more general function of reward-guided outcome evaluation. Conflict monitoring may be a subordinate variety of outcome evaluation, in which interconnected cingulate subregions coordinate the selection and execution of responses depending on their cost-benefit or motivational value. This perspective also accommodates the cingulate's role in pain processing and its sensitivity to action-reward contingencies (Botvinick *et al,* 2004; see also Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). By extension, it also accommodates its role in pain observation, where the roles of dACC and MCC are strongly linked to the learning, selection, and execution of appropriate behavioral responses. In this view even familiar or previously-learned associations are constantly recontextualized in order to allow flexible adaptation of behavior in a changing world, and the cingulate is pivotal in this ongoing process.

Considering what is known of the connectivity of this region with parietal cortex and dorsal PCC in humans, response-relevant visual information about others' pain may follow a dorsomedial visual pathway via dorsal projections through parietal cortex, as noted in chapter VI. Posterior parietal cortex has visuomotor properties (Rizzolatti, Fogassi, & Gallese, 1997; Calton, Dickinson, & Snyder, 2002) and has been reported in pain observation (Jackson *et al* 2005, 2006; Singer *et al,* 2004; see Table 2). Alongside midcingulate cortex, it also responds to noxious events in peripersonal hand space in humans, as observed in chapter IV (Lloyd *et al,* 2006). The dPCC (23d) activation seen in chapter VI is especially interesting in this light, as it receives inputs from dorsal-stream parietal areas (Vogt *et al,* 2006), and is also involved in orienting to and organizing motor responses to pain (Vogt *et al,* 2005, 2006). Overall, this dorsomedial cingulate network may constitute a pathway integrating visual object information from the dorsal stream for the purposes of selecting or suppressing an overt response during pain observation.

Somatotopy

The emphasis in this thesis on the motivational-affective and skeletomotor aspects of pain observation should not imply that sensory aspects are unimportant, especially as regards the localization of observed pain in particular body parts of the observer. The experiments presented here were not designed to address how vicarious sensations become associated with particular effectors or at what level of accuracy this may occur. Indeed, in the perspective taken throughout these studies, a fine degree of somatotopic mapping may even be superfluous if a gross level of information about effector-object interactions is

sufficient to indicate the presence of a potential threat and to influence behavioral dispositions towards it.

Table 2. Inferior and superior posterior parietal areas associated with pain observation.

Study	Contrast	Coordinates
Lloyd *et al,* 2006	Painful vs neutral stimulus to rubber hand in plausible position	-56, -30, 24* 68, -22, 26* -32, -56, 54*
Lloyd *et al,* 2006	Painful vs neutral stimulus to rubber hand in implausible position	60, -20, 22* -22, -60, 62*
Jackson *et al,* 2005	Seeing pain in others	-42, -44, 56 40, -50, 56
Jackson *et al,* 2006	Seeing pain in others, average self and other perspective	42, -45, 51 -30, 51, 54
Singer *et al,* 2004	Seeing pain in others	-60, 45, 30
Morrison *et al* (chapter VI)	Noxious vs innocuous hits regardless of response	-14, -52, 60

* = MNI coordinates

Yet if introspection is a suitable first guide, "pain empathy" does often seem to be associated with heightened awareness of particular body parts, such as hands. These feelings are usually more vague than vivid— and they may or may not always correspond to the observed body part receiving stimulation. The possible scope and variety of this experience has never been investigated. For example, for some people seeing pain may cause a throb in their right hand no matter where the other person is hurt, for some it may cause a prickly feeling

in their scalp; other people's toes may invariably curl, or tears spring into their eyes.

There is little evidence at this stage to motivate sharp hypotheses, but there are at least three alternative possibilities for investigating how observed pain becomes related to particular body parts in the observer. The first is that this is supported by the somatosensory cortices, in a veridical manner in which a specific body part is accurately mapped onto the corresponding body part in the observer. The second is that the coarse somatotopy in the MCC is sufficient for "highlighting" specific body parts, but possibly along non-veridical, imperfectly-veridical, or idiosyncratic principles which do not preserve an exact body-to-body mapping. A third possibility is that somatosensory cortices work in concert with the medial prefrontal areas implicated in pain observation— for instance in light of the inputs to MCC from SI and area 5 in the monkey (Russo *et al,* 2002)— but that the nature of their role has not been successfully captured by the imaging design and methods of the existing studies.

Further specific tests are required to tease apart the dependence of these regions' responses on time and other methodological factors. At this stage in neuroimaging empathy research it is important to bear in mind that features of the design and analysis, such as the sampling rate, planned contrasts, modelled interval, choice of threshold, and method for localizing regions-of-interest, may inadvertently hide meaningful signal change patterns in sensory-discriminative regions like the somatosensory cortices. For example, it was mentioned in the previous section that the results of a noxiousness (painful or nonpainful) and target (self or other) interaction search over the whole brain in Singer *et al*'s study yielded areas in which pain-related activation was greater in the self

condition: left SI/MI, left SII, and caudal ACC. The authors interpret this as ruling out areas in which the response to felt and seen pain was not equivalent or did not extend to viewing the partner's pain.

However, this result is also informative when considering the long timescale of the modelled period (9.5 seconds). Hemodynamic responses to all events in the trial, including the anticipation cue and the felt or seen painful or nonpainful stimulation, were convolved together with a single standard hemodynamic response function. The resulting activation maps therefore reflect the response over the whole trial interval, starting with the anticipation cue and ending with the offset of stimulation. Interactions between noxiousness (painful or nonpainful) and target (self or other) in certain brain areas, then, could reflect the average of differential changes in felt or seen pain over the length of this entire interval. Similar arguments could apply to the somatosensory activations: the absence of these areas from a conjunction analysis and the presence of interactions within them do not altogether rule out roles in coding aspects of others' pain.

The choice of baseline also affects profoundly the conclusions one may draw. A feature of both Keysers *et al*'s (2004a) and Wicker *et al*'s analyses is that the central comparison showing overlap was based on two contrast pairs with unmatched baselines. In Keysers *et al,* the tactile responses were compared to a fixation baseline, whereas the visual responses for touch were compared to the non-touching controls. In Wicker *et al*, the firsthand smell conditions were compared to a fixation baseline, while visual responses to disgusted facial expressions were compared to that for neutral expressions. This is potentially important because although both of the relevant activations were significant

with respect to their baselines in each study, it is difficult to compare the difference between two activations when one pair is a condition-resting baseline contrast and the other reflects the activation difference of two conditions that are each compared to a resting baseline. Although responses to observed and experienced touch/disgust may be significant compared to their respective baselines, they may also differ with respect to one another.

For example, the visual touch contrast in Keysers *et al* subtracts out potential motion-related activity from the sight of others being touched. However, tactile somatosensory discrimination is also affected by visual imagery (Sathian & Zangaladze, 2001, 2002), which may have been present in the tactile conditions as subjects felt the stimulus pass up or down their legs. A confound like this would obfuscate the interpretation of the overlapping activation as reflecting exclusively touch-related activation in both conditions. Similar concerns may apply in the case of disgust, in which processes underlying responses to facial expressions may be different than those underlying olfactory responses to an immediately-present odor. The results of chapter II may be similarly limited. Because there was no response to the innocuous visual cue at the selected threshold, the contrast pairs in the conjunction analysis were each compared to baseline. This decision was made in order to have equivalent baselines, if not ideal functional subtractions. Nevertheless, it also meant that the contrast for experienced pain may not have excluded mechanoreceptive tactile activations, confounding pain perception with pressure perception.

In summary, the clearest direction ahead is to relate pain-observation-related processing more closely to behavior. Although at present the results about somatosensory mapping are inconclusive, the studies in this thesis point to a

strong relationship of cingulate activation with motor responses. At present there is a greater weight of evidence for motor-related processing during pain observation than for a straightforward kind of somatosensory mapping. Indeed, the somatotopy seen in the monkey for cutaneous stimulation in the ACC receptive fields is not unambiguously distinct from, and is outnumbered by, the efferent skeletomotor responses produced by microstimulation here (Akazawa *et al,* 2000). If somatotopic mapping does indeed occur, it may not be in the service of pure sensory perception, nor for preservation of veridical mappings between other body parts and self body parts, but instead it may be in the service of preparing or producing motor responses.

II. A motivational-affective (M-A) framework

One of empathy's quintessential features is that it has a certain "from-the-inside" feel that ranks it with other varieties of emotional experience. Vicarious responding in affect-related networks may therefore represent a basic condition for the characteristic affective buzz so often granted to the visual perception of *others'* emotional states (Carr *et al,* 2003; Gallese, 2001, 2003). In this section I propose that the motivational and affective nature of processing in these systems suggests a framework within which to examine the foundations of vicarious responding. It draws together aspects of affective response dispositions, motivational learning, and subjective experience. This motivational-affective (M-A) framework identifies relevant information-processing aspects of neural systems and provides explanatory resources within which to situate hypotheses about empathy.

A functional neuroscientific view of affect

Increasingly, the neuroscience of emotion has begun to adopt a biology-inspired perspective that views emotions as dispositions to act (Brothers, 1990; Panksepp, 1998). In this view, the function of emotion is ultimately to produce specific responses which prepare the organism to act appropriately towards certain objects or contexts (*eg,* to approach or avoid them). These responses can occur at various levels, whether physiological or overtly behavioral, so a given affective response usually comes as a "package" that can include autonomic and endocrine as well as muscular responses. One of the most salient features of this perspective is its functionalist spirit: such responses are adaptive, and are shaped by evolution, learning, or both. Emotions are no longer seen as pathological disruptions of rational thought, but as doing very sophisticated, useful things. Organisms come equipped with the wherewithal to orient to, remember, and even anticipate the complexities of the world through complicated (if now and then imperfect) suites of dispositional mechanisms.

The learning, preparation, and production of flexible behavior are deeply bound up with the evaluation of objects and their contexts. These evaluations can be accompanied by positively- or negatively-hedonic subjective experiences. Some objects come with built-in hedonic value, like food and water. But hedonic value can also be learned and modified, influencing the kinds of behavior we make towards a hedonic object, as well as the effort we are willing to put into obtaining a pleasant stimulus or avoiding an unpleasant one. Hedonic value can also attach to objects that appear in the same context as hedonic objects, independently of a cognitive appreciation of the relevant cause-and-effect relationships or the instrumental means to obtain or avoid them

(Berridge, 2004). For example in humans, socially-relevant and semantic cues have been shown to modify motivated behavior. Happy face primes increase the quantity of food and drink consumed, whereas angry faces curb it (Winkielman, Berridge, & Wilbarger, 2005); and positively valenced words potentiate approach movements, whereas negative ones potentiate withdrawal movements (Chen & Bargh, 1999).

Chapters II and III suggest a crucial role for the dACC/MCC in felt and seen pain, and chapter VI suggests that these areas bear a relationship to the selection of overt motor responses in the presence of others' pain. This is important for elucidating the neuroanatomical details of the M-A framework, since as outlined earlier, these regions have also been implicated in motivation as well as reward-based response selection (Devinsky *et al,* 1995; Hadland *et al,* 2003; Paus, 2001; Rushworth *et al*, 2003; Williams *et al,* 2004; Bush *et al* 2002; Kennerly *et al,* 2006).

On the more hedonic or affective side, the ACC has also been consistently linked to subjective qualities such as pleasantness or unpleasantness, feelings of effort accompanying concentration of attention or performance of a difficult task, and consciousness (Rainville *et al*, 1997, 1999; Posner & Rothbart, 1998; Walton *et al*, 2003). Indeed, in his model of consciousness Damasio (1994, 1999) identifies the ACC as one of the key areas involved in the subjective awareness of bodily changes that occur with respect to an object. He proposes that a first-order representation of the body— the viscera, the skin, hormone levels, and so forth— is supported by certain brainstem structures alongside somatosensory cortices and insula. When the bodily situation changes in response to objects in the world (like your thudding heartbeat when a bear noses

around your tent) second-order "images" of the corresponding activity in these first-order maps are coded in areas such as ACC and orbitofrontal cortices. This dynamic re-mapping is thought to be accompanied by subjective awareness of emotional states and to contribute to flexible, goal-directed behavior via an influence on response dispositions and motivated decision-making.

Along similar lines, Craig (2003a) proposes an interoceptive network concerning afferent information about the physiological condition of internal tissues. In humans, phylogenetically unique projections from 1) the thalamus to anterior insula, and 2) dorsal ACC to anterior insula, are postulated to form the basis of a higher-order subjective awareness of self. In Craig's model, the anterior insula's role extends to the realms of conscious emotional experience. An fMRI study of heartbeat detection implicating the right anterior insula and dorsal ACC prompted Critchley *et al* (2004) to conclude that these two areas work in concert, with the right anterior insula possibly more directly involved in body mapping and the ACC in mobilizing a behavioral response (Craig, 2004; Bechara & Naqvi, 2004).

Although most of the discussion throughout this thesis has centered on the motivational-affective aspects of pain, the present motivational-affective perspective is not limited to pain. As mentioned in the introductory chapter, vicarious responses have also been observed for disgust, and damage to the insula has been associated with impairments in recognizing disgust-related expressions or behavior. Just as pain does, disgust involves many computations interacting in different ways and among different effector systems to produce particular responses (Rozin, Haidt & McCauley, 2000; Marzillier,.& Davey,

2004). The proposed motivational-affective framework for empathy, with its emphasis on flexible motor responses, can also apply to the case of disgust.

Disgust is closely associated with mechanisms that expel distasteful or noxious substances from the body. When an offensive item is swallowed, brainstem areas coordinate complicated emetic reflexes such as retching and vomiting. Before matters reach such a pass, however, orofacial movements of aversion or expulsion can preëmpt the need for vomiting, because the offensive object is spat out before being swallowed. These movements are of a skeletomotor nature and are more susceptible to voluntary control than retching and vomiting. The anterior insula and basal ganglia are involved in disgust and nausea (Calder, Lawrence, & Young, 2001), and may play a role in learning about distasteful items for the purposes of altering behavior in future circumstances. Just as pain can be considered a heuristic category of perception, nausea— which precedes and accompanies emetic reflexes— can also be thought of as a subjective warning bell based on past experience. Direct stimulation of the anterior insula in human epilepsy patients has produced nausea (Penfield & Rasmussen, 1955), as well as unpleasant, urgent motivational-affective feelings in the throat and nose (Krolak-Salmon, Henaff, Isnard, Tallon-Baudry, Guenot, Vighetto, Bertrand, & Mauguière, 2003). It is therefore possible that the insula, via its olfactory and gustatory involvement and connections with the motor-related basal ganglia (Augustine, 1996), contributes to the potentiation of orofacial aversive or expulsive movements.

The Potential Harm Hypothesis (PHH)

One of the results presented in chapter III was that images of potentially dangerous or noxious objects on their own, outside a "pain observation" context, did not engage the same regions involved when noxious objects were seen making contact with a person's hand. Moreover, chapters V and VI showed that the sight of a needle and hand together produce a specific effect on the motor system. With respect to the M-A view outlined above, what insight can this give us on the possible function of vicarious responding, and by extension, the nature of empathy? Although empathy is usually thought of as related to selfless, altruistic behavior, its underlying processes may ultimately serve selfish ends. In other words, pain observation may be a means for deriving indirect information about potentially harmful objects or situations. This idea can be called the Potential Harm Hypothesis (PHH; I am indebted to Paul Loader at the University of Sussex for the coinage of the term during personal communication, used with permission).

Observation of others' interactions with potentially harmful objects provides a means of learning about an object's aversive nature (Morrison, in press). This circumvention of trial-and-error learning by observational learning can reduce the time spent learning firsthand, as well as lowering the risk of potentially harmful interactions with dangerous features of the environment (Heyes, 1994). In the case of pain observation, the information value of a sharp implement interacting with a hand may even surpass that of the sight of a sharp implement alone in other contexts. The sight of a needle on its own can be perceived as potentially dangerous— but the sight of the needle in contact with the living tissue of a hand carries a much stronger message of potential harm. This is

important because it can facilitate learning about both the object (if unfamiliar) and of the context in which it occurs. The sight of a needle coming into contact with skin (Morrison *et al*, 2004), the intensity of the apparent injury (Avenanti *et al,* 2006), flinching, blood, or even an arbitrary cue associated with pain. (Singer *et al*, 2004), may all be examples of information-laden situational cues.

In a fear conditioning paradigm (Olsson *et al,* 2004), subjects were conditioned to anticipate an electrode shock to the wrist following the presentation of a conditioned stimulus on a video screen. In this paradigm, subjects classically show increased skin conductance when presented with a masked conditioned stimulus, in this case angry faces (Öhman & Soares, 1998). Olsson *et al* presented some of the subjects with videos of other people undergoing the paradigm. On the basis of observing the other participants' facial reactions, the observers developed increased SCRs to the masked angry faces in the display, despite the fact that these appeared too quickly to be available to conscious awareness. These observational learning trials were compared to trials for the subjects in the classical Pavlovian conditioning condition, as well as in a third condition in which the signal-shock contingencies were verbally described to the subjects. Interestingly, unlike the "instructed" learning condition, which showed no effect of conditioning for the masked conditioned stimulus, the results of the observational learning condition did not differ from that of the Pavlovian learning condition. This provides further evidence for the sufficiency of *others'* situation-related cues in eliciting responses that would be appropriate were the observer in the place of the observed.

So far there is no cohesive research program on M-A observational learning in primates as there is for other forms of observational learning, such as

imitation (see *eg* Meltzoff & Prinz, 2002). Preston & de Waal (2002) cover some germane research in primates and rodents in light of empathy. Controlled studies dealing specifically with observational learning and pain empathy in other animals are rare, but there is some evidence intimating that chimpanzees react aversively to others' pain (Parr, 2001; Itakura, 1994). Parr *et al* (2001) showed that when chimps watched videos of the vet visiting conspecifics to give them hypodermic injections, their finger temperature decreased, indicative of parasympathetic ("dampening down") nervous activation. There is also evidence that observation of conspecific behavior influences positive reward learning in capuchin monkeys, a New World primate much more distantly related to humans than chimpanzees (Brosnan & de Waal, 2004). The usefulness of observational learning about pain may be phylogenetically widespread— intriguingly, exposure to the sight of conspecifics reacting to fly bites (by jumping and burrowing) also reduces pain reflex latencies in deer mice (Kavaliers, Colwell, Choleris, & Ossenkopp,1999), and increases pain behavior of "observer" mice (Langford *et al,* 2006).

Prosocial and communicative acts

Where empathy is concerned, considering vicarious responding in a M-A framework may go some way towards explaining our ability to identify another's circumstances as aversive based on situational or expressive cues. It may also partially account for the "oomph" in empathy— why we are actually *motivated* to remove the source of discomfort, even though the body in question is not our own. When discomfort cannot be helped, or after a distressing event, primates often comfort each other with grooming gestures. In primates,

grooming is not just about hygiene. It has surpassed its basic cleaning function and taken on a new significance as a form of bonding and reinforcing alliances, sometimes even as a palliative measure after a fracas (Dunbar, 1996; de Waal & van Roosmalen, 1979).

Part of the calming effect of being groomed may have to do with the concomitant production of endogenous opiates (Keverne, Martensz, & Tuite, 1989; Dunbar, 1996). With respect to pain, it is interesting to note that opioids have analgesic properties and that the ACC contains a wealth of opioid receptors postulated to play a role in the modulation of the M-A dimension of pain (Vogt, *et al,* 1995). The benefits of comforting a hurt person by touching and stroking them may even apply at the level of the spinal cord. Gentle stimulation of large-diameter afferent fibers in the skin can inhibit nociceptive interneurons in the dorsal horn, which may explain why rubbing a wound alleviates pain (Melzack, 1999; Craig, 2003b)— regardless of who is doing the rubbing!

If it is ultimately advantageous for systems sensitive to potential harm to react to false positives to avoid the risk of false negatives (*eg,* LeDoux, 1996, Griffiths, 1997), then pain observation under the PHH may be a "runaway" form of anticipation that is not always necessarily truth-preserving. But if an overt response like a flinch, facial expression, or vocalization has even the slightest use as an information-bearing signal, it can take on new propensities in new contexts over the course of social and cultural evolution (Guildford & Dawkins, 1993). For example, competition among members of the same social group can result in the exploitation of others' communicative signals— as well as others' *responses* to communicative signals (Byrne & Whiten, 1997). This can take the form of outright deception, but can also manifest in the strategic deployment or

exaggeration of a display (Griffiths, 2004). Or now and then, in human interactions, it can take the form of social lubrication, as when we put on a pitying expression to communicate that we understand the other person's distress even though we actually remain relatively unmoved by it (Bavelas, Black, Lemery, & Mullett, 1997; Poole & Craig, 1992). Disjunctions between the experiential and communicative roles of pain (and disgust) displays should be borne in mind in developing a cognitive neuroscience of empathy.

Our dispositions and intentions regarding the people with whom we interact may also influence observational learning (see also Malle, 2004). This consideration is illustrated in a study in which subjects observed other subjects learning reward contingencies in a gambling card game (the Iowa Gambling Task; Bechara, Damasio, Tranel, & Damasio,1997) involving monetary gains and losses (Turnbull, Worsey, and Bowman, under review). Counterintuitively, the observers' performance when they subsequently performed the task themselves was even worse than that of subjects playing the game for the first time. This was despite the fact that they were able to predict the players' subjective ratings of rewarding and unrewarding card decks, suggesting that they had nevertheless gleaned the reward contingencies of the game from having watched the player. The authors interpret this as a type of *Schadenfreude* stemming from spontaneous adversarial or competitive attitudes which may have interfered with later performance on the task—because observers' facial expressions tended to be *positive* when the outcomes of the player's decisions in the game were *negative*. However, the observers' subsequent performance matched or even surpassed that of experienced players in two other observational conditions: first, when the observer also gained or lost money

depending on the players' choices, and second, when casual verbal communication between subjects was allowed in the observation phase.

In everyday life, observing others' interactions with potentially harmful objects is usually more like the condition in which the observer also stood to gain or lose: what can happen to the other person can (or does) happen to us. In the Turnbull *et al* study, the opportunity for verbal communication may also have been sufficient to facilitate a closer resemblance between the observers' and players' perspectives as to what the motivational goal of the game was (*ie,* for the player to gain money). These findings sit well alongside Singer *et al's* result that "empathic" responses decrease for unfair players, and under certain circumstances another person's bad outcome can even become positively-valenced. These results caution a simple account of observational learning by suggesting that merely *seeing* is not enough. There must be a basic agreement in the observer's mind as to what constitutes a good or bad outcome, and this may also be sensitive to the social parameters of the situation.

The context-sensitivity of cingulate areas presented in chapter VI reinforces the possibility that the element of social display may be an important determiner of an "empathic" response. Even if pain observation potentiates movement, it is not always appropriate to deploy overt movements, requiring that any such responses must be modulated by the contextual factors of the situation— and these can include social factors and "display rules" (Ekman, 1993), and even entire culturally-transmitted interpretive structures (Malle, 2004). Sometimes, especially in experimental settings, it is more appropriate to inhibit overt motor responses to observed pain, despite recognizing it as aversive. At other times,

perhaps more relevant to everyday social interactions, it is more acceptable to express the "cringe factor" inspired by the sight of others' pain.

III. Pain and motor processing

When one experiences an acute painful stimulus such as a pinprick, multiple variable components contribute to the sensorimotor response (Millan, 2002; Gebhart, 2004). These components involve the transmission and processing of the nociceptive signals and consequent modulation of nociceptive processing and muscle response. Such modulation can arise at the spinal level, for example from dorsal horn neurons, and at the supraspinal level, from subcortical and cortical regions. These mechanisms work together to regulate the painful sensation and to modify motor output, both of which ultimately function to shape appropriate behavioral responses to injury. This section explores ways in which mechanisms of descending modulation of motor systems during pain may be germane to pain observation.

Descending facilitation of pain-related sensorimotor responses

Although spinal reflexes can be very complex and even modularized (Sonnenburg, Andersen, & Arendt-Nielsen, 2000), they cannot provide relevant contextual information that may be important in present or future painful situations. For example, being unexpectedly pricked by a thorn while browsing for food calls for a different immediate response to the pain than receiving injuries in a territorial fight in which stamina is of the essence. Evidence is accumulating that such pain-related contextual information is provided by processing in areas of the brain that have direct or indirect influence on pain-

regulation and motor responses. Depending on the circumstances, the influence of these areas can have either inhibitory or facilitory effects at the level of the muscle.

In humans, there is growing evidence that cortical motor areas contribute to the processing of experimental pain. Positron emission tomography (PET) and fMRI studies consistently show activation of medial premotor areas such as ACC and SMA during pain (*eg,* Peyron *et al,* 2000). Primary motor cortex (MI) activation has also been reported, often in conjunction with SI (Peyron *et al,* 2000, Casey *et al,* 1996). Magnetoencephalography (MEG) research has also shown modulation of M1 oscillatory activity during pain (Raij, Forss, Stancak, & Hari, 2004), revealing coherence of M1 waves with electromyographical (EMG) waves recorded from the stimulated hand (Stancak, Raij, Pohja, Forss, & Hari, 2005). Transcranial magnetic stimulation (TMS) studies which measure motor-evoked potentials (MEPs) or laser-evoked potentials (LEPs) in response to pain have also shown motor cortex involvement, mainly in inhibition of muscles adjacent to the affected area (Valeriani *et al,* 2001; Farina *et al,* 2001, Inghelleri, Cruccu, Argenta, Polidori, & Manfredi, 1997; Le Pera *et al,* 2001).

Evidence for descending facilitation of withdrawal responses to pain comes mainly from rodent literature. These studies particularly implicate the ACC in descending facilitation of pain regulation and withdrawal responses. For example, exciting the ACC by direct microelectrode stimulation facilitates the tailflick response to a painful stimulus (Calejesan, Kim, & Zhuo, 2000). Lesions of the ACC also attenuate latencies for lifting a paw from a hotplate (Pastoriza, Morrow, & Casey, 1996) and impair fearful responses to environments previously associated with electrical shock (Johansen *et al,* 2001).

In primates, the caudo-medial portion of midcingulate cortex (Vogt *et al,* 2003, 2005) contains cells that represent cutaneous muscles (Akazawa *et al,* 2000) and show both sensory and motor responses to limb stimulation (Isomura & Takada, 2005).

The cingulate's flexible and context-sensitive modulatory role

To summarize the foregoing sections, a picture is emerging in which the dACC/MCC is involved in sensorimotor responses to pain. As outlined in previous chapters, this is supported by primate studies in which ACC neurons show flexible responses to pain-related contingencies. It also underscores the possibility that the ACC's function in pain processing may involve tracking contextual information about pain and relating it to situation-appropriate motor responses. Indeed, what is appropriate in a given situation may change depending on the context and task demands. ACC responses to noxious stimuli in the macaque monkey have shown *increased* activity during a pain-related escape task, but *decreased* activity to the same stimulation during illumination and temperature change-detection tasks which required suppression of any immediate motor responses to the pain (Iwata *et al,* 2005). This indicates that the same region of the brain can mediate facilitory or inhibitory control over motor responses during pain. The dACC activation profile seen in chapter VI also hints at a similar task-dependent pattern for pain observation, although it is difficult to interpret the nature of the processing underlying the BOLD signal changes here.

In Chapter VI, the paradigm involved preparing and executing motor responses to stimuli differing in their degree of inherent motivational relevance.

The behavioral reaction times and associated hemodynamic responses within cingulate regions changed depending not only on whether the observed stimulus was noxious or innocuous, but also on whether the subject was required to button-press for hits or misses. Critically, the noxiousness of the stimulus was not relevant to the task, nor was it immediately motivationally-relevant to the participant, who did not stand to experience actual harm at any point in the experiment. However, the noxiousness of the stimulus nevertheless modulated responses in the cingulate cortex during motor processing, specifically in combination with hits. This noxious-hit combination is the most likely to cause pain to the observed person as well as to signal potential danger to the observer. This implies that the presence of potential harm to another individual influences motor response selection processes in the observer.

An important issue for future research is the timecourse of vicarious responses to pain, not only in behavior, but also in the cingulate and elsewhere in the brain. The behavioral results in chapter VI showed that when button-press responses are made at the moment the implement contacts the other's hand, noxious hits reduce reaction times. In other studies, the behavioral or neural response is measured after intervals along the order of one second or more after the contact happens. In chapter V, responses occurred 500-900 ms after seeing the needle go into the hand (100-500 ms after the offset of the 1-second video). By 900 ms participants had developed specific responses to the needle stimuli, slowing press (approach-type) movements and speeding release (withdrawal-type) movements.

In Avenanti *et al* (2005), the measure was taken even later. The TMS pulse occurred 1100-1800 seconds after seeing the needle go into the hand or foot. It

is possible that an initial pain-related response becomes inhibited under the task and/or timing conditions of the experiment, requiring time to recover. Alternatively, pain observation may elicit initial general urgent responses (for example, "move hand!") that only later resolve into specific, differentiated movements ("move right index finger away!") or even the suppression of movement ("don't move, you're in an experiment!"). Consistent with the character of the ACC, any initial response may be suppressed or attenuated by top-down processes that depend on task factors and the length of the interval between stimulus and measure.

The longest interval so far in the literature is that in Singer *et al* (2004), who modelled together all events in trials lasting 9.5 seconds. This brings up the importance of timing with respect to the localization of areas in the brain. As mentioned earlier, a pain-related area in the caudal ACC showed an interaction between pain in self and other and had an initial visual response. It showed higher average responses to self-pain than to other-pain, but with a decrease in the seen pain response not beginning until 4 seconds into the 9.5-second trial. This could reflect a dropoff in an initial anticipatory or even vicarious response, decaying with increasing certainty about the nature of the stimulus and the expected behavioral outcome (*eg* whether it is necessary to brace for a shock or simply to watch). In everyday life, however, vicarious responses occur on a much shorter timescale. This result indicates that the "seen pain" response here is time-dependent, but in itself does not rule out a role for the caudal cingulate in processes coupling felt and seen pain— perhaps through an early evaluation of others' pain and preparation of the appropriate behavioral response.

Observed pain and motor processing

Further insight into the general relationship between motor processing and pain observation is offered by two recent studies measuring hand MEPs to pain observation during TMS over M1 (see chapter V). These showed a decrease in MEP amplitude when subjects viewed a hypodermic needle apparently injected deep into the tissue of a hand (Avenanti *et al* 2005, 2006). In the first series of experiments (Avenanti *et al,* 2005) the authors measured responses of two hand muscles to noxious or innocuous stimuli entering a) either of the two hand muscles (abductor digiti minimi, ADM and first dorsal interosseus, FDI); b) a foot; c) a tomato (a non-body part). Significant amplitude decreases were specific not only for the body part observed but also for the muscle observed, compared to the tomato or the innocuous cotton bud control. In both direction and magnitude, the decrease in MEP amplitude during pain observation resembles the decrease other studies have shown in response to experienced painful stimuli (Farina *et al,* 2001; Valeriani *et al,* 2001; Le Pera *et al,* 2001). The authors interpret the decrease as indicative of motor cortex inhibition of the distal muscles.

These results, suggesting motor cortex *inhibition* during pain observation, may seem at odds with those of the studies in this thesis, especially in chapters V and VI which suggest selective *facilitation* of *overt* finger responses. The experiment in chapter V indicates that at the behavioral level, finger movements are facilitated in a response-specific manner after a delay. The experiment in chapter VI shows that reaction times are also faster when the subject responds immediately at the moment of contact. The MEP results, on the other hand, suggest muscle-specific cortical *inhibition* of muscle excitability. Is it possible

to make a general statement about whether pain observation facilitates or inhibits motor responses?

There are several factors which make these results difficult to compare. First, although the modulation is likely to originate in cortex, it is not certain whether a decrease in MEP amplitude reflects cortical inhibition of the muscles. Second, in this and in other TMS studies in which pain is directly experienced on the hand, no overt behavioral response is required; indeed, movement of the stimulated hand must be suppressed. In contrast, the two behavioral experiments described in chapters V and VI explicitly required motor responses and the stimuli were viewed in the context of producing a finger movement.

Many other important factors also differ among these pain observation experiments, as well as among other TMS pain experience studies which provide the source for comparison for interpreting the pain observation results. For example, the type of pain administered (capsaicin injection, topical capsaicin cream, CO^2 laser) and the timescale of the painful stimulation (immediate or sustained, within milliseconds or 20-40 minutes) varies among studies. Inhibitory or facilitory effects on muscle potential could vary accordingly, prolonged pain being more likely to involve secondary pain mechanisms associated with protective behavior and immobilization of the injured body part (Price, 2002).

As mentioned in chapter V, these results can be interpreted in terms of a broad defensive/protective role of motor responses to real or potential pain. One interpretation is that, in the presence of pain in distal effectors such as the hand, a rapid interruption of prehension would be adaptive (Farina *et al,* 2001). For example, if one mistakenly grasped a hot object it would be advantageous to

cease closing one's hand around it as soon as possible; likewise, if previously-learned contextual cues warn that an object *may* be hot, it would be best to proceed with caution and be prepared to drop it. Further, there is evidence that complex interactions among arm and hand muscles can be instigated by cortical motor systems during pain, with reduced MEPs in distal (hand) muscles alongside a slight facilitation of proximal (upper arm) muscles, which might enhance an arm retraction simultaneously with prehension interruption.

The intensity of the apparently painful stimulus also may matter. An important inconsistency with the MEP results and those of neuroimaging studies (Morrison *et al* 2004; Singer *et al* 2004; Jackson *et al* 2005) is that the MEP amplitude decrease correlated with self-report measures of the sensory (*eg* intensity) components of the observed pain. The authors interpreted this as reflecting a sensorimotor, effector-specific mapping, implying that observed pain processing is not limited to motivational-affective systems, but that a sensory somatotopy exists. Avenanti *et al* (2005, 2006) used a trick syringe with a retractable needle, so that it was possible to make it look as if the lancet were plunging very deep into the hand in the videos. The resulting "injuries" could be considered more intense than the pinprick videos used by Morrison *et al* (2004; chapter II).

To test the hypothesis that greater apparent intensity may lead to greater modulation of sensorimotor cortices, Avenanti *et al* (2006) created their own pinprick stimuli to compare to the more intense original versions. The so-called "flesh-and-bone"- injury version of the video produced MEP amplitude decreases as in the previous study, but the pinprick did not show significant decreases compared to the more intense version. But further experimentation is

needed to determine whether the underlying cortical processing codes intensity absolutely or relatively. That is, if the midcingulate contributes to the motor cortex response, then it is conceivable that it encodes trials within the same block comparatively with respect to one another, rather than in terms of some absolute scale of intensity. For example, one might expect to see amplitude decreases to pinpricks if these trials occurred in the context of (*eg,* in the same blocks as) cotton bud touches, as in chapters II and III.

However, at present the methodological differences do not obscure the major points of agreement between the TMS study and the present behavioral study (which to date represent the only studies investigating motor-pain observation relationships). Most importantly, each demonstrates an effect of pain on the motor system. Furthermore, each reveals stimulus-specificity, with the effects for hands and needles failing to generalize to non-body objects such as tomatoes and sponges. They also show specificity of response on the output side, either for response type (press vs release) or muscle (ADM vs FDI).

IV. Common coding and the analogy with mirror neurons

Common coding, action, and empathy

This evidence covered in the foregoing section points to a relationship between visual perception and output-related processing in pain. As emphasized in the introductory chapter, many current models of empathy and interpersonal representation hinge on the notion that visual perception and output-related processing are supported in crucial ways by the same neural mechanisms. An important contemporary articulation of the underlying functional idea comes from Prinz' "common coding" hypothesis (Prinz, 1990,

1997). It proposes that the brain parsimoniously encodes certain perceptual representations (*eg* visual) and action-related representations in the same terms, rather than their being "informationally incapsulated" (Fodor, 1983) from one another in higher-level processing. In many cases this has been interpreted as implying that activition of the same neural substrate in two domains is a sufficient condition for common coding, an assumption that was called into question by the results of chapter III.

In various senses, this idea has been incorporated by other models of empathy, especially those that have been inspired or informed by neuroscientific evidence. The four major models that have emerged in recent years are Gallese's "shared manifold hypothesis" (Gallese 2001, 2003); the Perception-Action Model (Preston & de Waal, 2003); Meltzoff and Decety's application of the Active Intermodal Mapping model (Meltzoff 2002, Meltzoff & Decety 2003), and Cole's model centering on the importance of facial expression to the development of empathy (Cole, 2001). These models often implicitly even take action to be at the core of perception itself (*eg* Noë, 2004).

Gallese's "shared manifold hypothesis" (2001, 2003) explores the relationship between action understanding and empathy. This model is primarily influenced by the idea of common coding between perception and action systems (Prinz, 1990; see chapter III), and another current idea, forward modelling in action representation networks (Wolpert, Ghahramani, Flanagan, 2001, Wolpert, Doya, & Kawato, 2003). Gallese concentrates on the primate frontal-parietal action representation network, using it as both an illustrative model for empathy networks, and also as a possible functional route to empathy-related intersubjective phenomena. The model draws on a proposed network for

social action representation in the monkey in which higher-level visual descriptions of perceived actions are handled among direct and indirect connections between inferior parietal cortex (area PF), STS, and lateral premotor cortex (area F5) (see Keysers & Perrett, 2004). Within this network, mirror neurons have the role of representing observed goal-directed actions in egocentric terms.

The shared manifold model also relies on the idea that the output of processing in motor networks is predictive of the action's consequences. This is postulated to occur via mechanisms which circumvent noise and transmission delays in sensorimotor systems by sending "copies" of predicted efferent sensorimotor feedback among interconnected areas (Wolpert *et al,* 2001; 2003, Grush, 2004). These efference copies can be the result of forward mapping, in which current states of the motor system are used to predict subsequent motor commands; or inverse mappings, in which predictions are made about what motor commands would be necessary to achieve a given goal state (see Grush, 2004 for a thorough evaluation of such models). Gallese's model relies heavily upon the presence of the extensive interprojections of action representation areas (such as inferior frontal regions) and other regions of the brain in postulating such efference copies of predictive sensorimotor signals among parts of the proposed network. For Gallese it is the multidimensionality of the action representation network and its levels that give it the properties of a "manifold"; and it is the efference signals that deal in predictive representations of *others'* actions (*eg* from mirror neurons) that render the manifold interpersonal, or "shared."

The emphasis on action representation is also explicit in two other models, Preston and de Waal's Perception-Action Model (PAM) (Preston & de Waal, 2003), and Meltzoff's Active Intermodal Mapping model (AIM) (Meltzoff 2002, Meltzoff & Decety 2003). PAM postulates that any mechanism that maps a perceptual input onto a behavioral response— actual or potential— can be seen as a candidate for a proximal mechanism of empathy. Through these mechanisms recognition and understanding of others' mental and emotional states can be built up. Again, the underlying idea is that others are understood via access to one's own mental and emotional states.

This idea is also a central feature of Meltzoff's AIM model (Meltzoff, 2002; Meltzoff & Decety, 2003). In the AIM model, cognitive representations of other's mental states are products of inferences forged through repeated "mappings" of perceptual representations of others' movements and behavior onto representations of one's own movements, behavior, and mental states. This mapping procedure begins in infancy and continues throughout the course of normal development. Because it places others in an analogical relation to self, active intermodal mapping can give rise to empathy in principle.

A different, though related, model of empathy has been put forward by Cole (2001). This model emphasizes the putative role of the facial muscles in the ability to decode emotion from facial expression. In this respect, it draws predominantly on the "facial feedback hypothesis," characterized by Ekman as "a very literal means by which we feel the sensations that the other feels" via proprioceptive feedback from facial muscles (Buck, 1980; Adelmann & Zajonc, 1989). In the social domain, a possible source of such feedback could be from unconscious mimicry of others' expressions. EMG studies of facial muscle

facilitation to masked emotional facial stimuli have shown that happy faces tend to give rise to increased zygomatic (smiling) muscle activity; likewise, angry faces elicit increased corrugator (frowning) muscle activity (Dimberg, Thunberg, & Elmehed, 2000; Lundqvist & Dimberg, 1995). The degree of facilitation has also been shown to correlate positively with scores on an empathy inventory (Sönnby-Borgstrom, 2002).

Cole himself has observed patients with Moebius syndrome, a congenital total paralysis of the facial muscles (Cole, 2001). On the basis of structured interviews, he has suggested that these patients may differ from normal individuals in the way they experience emotions— including empathy— because they lack direct experience of the connection between felt emotions and facial expressions. Cole suggests that both expression production and feedback from others are crucial for recognizing and learning about emotion itself, at least as far as its expression and control during social interactions is concerned.

On the other hand, the results of chapter III qualify the idea that pain observation involves the activation of the same neural substrate in felt and seen pain. Much of the neuroimaging research on the human mirror system and action perception— as well as empathy— relies on this "substrate identity" assumption (*eg* Calvo-Merino, Glaser, Grèzes, Passingham, & Haggard, 2004; Buccino, Lui, Canessa, Patteri, & Lagravinese, 2004). However, the common coding hypothesis merely stipulates that the terms in which different representations are encoded be commensurate, for example with respect to spatial and temporal reference frames or semantic content (Hommel & Prinz, 2001). Substrate identity may be an avenue to commensurate coding, and surely often a very economical one. But commensurate codes can also be implemented

by non-identical substrates, a possibility that is *not* excluded by the results of chapter III (nor examined in most human mirror system research!). In fact, it is an intriguing possibility that commensurate coding between felt and seen pain in the cingulate is subserved by distinct and proximal, or distinct and intertwined neural populations (or even dynamically distinct *or* identical, for instance depending on individual cell responses over a whole session, or adaptation to repeated stimulation). This prompts the question of whether vicarious responding in pain observation could represent a common coding mechanism coding *felt and seen pain* in commensurate terms, analogous to the way mirror neurons code *vision and action* in commensurate terms.

The analogy with mirror neurons

Vicarious responding effects in motivational-affective networks would not have been so eagerly sought, nor their significance quite so readily grasped, if it had not been for the prior discovery of mirror neurons in action representation networks. As noted in the introductory chapter and elsewhere, mirror neurons provide the paradigmatic empirical example of how a common coding mechanism can collapse perceptual with motor information (Prinz, 1990; Rizzolatti *et al*, 1996, Gallese *et al*, 1996). Altogether, the evidence presented in this thesis indicates that brain regions involved in M-A aspects of pain processing also become active during pain observation. This suggests a basic mechanism for understanding others' pain. Intriguingly, it also resembles mirror responses in action representation pathways, pointing to parallels between action and pain observation.

But how deep does the analogy go? Have we now discovered *affective* mirror neurons? Motivational-affective and action representation networks handle different kinds of information, but there are numerous formal points of similarity which may nudge us closer to a functional understanding of organizational principles in the social brain. Though different, action-representation (A-R) and motivational-affective (M-A) networks in the primate brain each play crucial roles in preparing and generating motor responses. The former supports spatial and metrical guidance for action on objects, and the latter uses motivational features to guide aversive behavior to harmful objects. To conclude this thesis, I propose in this section that "mirrorlike" responding to others' circumstances is but one among a wider set of functional properties shared by M-A and A-R systems.

Similarities between M-A and action representation networks

The ambition of a number of recent cognitive neuroscience studies is to identify neural correlates of fairly high-level aspects of empathy— among them self-other distinctions (Lawrence *et al,* 2006), perspective-taking (Jackson *et al,* 2006, Lamm *et al* in press), prosocial responding (Singer *et al,* 2006), compassion (Farrow *et al,* 2001), and associated subjective experiences. Yet in my view, at the heart of pain empathy research lie more basic questions about pain observation. How is the brain able to recognize that something happening to another person is painful *at all*, independently of whether the observer empathizes with this person? Indeed, in everyday life we are able to recognize others' injuries as being of a painful nature even if our emotional reaction is minimal or nonexistent. Such questions parallel analogous problems faced by

action perception researchers: how do we recognize an intentional action *at all,* merely on the basis of visual information?

The premotor and parietal action representation circuits discussed in the foregoing section provide the model case for vicarious responding. Although some theorists distinguish between "motor empathy" and "cognitive empathy" (Blair, 2005) as well as forms of contagion and mimicry often grouped with action perception phenomena (Goldie, 2000), other theorists propose relatively direct relationships between mirror neurons in action representation networks and the affective element associated with empathy (Carr *et al,* 2002; Panksepp, 2005; Leslie *et al,* 2004). In contrast, the analysis presented here does not assign a direct or necessary role to action representation in the recognition and interpretation of others' affective states. But it does consider that mirror neurons are a rich source for analogy when it comes to understanding general principles of perception-response transformations in the social domain. In making the following comparisons, I consider only those areas in which microelectrode recordings in macaques or humans have demonstrated vicarious responding. These are monkey premotor area F5, monkey parietal area PF (7b), and human MCC/dACC.

At least five major similarities between these M-A and frontal-parietal A-R regions can be drawn (Table 3). They are: *1) transformational coding; 2) goal-level coding; 3) movement preparation; 4) relationship to sensory integration processes* and *5) cytological heterogeneity.* Premotor F5, parietal PF, and MCC/dACC each subserve a translation of sensory information into response codes. The clearest illustrations of this are provided by neural populations in macaque premotor F5, which transform visual shape- and space-related object

information into a motor-specific vocabulary of potential actions (Rizzolatti & Luppino, 2001; Rizzolatti, Fogassi, & Gallese 2002; Kakei, Hoffman, & Strick, 2003). These transformations are based on object features or other relevant cues, as in the case of "canonical" neurons (Rizzolatti & Craighero, 2004; Grèzes *et al,* 2003). In the case of mirror neurons, the relevant transformations are based upon the observation of others' actions (di Pellegrino *et al,* 1992; Rizzolatti *et al* 1996). Mirror neurons have also been observed to discharge when the object of the action is out of sight (Umiltá *et al,* 2001), as well as to sounds associated with certain actions, like tearing a paper or cracking open a peanut (Keysers *et al,* 2003). There is also compelling early evidence that a proportion of mirror neurons are sensitive to intransitive ingestive and communicative facial gestures (Ferrari *et al*, 2003; Buccino *et al,* 2004).

However, the "motor vocabularies" in which F5 and ACC trade are relatively flexible with regard to specific effectors. The potential actions coded by F5 neurons pertain to the hand, foot, and mouth (Godschalk, Mitz, van Duin, & van der Burg, 1995), but representation here exists at the level of the *goal* of action, not the particular effector (Castiello, 2005; Hommel *et al*, 2001; Metzinger & Gallese, 2003). There are neurons that fire when the monkey makes a tearing action, regardless of whether it is the hands or the mouth that is actually carrying out the tearing (Rizzolatti & Luppino, 2001). In a comparable manner, ACC neurons may operate at the level of "urge representation", a notion supported by human microstimulation reports (Bancaud & Talairach, 1993; Matsumoto, Suzuki &Tanaka, 2004). Goal-level representation also exists in inferior parietal cortex (Andersen & Buneo, 2002), which includes PF, when monkeys perform the same actions with different goals (Fogassi *et al* 2005;

Fogassi & Luppino, 2005). Evidence for goal-level representation in human parietal cortex is emerging as well (Hamilton & Grafton, 2006).

Parietal area PF (7b) is associated with face and arm representation. In the monkey, the inferior and superior posterior parietal areas chiefly receive visual inputs from striate cortex, but are also the first regions along the dorsal visual stream to integrate these retinally-derived signals with other sensory signals (such as somatosensory and proprioceptive afferents) to form a higher-order representation of visual space (Driver & Mattingley, 1998). Like F5 and dorsal ACC, the cell types in PF are not functionally segregated (Rizzolatti & Craighero, 2004). More importantly, however, PF contains neurons that discharge when the monkey performs specific movements. Mirror neurons with both visual and motor properties have been discovered here too (Rizzolatti & Craighero, 2004; Rizzolatti, Fogassi, & Gallese 2002).

Found among these mixed populations are also *pain*-related sensory neurons with visual properties (Dong *et al*, 1994). A proportion of these fired both when a part of the skin on the face was stimulated with noxious heat, and when the monkey viewed a threatening stimulus coming towards or hovering near that part of the skin. Moreover, the responses of these cells closely matched the behavioral response curves for the tolerance-escape task the monkeys performed. In nearby ventral intraparietal sulcus (VIP), part of the fronto-parietal action circuit, microstimulation has produced eye, lip, and arm movements comparable to those elicited by an airpuff into the eyes (Cooke *et al*, 2003). This indicates a role for the parietal cortex in the orchestration of aversive movements that require the integration of visuotactile information into an egocentric coordinate frame. The results of chapter IV suggest that a human

homologue may exist, involved in the encoding of noxious visual events within peripersonal hand space (Lloyd, *et al,* 2006).

Each of these areas, then, plays a more or less direct role in relating integrated sensory information to potential motor responses. That they interact with each other too is evidenced by the numerous reciprocal projections from PF to some of the key regions in the preparation of actions and motivated movements. PF sends connections to premotor and supplementary motor cortices, to the cingulate cortex, and to the anterior insula (Dong *et al*, 1994). It is quite plausible that reciprocal communication between PF and these other quarters of M-A and A-R circuitry influences the preparation and initiation of motor responses. When the stimulus possesses noxious associations or a negative hedonic impact based on past interactions, M-A processing may mediate motor response via cingulate motor, supplementary motor, and premotor projections. Other complex aversive muscular responses (like the airpuff reaction) that do not necessarily involve flexible, motivated response learning, but do require visuo-tactile, spatio-temporal integration within peripersonal space, may be mediated primarily by sensorimotor circuits in parietal cortex (Graziano & Cooke, 2006) via projections to premotor and motor cortices.

Premotor F5, parietal PF, and MCC/dACC are also cytologically heterogeneous areas (Vogt *et al* 1995, 2003; Picard, Strick, & Dum, 1998; Matelli *et al* 1991; Rizzolatti & Luppino, 2001). This means that they contain mixed cell populations, in which either the morphological or response properties (or both) of the cells differ, even though they are found in the same neighborhood of tissue. In the case of ACC, nociceptive and reward-sensitive

neurons have been found in area 24 (Koyama, Kato, Tanaka, & Mikami, 2001), as well as "spindle cells" and large clusters of pyramidal cells in layer V which are postulated to operate in a motor capacity (Nimchinsky, Vogt, Morrison, & Hof, 1995; Vogt *et al* 1995).

Analogies always rest on comparisons. The more resemblances there are between two systems, the greater one's confidence that these reflect a more fundamental relationship of similarity. Functional similarities frequently indicate comparable organizational constraints (think of insect wings and bird wings). The hypothesis that vicariously responding neurons in M-A regions belong in the same category as mirror neurons depends on how deep these similarities go. The analysis presented here is intended merely as an initial step towards determining this through the shaping of further hypotheses.

Table 3. Similarities between action-representation and motivational-affective areas observed to respond vicariously.

Property	Monkey premotor F5	Monkey parietal PF	Human dorsal ACC
Transformational coding (perception/response)	Visual and auditory object features in space/ egocentric motor code	Propriceptive and visual/ motor code	Nociceptive, visual/ motor code
Goal-level coding	Grasping, tearing, etc; intentions	Grasping embedded in action chains	Aversive motivational urges
Movement preparation	Actions of hand and mouth	Distal, proximal limb and face movements	Aversive, nocifensive skeletomotor responses
Relationship to sensory integration	Inputs from parietal multisensory areas	Inputs from multiple sensory modalities	Inputs from temporal and parietal multisensory areas
Cytological heterogeneity (functional or morphological)	Hand-, face-, and arm-visual- and motor-selective cells	Proprioceptive face and arm, visual-, touch-, motor-selective cells	Pain, reward; pyramidal, spindle cells

Differences: "hot" vs. "cold" motor processing

By definition, M-A and A-R networks selectively process information from different domains. M-A networks are more concerned with potentially rewarding or aversive states of affairs. A-R networks, on the other hand, deal with relating kinesthetic and proprioceptive information with features of objects in space. This distinction may not always seem so obvious. Considering that motor output is the end result of the examples discussed here, one might be tempted to consolidate the M-A and A-R into a single framework. Conversely, one might wish to keep feelings and actions entirely separate, especially since M-A processing is not limited to skeletomotor efference, but also influences behavioral disposition and visceral responses via autonomic and endocrine channels too.

Yet computationally, M-A and A-R pathways are distinct but related axes for the encoding of perceptual information. They are neither wholly divergent nor wholly convergent. Indeed, partly because they both result in skeletomotor output, M-A and A-R systems are continuous and certainly interconnected (MacDonald, *et al,* 2000; Ridderinkhof, Ullsperger, Crone& Nieuwenhuis, 2004). The important difference is that they are essentially concerned with pulling apart and putting together different *kinds* of information. M-A systems have to do with learning flexible responses regarding the properties of objects: will it bite? can I eat it? The A-R system, in contrast, is concerned with kinesthetic body representation and the more metrical properties of objects: where is it? can I grab it?

Considering these functional differences, the two systems are likely to differ in more specific ways too. Spatial information, such as an object's coordinates

within the visual field or a sensation's location on the body, may not be as important for M-A networks as they are for A-R networks. Although aversive responses do require context-dependent flexibility, they are not likely to necessitate such highly coordinated distal, digital manipulation as actions do. When encountering a threat to tissue, less precise movements often suffice to remove oneself from the offending object. As opposed to reaching-grasping actions, aversive or nocifensive actions often do not need to be more refined than the coordinated movement of the forelimb and/or hand away from the noxious object, or (as suggested by chapter V and MEP research) the cessation of hand prehension.

Withdrawal actions in M-A networks and grasping actions in A-R networks are each special cases of movements that cluster toward one or the other end of a figurative "hot-cold" spectrum (Fig. 3; Table 4). Processing in lateral premotor areas is more associated with "cold" action representation. Generally, cold actions and intentions are directed towards object manipulation. This requires the integration of spatial properties of the object in the environment to coordinate accurate reaching and grasping movements, as well as the fine distal and digital control needed to manipulate them once grasped. Subjectively, cold actions may have a relatively dispassionate feel, such as reaching for a cup or a pen or adjusting the steering wheel to curves in the road.

In contrast, the anticipation and execution of movements in response to potentially harmful (or motivationally desirable) objects or events are "hot"—quick, valenced, and with that elusive subjective sense of urgency. Such movements and urges may be preferentially represented in medial premotor pathways including the cingulate, pre-SMA, and SMA. In the specific case of

pain as a "motivational" category, hot actions are most likely to be aversive or nocifensive movements. A withdrawal action is a typical hot action in the context of pain.

In either case, movements are coded on the basis of the goal or probable consequences of the interaction with the object. The behavioral results of chapter V point to the idea that, just as objects may be thought of as having "affordances" with respect to cold reaching-grasping actions, they can similarly be thought of as having aversive affordances with respect to hot withdrawal actions. Where pain is concerned, hot action representation in medial premotor cortices may have at least two important aspects. First, it may represent certain surface features of withdrawal or grasping movements, especially their initiation or disengagement. That is, M-A processing in medial areas may be concerned with whether the object affords grasping or letting go, and representing the decision to initiate or terminate a hand movement. Some patients with lesions in this region have shown an inability to inhibit grasping when the hand's skin is touched, and others have been impaired in the voluntary releasing of objects already in the grasp (Rushworth & Denny-Brown, 1959; Rostomily, Berger, Ojemann, & Lettich, 1991).

Second, it may also represent the goal of the movement in motivational terms. The more something hurts, the greater the desire to let go of it or withdraw from it. Although the emphasis here has been on aversive movements, it is important to reiterate that in principle hot actions are not limited to withdrawal actions. Motivational urges to take hold of an object (*eg* a food item, a good book) can be just as strong. Both grasping and withdrawing can thus be thought of as cases of hot movement depending on the motivational

features of the object or context. However, even when it is "hotly" initiated, grasping ultimately makes use of spatial and metric information and requires a degree of reach-grasp coordination. In contrast, hot withdrawal actions for pain can be independently planned and executed by medial premotor cortex without recourse to lateral premotor systems. This occurs with reference to motivational object features (*eg* sharpness, heat, aversiveness, unpredictability, etc) rather than geometrical object features such as shape, size, or contour. Where the action itself is concerned withdrawal need not be coordinated to such a degree as reaching-grasping actions. Often even a proximally-effected "flail" does the trick. Flailing, wincing, flinching, twitching: undignified perhaps, but they may ultimately represent main tap-roots for our lack of indifference to the pain of others.

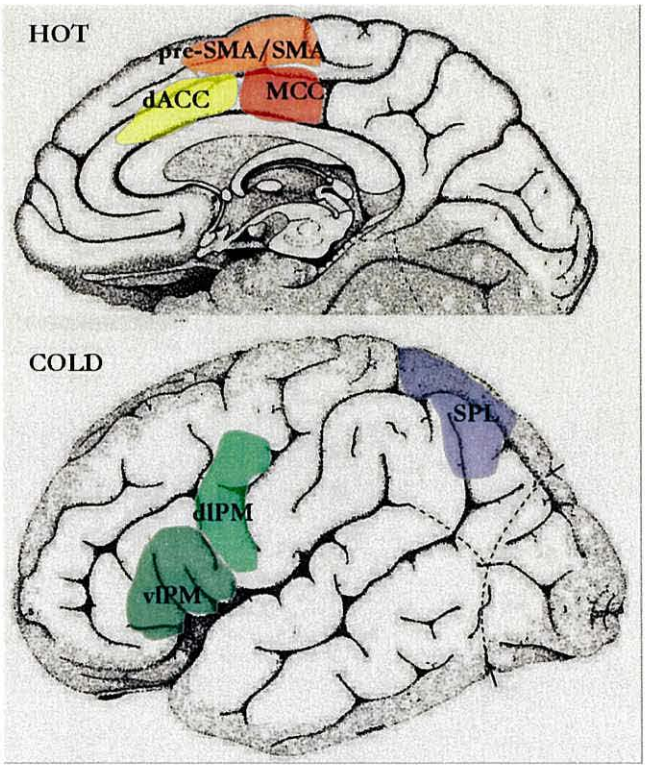


Figure 3. Proposed pathways for the preparation and execution of "hot", motivationally-based movements and "cold", spatial/metrically-based movements. SMA = supplementary motor cortex, dACC = dorsal anterior cingulate cortex, MCC = midcingulate cortex, SPL = superior parietal lobe, dlPM = dorsolateral premotor cortex, vlPM = ventrolateral premotor cortex.

Table 4. Functional and anatomical differences between "hot" and "cold" motor representation pathways.

Property	"Cold" motor representation	"Hot" motor representation
Anatomical regions	Fronto-parietal action representation networks	Mediofrontal pathways
Type of coding	Metrical, spatial information	Reward, aversion information
Level of coding	Action goals, intentions	Motivational urges, impulses
Domain	"Graspability" and location of objects	Affective evaluation of objects
Function	Visual action guidance in egocentric reference frame	Linking events with consequences in organism-centered terms

Conclusions

The findings of the studies presented in this thesis indicate that both feeling pain directly and seeing others' apparent injury give rise to activations in the dACC and MCC, which are involved in coding the motivational-affective dimension of pain processing. The converging behavioral and neuroanatomical results presented here also reinforce the relationship between pain observation and motor processing in medial premotor areas. The implications of this research for our understanding of empathy are that the compassionate and prosocial reactions that we often experience when we see others in distress may be underpinned by neural systems involved in relating situations and contexts to aversive outcomes and associated motor responses. Responses in these neural systems are modulated by both low-level features, such as the spatial location

and orientation of others' body parts with respect to our own (*eg,* chapter IV), and by high-level factors such as the constraints of the current task (*eg,* Chapter VI). Taken together, these results loosen the three problems set out at the beginning— the problem of foreign experience, the sense-datum problem, and the functional mechanism problem— by pointing to mechanisms by which the brain interprets others' aversive situations as possessing intrinsic motivational relevance in first-person terms.

REFERENCES

Adams, A. (2001). Empathy, neural imaging, and the theory versus simulation debate. *Mind and Language* 16, 368-92.

Adelmann, P.K. & Zajonc, R.B. (1989). Facial efference and the experience of emotion. *Annual Review of Psychology* 40, 249-280.

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., & Damasio, A.R. (2000). A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. *The Journal of Neuroscience*, 20, 2683-2690.

Adolphs, R. (2002). Neural systems for recognizing emotion. *Current Opinion in Neurobiology* 12:2, 169-177.

Adolphs, R., Tranel, D., and Damasio A.R. (2003). Dissociable neural systems for recognizing emotions. *Brain and Cognition* 52, 61–69.

Akazawa, T., Tokuno, H., Nambu, A., Hamada, I., Ito, Y., Ikeuchi, Y., Imanishi, M., Hasegawa, N., Hatanaka, N., & Takada, M. (2000). A cortical motor region that represents the cutaneous back muscles in the macaque monkey. *Neuroscience Letters* 282, 125-28.

Akkal, D., Bioulac, B., Audin, J., & Burbaud, P. (2002). Comparison of neuronal activity in the rostral supplementary and cingulate motor areas during a task with cognitive and motor demands. *European Journal of Neuroscience* 15, 887-904.

Amodio, D.M., Frith, C.D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience* 7, 268-77.

Andersen, R.A. & Buneo, C.A. (2002). Intentional maps in posterior parietal cortex. *Annual Review Neuroscience* 25, 189–220.

Armel, K.C. & Ramachandran, V.S. (2003). Projecting sensations to external objects: evidence from skin conductance response. *Proceedings of the Royal Society London B: Biological Sciences* 270, 1499–1506.

Armstrong, D.M. (1962). *Bodily Sensations.* London: Routledge & Kegan Paul Ltd.

Augustine, J.R. (1996). Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Research Reviews* 22, pp. 229-244.

Avenanti, A., Bueti D., Galati, G., & Aglioti, S.M. (2005). Transcranial magnetic stimulation highlights the sensorimotor side of empathy for pain. *Nature Neuroscience* 8, 955-60.

Avenanti, A., Paluello, I.M., Bufalari, I., & Aglioti, S.M. (in press). Stimulus-driven modulation of motor-evoked potentials during observation of others' pain. *Neuroimage,* epub ahead of print.

Aydede, M.(2005). "The main difficulty with pain." In Murat Aydede (Ed.), *Pain: New Essays on Its Nature and the Methodology of Its Study,* 123-136. Cambridge: MIT Press.

Badre, D. & Wagner, A.D. (2004). Selection, integration, and conflict monitoring; assessing the nature and generality of prefrontal cognitive control mechanisms. *Neuron* 41, 473–487.

Baird, A., Dewar, B.K., Critchley, H., Gilbert, S., Dolan, R.J., & Cipolotti, L. (2006). Cognitive function after medial frontal lobe damage including the anterior cingulate cortex: a preliminary investigation. *Brain and Cognition* 60, 166-75.

Bancaud, J., & Talairach, J. (1992). Clinical semiology of frontal lobe seizures. *Advances in Neurology* 57, 3-58.

Barch, D.M., Braver, T.S., Akbudak, E., Conturo, T., Ollinger, J.,& Snyder, A. (2001). Anterior cingulate cortex and response conflict: effects of response modality and processing domain. *Cerebral Cortex* 11, 837-848.

Batson, C. D., Early, S., & Salvarani, G. (1997). Perspective taking: Imagining how another feels versus imagining how you would feel. *Personality and Social Psychology Bulletin* 23, 751-758.

Bavelas, J. B., Black, A., Lemery, C. R., & Mullett, J. (1987). Motor mimicry as primitive empathy. In *Empathy and its development* (N. Eisenberg & J. Strayer Eds.), 317-338. Cambridge: Cambridge University Press.

Bechara, A., Damasio, H., Tranel, D., & Damasio, A.R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science* 28, 1293-5.

Bechara, A., & Naqvi, N. (2004). Listening to your heart: interoceptive awareness as a gateway to feeling. *Nature Neuroscience* 7, 102-103.

Beckmann, C.F., Jenkinson, M., & Smith, S.M. (2003). General multilevel linear modeling for group analysis in FMRI. *Neuroimage* 20, 1052–1063.

Berridge, K.C. (2004). Motivation concepts in behavioral neuroscience. *Physiology and Behavior* 81, 179-209.

Berridge, K.C., & Robinson, T.E. (2003). Parsing reward. *Trends in Neurosciences* 26, 507-13.

Berthier, M., Starkstein, S., & Leiguarda, R. (1988). Asymbolia for pain: a sensory-limbic disconnection syndrome. *Annals of Neurology* 24, 41–49.

Bingel, U., Glascher, J., Weiller, C., & Buchel, C. (2004). Somatotopic representation of nociceptive information in the putamen: an event-related fMRI study. *Cerebral Cortex* 14, 1340–1345.

Blair, R.J.R. (2005). Responding to the emotions of others: dissociating forms of empathy through the study of typical and psychiatric populations. *Consciousness and Cognition* 14, 698-718.

Blakemore, S.J., Frith C.D., &Wolpert D.M. (2001). The cerebellum is involved in predicting the sensory consequences of action. *Neuroreport* 12, 1879-1884.

Blakemore, S.-J., Bristow, D., Bird, G., Frith, C., & Ward, J. (2005). Somatosensory activations during the observation of touch and a case of vision-touch synaesthesia. *Brain* 128, 1571-83.

Blakemore, S.-J. & Frith (2005). The role of motor contagion in the prediction of action. *Neuropsychologia* 43, 260-67.

Blankenburg, F., Ruben, J., Meyer, R., Schwiemann, J., & Villringer, A. (2003). Evidence for a rostral-to-caudal somatotopic organization in human primary somatosensory cortex with mirror reversal in areas 3b and 1. *Cerebral Cortex*, 13, 987-993.

Botvinick M & Cohen J. (1998). Rubber hands "feel" touch that eyes see. *Nature* 391, 756.

Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S., & Cohen, J.D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 402, 179-81.

Botvinick, M.M., Cohen, J.D., & Carter, C. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends in Cognitive Sciences* 8, 539-46.

Bowsher, D., Brooks, J., & Enevoldson, P. (2004). Central representation of somatic sensations in the parietal operculum (SII) and insula. *European Neurology* 52, 211–225.

Botvinick M., Jha A.P., Bylsma L.M., Fabian S.A., Solomon P.E., & Prkachin K.M. (2005). Viewing facial expression of pain engages cortical areas involved in the direct experience of pain. *Neuroimage* 25, 312-9.

Bozkurt, A., Zilles, K., Schleicher, A., Kamper, L., Arigita, E.S., Uylings, H.B., & Kotter, R. (2005). Distributions of transmitter receptors in the macaque cingulate cortex. *Neuroimage* 25, 219–229.

Bradshaw, J. L., & Mattingley, J. B. (2001). Allodynia: A sensory analogue of motor mirror neurons in a hyperaesthetic patient reporting instantaneous discomfort to another's perceived sudden minor injury? *Journal of Neurology, Neurosurgery, & Psychiatry*, 70, 135-136.

Braver, T.S., Barch, D.M., Gray, J.R., Molfese, D.L., & Snyder A. (2001). Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. *Cerebral Cortex*11, 825-36.

Bremmer, F., Schlack, A., Shah, N.J., Zafiris, O., Kubischik, M., Hoffmann, K.-P., Zilles, K., & Fink, G.R. (2001). Polymodal motion processing in posterior parietal and premotor cortex: a human fMRI study strongly implies equivalencies between humans and monkeys. *Neuron*29, 287-96.

Brooks, J.C., Nurmikko, T.J., Bimson ,W.E., Singh K.D., & Roberts N. (2002). fMRI of thermal pain: effects of stimulus laterality and attention. *Neuroimage* 15, 293–301.

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

Brosnan S.F.& de Waal .FB. (2004). Socially learned preferences for differentially rewarded tokens in the brown capuchin monkey (*Cebus apella*). *Journal of Comparative Psychology* 118, 33-9.

Brothers, L.(1990). The social brain: A project for integrating primate behavior and neurophysiology in a new domain. *Concepts in Neuroscience* 1, 27-61.

Buccino, G., Binkofski, F., Fink, G. R., Fadiga, L., Fogassi, L., & Gallese, V., (2001). Action observation activates premotor and parietal areas in somatotopic manner: An fMRI study. *European Journal of Neuroscience, 13*, 400–404.

Buccino, G., Lui, F., Canessa, N., Patteri, I., & Lagravinese, G. (2004). Neural circuits involved in the recognition of actions performed by non-conspecifics: an fMRI study. *Journal of Cognitive Neuroscience*16, 1–14.

Buccino, G., Vogt, S., Ritzl, A., Fink, G.R., Zilles, K., Freund, H.J., & Rizzolatti G. (2004). Neural circuits underlying imitation learning of hand actions: an event-related fMRI study. *Neuron* 42, 323-34.

Buck, R. (1980). Nonverbal behavior and the theory of emotion: the facial feedback hypothesis. *Journal of Personality and Social Psychology* 38, 811-824.

Burton, H., MacLeod, A. M., Videen, T. O., & Raichle, M. E. (1997). Multiple foci in parietal and frontal cortex activated by rubbing embossed grating patterns across fingerpads: A positron emission tomography study in humans. *Cerebral Cortex*, 7, 3-17.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, 4, 215-222.

Bush G., Vogt, B.A., Holmes, J., Dale, A.M., Greve, D., Jenike, M.A., & Rosen, B.R. (2002). Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proceedings of the National Academy of Sciences USA,* 99, pp. 523-528.

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 USA* 96, pp 7705-9.

Byrne, R.W. & Whiten, A. (1997). Machiavellian intelligence. In: *Machiavellian Intelligence II* (A. Whiten & R. W. Byrne, Eds.), 1-23. Cambridge: Cambridge University Press.

Cadoret, G., & Smith, A.M. (1995). Input-output properties of hand-related cells in the ventral cingulate cortex in the monkey. *Journal of Neurophysiology* 73, 2584-90.

Calejesan, A.A., Kim, S.J., & Zhuo, M. (2000). Descending facilitatory modulation of a behavioral nociceptive response by stimulation in the adult rat anterior cingulate cortex. *European Journal of Pain* 4, 83-96.

Calder, A.J., Keane, J., Manes, F., Antoun, N., & Young, A.W. (2000). Impaired recognition and experience of disgust following brain injury. *Nature Neuroscience* 3:11, 1077-8.

Calder, A.J., Lawrence, A.D., & Young, A.W. (2001). Neuropsychology of fear and loathing. *Nature Reviews Neuroscience* 2, 352-363.

Calton, J.L., Dickinson, A.R., Snyder, L.H.. (2002). Non-spatial, motor-specific activation in posterior parietal cortex. *Nature Neuroscience* 5, 580-8.

Calvert, G. A., Campbell, R., & Brammer, M. J. (2000). Evidence from functional magnetic resonance imaging of crossmodal binding in the human heteromodal cortex. *Current Biology*, 10, 649-657.

Calvert, G. A., Hansen, P. C., Iversen, S. D., & Brammer, M. J. (2001). Detection of audio-visual integration sites in humans by application of electrophysiological criteria to the BOLD effect. *NeuroImage*, 14, 427-438.

Calvo-Merino, B., Glaser, D.E., Grèzes, J., Passingham, R.E., & Haggard, P. (2005). Action observation and acquired motor skills: an FMRI study with expert dancers. *Cerebral Cortex* 15, 1243-9.

Caplan D., & Moo L. (2004). Cognitive conjunction and cognitive functions. *Neuroimage,* 21, 751-6.

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 USA* 100, 5497-5502.

Carter, C.S., Macdonald, A.M., Botvinick, M., Ross, L.L., Stenger, V.A., Noll, D., & Cohen, J.D. (2000). Parsing executive processes: strategic vs evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Science USA* 97, 1944-48.

Casey, K.L., Minoshima, S., Morrow, T.J., Koeppe, R.A., & Frey, K.A. (1996). Comparison of human cerebral activation patterns during cutaneous warmth, heat pain, and deep cold pain. *Journal of Neurophysiology* 76, 571-81.

Castiello, U. (2005). The neuroscience of grasping. *Nature Reviews Neuroscience* 6, 726-36.

Clark, R. (2005). Why painfulness is not a quale. In Murat Aydede (Ed.), *Pain: New Essays on Its Nature and the Methodology of Its Study,* 175-191. Cambridge: MIT Press.

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, 1934-43.

Cole, J. (2001). Empathy needs a face. *Journal of Consciousness Studies* 8, 51-68.

Cooke, D.F. Taylor, C.S.R., Moore, T. & Graziano, M.S.A. (2003). Complex movements evoked by microstimulation of the ventral intraparietal area. Proceedings *of the National Academy of Sciences, USA* 100, 6161-6168.

Cooke D.F., & Graziano, M.S. (2004). Super-flinchers and nerves of steel: defensive movements altered by chemical manipulation of a cortical motor area. *Neuron* 19, 585-93.

Chen, M., & Bargh, J.A. (1999). Consequences of automatic evaluation: immediate behavioral predispositions to approach or avoid the stimulus. *Personality and Social Psychology Bulletin* 25, 215-224.

Craig, A.D., Reiman, E.M., Evans, A., & Bushnell, M.C. (1996). Functional imaging of an illusion of pain. *Nature* 384, 217-8.

Craig, A.D. (2004). Human feelings: why are some more aware than others? *Trends in Cognitive Science* 8, 239-241.

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

Craig, A.D. (2003b). Interoception: the sense of the physiological condition of the body. *Current Opinion in Neurobiology* 13, pp. 500-505.

Critchley, H.D., Wiens, S., Rotshtein, P., Öhman, A., & Dolan R.J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience* 7, 189-195.

De Houwer, J., Crombez, G., Baeyens, F., & Hermans, D. (2001). On the generality of the affective Simon effect. *Cognition and Emotion* 15, 189-206.

Damasio, A.R. (1994). *Descartes' Error.* New York: Picador.

Damasio, A.R. (1999). *The Feeling of What Happens: Body and Emotion in the Making of Consciousness,* New York: Harcourt Brace.

Davis, M.H. (1996). *Empathy: a social psychological approach.* Madison: Westview Press.

Davis, K.D., Hutchison, W.D., Lozano, A.M., & Dostrovsky, J.O. (1994). Altered pain and temperature perception following cingulotomy and capsulotomy in a patient with schizoaffective disorder. *Pain* 59, 189-1 99.

Davis, K.D., Taylor, S.J., Crawley, A.P., Wood, M.L., Mikulis, D.J. (1997). Functional MRI of pain- and attention- related activations in the human cingulate cortex. *Journal of Neurophysiology* 77, 3370-3380.

Decety, J. and J. Grèzes (1999). Neural mechanisms subserving the perception of human actions. *Trends in Cognitive Science* 3:5, pp 172-178.

Decety, J., & Chaminade T. (2003). Neural correlates of feeling sympathy. *Neuropsychologia* 1483, 1-12.

Decety, J., & Jackson P.L. (2004). The functional architecture of human empathy. *Behavioral and Cognitive Neuroscience Reviews* 3, 71-100.

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, 3065-77.

Derbyshire, S.W., Whalley, M.G., Stenger, V.A., & Oakley, D.A. (2004). Cerebral activation during hypnotically induced and imagined pain. *Neuroimage* 23, 392-401.

de Waal, F.B.M., & van Roosmalen, A. (1979). Reconcilation and consolation among chimpanzees. *Behavioral Ecology and Sociobiology* 5, 55-56.

Devinsky O., Morrell, M.J., & Vogt, B.A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain,* 279-306.

Deyo, K.S,. Prkachin, K.M., & Mercer, S.R. (2004). Development of sensitivity to facial expression of pain. *Pain* 107, 16-21.

di Pellegrino G., Fadiga L., Fogassi L., Gallese V., & Rizzolatti G. (1992). Understanding motor events: a neurophysiological study. *Experimental BrainResearch* 91, pp 176-809.

Dimberg, U., Thunberg, M., & Elmehed, K. (2000). Unconscious facial reactions to emotional facial expressions. *Psychological Science* 11, 86-9.

Dong, W.K., Chudler, E.H., Sugiyama, K., Roberts, V.J., & Hayashi, T. (1994). Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. *Journal of Neurophysiology* 72, 542-64.

Dong, W.K., Hayashi, T., Roberts, V.J., Fusco, B.M., & Chudler, E.H. (1996). Behavioral outcome of posterior parietal cortex injury in the monkey. *Pain* 64, 579–587.

Downar, J., Crawley, A. P., Mikulis, D. J., & Davis, K. D. (2002). A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. *Journal of Neurophysiology,* 87, 615-620.

Downar, J., Mikulis, DJ.,& Davis, KD. (2003). Neural correlates of the prolonged salience of painful stimulation. *NeuroImage* 20, 1540–1551.

Dretske, F. (2005). The epistemology of pain." In Murat Aydede (Ed.), *Pain: New Essays on Its Nature and the Methodology of Its Study,* 59-73. Cambridge: MIT Press.

Driver J. & Mattingley J.B. (1998). Parietal neglect and visual awareness. *Nature Neuroscience* 1, 17-22.

Dum, R.P. & Strick, P.L. (1996). Spinal cord terminations of the medial wall motor areas in macaque monkeys. *Journal of Neuroscience* 16, 6513-25.

Dunbar, R. (1996). *Grooming, Gossip, and the Evolution of Language.* Cambridge, MA: Harvard University Press.

Ehrsson, H.H., Spence C., & Passingham R.E. (2004). That's my hand! Activity in premotor cortex reflects feeling of ownership of a limb. *Science* 305, 875–877.

Eisenberg, N. (1991). Empathy-related responding and cognition: A "chicken and the egg" dilemma. In *Handbook of Moral Behavior and Development (vol 2)*, W.M. Kurtines and J.L. Gewirtz (Eds.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Eisenberg, N., Murphy, B. C., & Shepard, S. (1997). The development of empathic accuracy. In W. Ickes (Ed.), *Empathic Accuracy*, 3-116. New York: Guilford.

Eisenberger, N. I., Lieberman, M. D., & Williams, K. D. (2003).Does rejection hurt? An f MRI study of social exclusion. *Science* 302, 290-292.

Ekman, P.& Friesen, W.V. (1971). Constants across culture in face and emotion. *Journal of Personality and Social Psychology* 17, 124-129.

Ekman, P. (1993). Facial expression and emotion. *American Psychologist* 48, 384-392.

Fadiga, L., Fogassi, L., Pavesi, G., & Rizzolatti, G. (1995). Motor facilitation during action observation: a magnetic stimulation study. *Journal of Neurophysiology* 73, 2608-11.

Farnè, A., Pavani, F., Meneghello, F., & Ladavas, E. (2000). Left tactile extinction following visual stimulation of a rubber hand. *Brain* 123, 2350–2360.

Farina, S., Tinazzi, M., Le Pera, D., & Valeriani, M. (2003). Pain-related modulation of the human motor cortex. *Neurological Research* 25, 130-42.

Farrow, T.F., Zheng, Y., Wilkinson, I.D., Spence, S.A., Deakin, J.F., Tarrier, N., Griffiths, P.D., & Woodruff, P.W. (2001). Investigating the functional anatomy of empathy and forgiveness. *NeuroReport* 12, 2433-2438.

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, 1703-14.

Fields, H.L. (1999). Pain: an unpleasant topic. *Pain* Suppl 6:S (Aug), pp 61-69.

Fodor, J.A. (1981). Operationalism and ordinary language. In *Representations: Philosophical Essays on the Foundations of Cognitive Science,* 35-62. Cambridge, MA: MIT Press.

Fodor, J.A. (1983). *The Modularity of Mind: An essay on faculty psychology.* Cambridge, MA: MIT Press.

Fogassi, L., Ferrari, P.F., Gesierich, B., Rozzi, S., Chersi, F., & Rizzolatti, G. (2005). Parietal lobe: from action organization to intention understanding. *Science* 308, 662-7.

Fogassi, L. & Luppino, G. (2005). Motor functions of the parietal lobe. *Current Opinion in Neurobiology* 15, 626-31.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magnetic Resonance in Medicine*, 33, 636-647.

Francis, S. T., Kelly, E. F., Bowtell, R., Dunseath, W. J., Folger, S. E., & McGlone, F. (2000). f MRI of the responses to vibratory stimulation of digit tips. *NeuroImage* 11, 188-202.

Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J., & Evans, A. C. (1994). Assessing the significance of focal activationsusing their spatial extent. *Human Brain Mapping* 1, 214-220.

Friston, K.J., Penny, W.D., & Glaser, D.E. (2005). Conjunction revisited. *Neuroimage* 25, 661-7.

Gallese V., Fadiga L., Fogassi L., & Rizzolatti G. (1996). Action recognition in the premotor cortex. *Brain* 119, 593-609.

Gallese, V. (2001). The shared manifold hypothesis: from mirror neurons to empathy. *Journal of Consciousness Studies* 8, no. 5-7, 51-68.

Gallese, V. (2003). The manifold nature of interpersonal relations: the quest for a common mechanism. *Philosophical Transactions of the Royal Society of London: Biology* 358, 517-528.

Gallese, V., Keysers, C., & Rizzolatti, G. (2004). A unifying view of the basis of social cognition. *Trends in Cognitive Sciences* 8, 396-403.

Garavan, H., Ross, T.J., Kaufman, J., & Stein, E.A. (2003). A midline dissociation between error-processing and response-conflict monitoring. *Neuroimage* 20, 1132-9.

Gebhart, G.F. (2004). Descending modulation of pain. *Neuroscience and Biobehavioral Reviews* 27, 729-37.

Gehring, W.J. & Willoughby, A.R. (2002). The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* 295, 2279–2282.

Gelnar, P. A., Krauss, B. R., Szeverenyi, N. M., & Apkarian, A. V. (1998). Fingertip representation in the human somatosensory cortex: An fMRI study. *NeuroImage* 7, 261-283.

Godschalk, M., Mitz, A.R., van Duin, B., & van der Burg, H. (1995). Somatotopy of monkey premotor cortex examined with microstimulation. *Neuroscience Research* 23, 269-79.

Goldie, P. (1999) How we think of others' emotions. *Mind and Language* 14, 394-423.

Graziano, M.S., & Cooke, D.F. (2005). Parieto-frontal interactions, personal space, and defensive behavior. *Neuropsychologia* 44, 845-59.

Graziano, M.S. (1999). Where is my arm? The relative role of vision and proprioception in the neuronal representation of limb position. *Proceedings of the National Academcy of Science USA* 96, 10418–10421.

Graziano, M.S., Cooke, D.F., & Taylor, C.S. (2000). Coding the location of the arm by sight. *Science* 290, 1782–1786.

Graziano, M.S., Gross, C.G., Taylor, C.S.R., & Moore, T. (2004). A system of multimodal areas in the primate brain. In: *Crossmodal Space and Crossmodal Attention,* edited by Spence C. & Driver J. Oxford: Oxford University Press, 51–67.

Greenspan, J.D. & Winfield, J.A. (1992). Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum. *Pain* 50, 29–39.

Grefkes, C. & Fink, G.R.(2005). The functional organization of the intraparietal sulcus in humans and monkeys. *Journal of Anatomy* 207, 3–17.

Grèzes, J., Costes, N., & Decety, J. (1999). The effects of learning and intention on the neural network involved in the perception of meaningless actions. *Brain* 122, 1875-87.

Grèzes, J., Armony, J.L., Rowe, J., & Passingham, R.E. (2003). Activations related to "mirror" and "canonical" neurones in the human brain: an fMRI study. *NeuroImage* 18, 928-37.

Griffiths, P.E. (1997). *What Emotions Really Are.* Chicago: University of Chicago Press.

Griffiths, P. E. (2004). Towards a Machiavellian theory of emotional appraisal. Emotion. In *Evolution and Rationality.* P. Cruse and D. Evans, Eds. Oxford: Oxford University Press, 89-105.

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.

Gruen, R.J., & Mendelsohn, G. (1986). Emotional responses to affective displays in others: the distinction between empathy and sympathy. *Journal of Personality and Social Psychology* 51, 609-614.

Grush, R. (2004). The emulation theory of representation: motor control, imagery, and perception. *Behavioral and Brain Sciences* 27, 377-442.

Guilford, T. & Dawkins, M.S. (1993). Reciever psychology and the design of animal signals. *Trends in Neurosciences* 16, 430-6.

Gusnard, D.A., Akbudak, E., Shulman, G.L., & Raichle, M.E. (2001). Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proceedings of the National Academy of Sciences USA* 98, 4259-4264.

Hadland, K.A, Rushworth, M.F,, Gaffan, D., & Passingham, R.E. (2003a). The anterior cingulate and reward-guided selection of actions. *Journal of Neurophysiology* 89, 1161-1164.

Hadland, K. A., Rushworth, M. F. S., Gaffan, D., & Passingham, R. E. (2003b). The effect of cingulate lesions on social behavior and emotion. *Neuropsychologia* 41, 919-931.

Haggard, P. (2001). The psychology of action. *British Journal of Psychology* 92, 113-128.

Hamilton, A., & Grafton, S.T. (2006). Goal representation in human anterior intraparietal sulcus. *Journal of Neuroscience* 26, 1133-7.

Hari, R., Forss, N., Avikainen, S., Kirveskari, E., Salenius, S., & Rizzolatti, G. (1998). Activation of human primary motor cortex during action observation: A neuromagnetic study. *Proceedings of the National Academy of Sciences* 95, 15061-15065.

Haxby, J.V., Gobbini, M.I., Furey, M.L., Ishai, A., Schouten, J.L,, & Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science* 293, 2425-30.

Henderson, L.A., Bandler, R., Gandevia, S.C., & Macefield, V.G. (2006). Distinct forebrain activity patterns during deep versus superficial pain. *Pain* 120, 286-96.

Heyes, C.M. (1994). Social learning in animals: categories and mechanisms. *Biological Reviews* 69, 207-231.

Hill, M.L. and Craig, K.D. (2002). Detecting deception in pain expressions: the structure of genuine and deceptive facial displays. *Pain* 98, 135-144.

Hikosaka, K. (1997). Responsiveness of neurons in the posterior inferotemporal cortex to visual patterns in the macaque monkey. *Behavioural Brain Research* 89, 275-283.

Hodges, S.D., & Wegner, D.M. (1997). Automatic and controlled empathy. In *Empathic Accuracy*, W. Ickes, Ed. New York:Guildford Press.

Hofbauer, R. K., Rainville, P., Duncan, G. H., & Bushnell, M. C. (2001). Cortical representation of the sensory dimension of pain. *Journal of Neurophysiology* 86, 402-411.

Holmes, N.P., Calvert, G.A., & Spence, C. (2004). Extending or projecting peripersonal space with tools? Multisensory interactions highlight only the distal and proximal ends of tools. *Neuroscience Letters* 372, 62–67.

Holmes, N.P., Snijders, H.J., & Spence, C. (in press). Reaching with alien limbs: Visual exposure to prosthetic hands in a mirror biases proprioception without accompanying illusions of ownership. *Perceptual Psychophysics.*

Hommel, B., Müsseler, J., Aschersleben, G., & Prinz, W. (2001). The theory of event coding (TEC): A framework for perception and action planning. *Behavioral and Brain Sciences* 24.

Hoshi, E., Sawamura, H., & Tanji, J. (2005). Neurons in the rostral cingulate motor area monitor multiple phases of visuomotor behavior with modest parametric selectivity. *Journal of Neurophysiology* 94, 640-56.

Hsieh, J.C., Stone-Elander, S., & Ingvar, M. (1999). Anticipatory coping of pain expressed in the human anterior cingulate cortex: a positron emission tomography study. *Neuroscience Letters* 262, 61-64.

Huettel, S.A., Misiurek, J, Jurkowski, A.J., & McCarthy G. (2004). Dynamic and strategic aspects of executive processing. *Brain Research* 1000, 78-84.

Hume, D. (1779). *Treatise of Human Nature.* Reprinted 1960, Ed. L.A. Selby-Bigge. Oxford: Oxford University Press.

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, 403-5.

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

Inghelleri, M., Cruccu, G., Argenta, M., Polidori, L., & Manfredi, M. (1997). Silent period in upper limb muscles after noxious cutaneous stimulation in man. *Electroencephalogical Clinical Neurophysiology* 105, 109-115.

Ingvar, M. (1999). Pain and functional imaging. *Philosophical Transactions of the Royal Society of London: Biology* 354,1347-58.

International Association for the Study of Pain Subcommittee on Taxonomy. (1986). Classification of chronic pain syndromes and definitions of pain terms. *Pain*, Volume 3 (Suppl.3), S1-S226.

Itakura S. (1994). Differentiated responses to different human conditions by chimpanzees. *Perceptual and Motor Skills* 79, 1288-1290.

Isomura Y. & Takada M. (2004). Neural mechanisms of versatile functions in primate anterior cingulate cortex. *Reviews in Neuroscience* 15, 279-91.

Iwata, K., Kamo, H., Ogawa, A., Tsuboi, Y., Noma, N., Mitsuhashi, Y., Taira, M., Koshikawa, N., & Kitagawa, J. (2005). Anterior cingulate cortical neuronal activity during perception of noxious stimuli in monkeys. *Journal of Neurophysiology* 84, 1980-91.

Jackson, P.L., Meltzoff, A.N., & Decety, J. (2005). How do we perceive the pain of others? *Neuroimage* 24, 771-9.

Jackson, P.L, Brunet, E., Meltzoff, A.N., & Decety, J. (2006). Empathy examined through the neural mechanisms involved in imagining how I feel versus how you would feel pain: an event-related fMRI study. *Neuropsychologia* 44, 752-61.

Jacob, P., & Jeannerod, M. (2005). The motor theory of social cognition: a critique. *Trends in Cognitive Sciences* 9, 21-5.

James, W. (1892). *Psychology: The Briefer Course*, reprinted 1985, Chicago: University of Notre Dame Press.

Jenkinson, M. & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis* 5. 143–156.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage* 17, 825-841.

Johansen, J.P., Fields, H.L., & Manning, B.H. (2001) The affective component of pain in rodents: direct evidence for a contribution of the anterior

cingulate cortex. *Procedings of the National Academy of Science USA* 9, 8077–8082.

Johansen-Berg, H., Behrens, T.E., Robson, M.D., Drobnjak, I., Rushworth, M.F., Brady, J.M., Smith, S.M., Higham, D.J., & Matthews, P.M. (2004). Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. *Proceedings of the National Academy of Science USA*.101, 13335-40.

Jueptner, M., Stephan, K.M, Frith, C.D., Brooks, D.J., Frackowiak, R.S.J., & Passingham, R.E. (1997). Anatomy of motor learning I. Frontal cortex and attention to action. *Journal of Neurophysiology* 77, 1313-24.

Julius, B. & Basbaum, A.I. (2001). Molecular mechanisms of nociception. *Nature* 413, 203-10.

Kaas, J. H., & Collins, C. E. (2001). The organization of sensory cortex. *Current Opinion in Neurobiology* 11, 498-504.

Kakei, S., Hoffman, D.S., Strick, P.L. (2003). Sensorimotor transformations in cortical motor areas. *Neuroscience Research* 46, 1-10.

Kanda, M., Nagamine, T., Ikeda, A., Ohara, S., Kunieda,T., Fujiwara, N., Yazawa, S., Sawamoto, N., Matsumoto, R., Taki, W., & Shibasaki, H. (2000). Primary somatosensory cortex is actively involved in pain processing in human. *Brain Research* 853, 282-89.

Kavaliers, M., Colwell, D.D., Choleris, E. and Ossenkopp, K.-P. (1999). Learning to avoid biting flies: rapid NMDA acquisition of conditioned analgesia. *Behavioral Neuroscience*, 113: 126-135.

Keightley, M. L., Winocur, G., Graham, S. J., Mayberg, H. S., Hevenor, S. J., & Grady, C. L. (2003). An fMRI study investigating cognitive modulation of brain regions associated with emotional processing of visual stimuli. *Neuropsychologia*, 41, 585-596.

Kennerley, S.W., Walton, M.E., Behrens, T.E., Buckley, M.J., & Rushworth, M.F. (2006). Optimal decision making and the anterior cingulate cortex. *Nature Neuroscience* 9, 940-7.

Kenshalo, D. R., Iwata, K., Sholas, M., & Thomas, D. A. (2000). Response properties and organization of nociceptive neurons in area 1 monkey primary somatosensory cortex. *Journal of Neurophysiology*, 84, 719-729.

Kerns, J.G., Cohen, J.D., MacDonald, A.W. III, Cho, R.Y., Stenger, V.A., & Carter, C.S. (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science* 303, 1023, 26.

Keysers C., Kohler E., Umiltá M.A., Nanetti L., Fogassi L., & Gallese V. (2003). Ausiovisual mirror neurons and action recognition. *Experimental Brain Research* 153, 628-36.

Keysers, C., Wicker, B., Gazzola, V., Anton, J.L., Fogassi, L., & Gallese, V. (2004a). A touching sight: SII/PV activation during the observation and experience of touch. *Neuron* 42, 335–346.

Keysers, C. & Perrett, D.I. (2004b). Demystifying social cognition: a Hebbian perspective. *Trends in Cognitive Sciences* 8, 501-7.

Keverne, E.B., Martensz, N.D., & Tuite, B. (1989). Beta-endorphin concentrations in cerebrospinal fluid of monkeys are influenced by grooming relationships. *Psychoneuroendocrinology* 14, 155-61.

Koski, L., & Paus, T. (2000). Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. *Experimental Brain Research* 133, 55-65.

Koyama, T., Tanaka, Y.Z., & Mikami, A. (1998). Nociceptive neurons in the macaque anterior cingulate cortex activate during anticipation of pain. *Neuroreport* 9, 2663-7.

Koyama, T. Kato, K., Tanaka, Y.Z., & Mikami, A. (2001). Anterior cingulate activity during pain-avoidance and reward tasks in monkeys. *Neuroscience Research* 39, 421-430.

Krams, M., Rushworth, M.F., Deiber, M.P., Frackowiak, R.S., & Passingham, R.E. (1998) The preparation, execution and suppression of copied movements in the human brain. *Experimental Brain Research* 3, 386-98.

Krolak-Salmon, P., Henaff, M.A., Isnard, J., Tallon-Baudry, C., Guenot, M., Vighetto, A., Bertrand, O., & Mauguière, F. (2003). An attention modulated response to disgust in human ventral anterior insula. *Annals of Neurology* 53, 446-53.

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, 3133-42.

Kwan, C.L., Crawley, A.P., Mikulis, D.J., & Davis, K.D. (2000). An fMRI study of the anterior cingulate cortex and surrounding medial wall activations evoked by noxious heat and cold stimuli. *Pain* 85, 359-74.

LaBar, K.S., Gatenby, J.C., Gore, J.C., LeDoux, J.E., & Phelps, E.A.(1998). Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron*, 20, 937-45.

Lamm, C., Batson, D.C., & Decety, J. (in press). The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *Journal of Cognitive Neuroscience.*

Langford, Crager, S.E., Shehzad, Z., Smith, S.B., Sotocinal, S.G., Levenstadt, J.S., Chanda, M.S., Levitin, D.J., & Mogil, J.S. (2006). Social modulation of pain as evidence for empathy in mice. *Science* 312, 1967-70.

Lawrence, E.J., Shaw, P., Giampietro, V.P., Surguladze, S., Brammer, M.J., & David, A.S. (2006). The role of 'shared representations' in social perception and empathy: an fMRI study. *NeuroImage* 29, 1173-84.

Le Doux, J. (1998). *The Emotional Brain: The Mysterious Underpinnings of Emotional Life.* London: Weidenfeld and Nicolson.

Le Pera, D. Graven-Nielsen, T., Valeriani, M., Oliviero, A., Di Lazzaro, V., Tonali, P.A., & Arendt-Nielsen, L. (2001). Inhibition of motor system excitability at cortical and spinal level by tonic muscle pain. *Clinical Neurophysiology* 112, 1633-1641.

Leis, A.A. Stokic, D.S., Fuhr, P., Kofler, M., Kronenberg, M.F., Wissel, J., Glocker, F.X., Seifert, C., & Stetkarova, I. (2000). Nociceptive fingertip stimulation inhibits synergistic motoneuron pools in the human upper limb. *Neurology* 55, 1305-9.

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. & Ruef, A.M. (1992). Empathy: a physiological substrate. *Journal of Personality and Social Psychology* 63:2, pp 234-246.

Lipps, T (1903). Einfühlung, innere Nachahmung, und Organempfinaugen. *Archiv für die gesamte Psychologie* 2, pp 185-204. Partial informal translation provided by Tom Ziemke.

Lloyd, D.M., Shore, D.I., Spence, C., & Calvert, G.A. (2003). Multisensory representation of limb position in human premotor cortex. *Nature Neuroscience* 6: 17–18.

Lloyd, D.M., Morrison, I., & Roberts, N. (2006). Role for human posterior parietal cortex in visual processing of aversive objects in peripersonal space. *Journal of Neurophysiology,* 95, 205-14.

Lundqvist, L.-O. & Dimberg U. (1995). Facial expressions are contagious. *Journal ofPsychophysiology,* 9, 203-211.

Luppino, G., Murata, A,, Govoni, P., & Matelli, M. (1999). Largely segregated

parietofrontal connections linking rostral intraparietal cortex (areas AIP and VIP) and the ventral premotor cortex (areas F5 and F4). *Experimental Brain Research* 128, 181–187.

MacDonald, A.W. III, Cohen, J.D., Stenger, V.A., & Carter, C.S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 288: 1835–1838.

Malle, B.F. (2004). *How the Mind Explains Behavior: Folk Explanations, Meaning, and Social Interaction.* Cambridge, MA: MIT Press.

Maravita, A., Husain, M., Clarke, K., & Driver, J. (2001). Reaching with a tool extends visual-tactile interactions into far space: evidence from cross-modal extinction. *Neuropsychologia* 39, 580–585.

Maravita, A., Spence, C., & Driver, J. (2003). Multisensory integration and the body schema: close to hand and within reach. *Current Biology* 13, R531–R539.

Maravita, A., Spence, C., Kennett, S., & Driver, J. (2002). Tool-use changes multimodal spatial interactions between vision and touch in normal humans. *Cognition* 83: B25–B34.

Marshall, J.C. & Halligan, P.W.(1988). Blindsight and insight in visuo-spatial neglect. *Nature* 336: 766–767.

Marzillier, S.L .& Davey, G.C.L. (2004). The emotional profiling of disgust-eliciting stimuli: evidence for primary and complex disgusts. *Cognition and Emotion* 18, 313-336.

Matelli, M., Luppino, G., & Rizzolatti, G. (1991). Architecture of superior and mesial area 6 and the adjacent cingulate cortex in the macaque monkey. *Journal of Comparative Neurology* 311, 445-462.

Matsumoto, K., Suzuki, W.,& Tanaka, K. (2004). Neuronal correlates of goal-based motor selection in the prefrontal cortex. *Science* 11, 229-32.

McGlone, F., Kelly, E. F., Trulsson, M., Francis, S. T., Westling, G., & Bowtell, R. (2002). Functional neuroimaging studies of human somatosensory cortex. *Behavioural Brain Research*, 135, 147-158.

Mehrabian, A., & Epstein, N. (1972). A measure of emotional empathy. *Journal of Personality*, 40, 525-43.

Meltzoff, A. & Prinz, W. (Eds.) (2002). *The Imitative Mind: Development, Evolution, and Brain Bases.* Cambridge: Cambridge University Press.

Meltzoff, A. (2002). Elements of a developmental theory of imitation. In *The Imitative Mind: Development, Evolution, and Brain Bases*, A. Meltzoff and W. Prinz, Eds. Cambridge: Cambridge University Press.

Meltzoff, A. & Decety, J. (2003). What imitation tells us about social cognition: a rapprochement between developmental psychology and cognitive neuroscience. *Philosophical Transactions of the Royal Society of London: Biology* 358, 491-500.

Melzack, R. (1999). From the gate to the neuromatrix. *Pain,* Suppl 6:S, 121-6.

Melzack, R. & Wall, P.D. (1968). Pain mechanisms: a new theory. Reprinted in *Psychosocial Processes and Health: A Reader*, A. Steptoe and J. Wardle, Eds. Cambridge: Cambridge University Press, 1994.

Melzack, R. & Casey, K.L. (1968). Sensory, motivational and central control determinants of pain. In D. Kenshalo (Ed.), *The Skin Senses* (pp. 423-443). Springfield, IL: Charles C. Thomas.

Menon, V., Adleman, N.E., White, C.D., Glover, G.H., & Reiss, A.L. (2001). Error-related brain activation during a Go/NoGo response inhibition task. *Human Brain Mapping* 12, 131-143.

Mesulam, M.M. (1999). Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philosophical Transactions of the Royal Society of London: Biology* 354, 1325-1346.

Metzinger, T. & Gallese, V. (2003). The emergence of a shared action ontology: building blocks for a theory. *Consciousness and Cognition* 12, 549-571.

Milham, M. P., Banich, M. T., Claus, E. D., & Cohen, N. J. (2003). Practice-related effects demonstrate complementary roles of anterior cingulate and prefrontal cortices in attentional control. *NeuroImage*, 18, 483-493.

Millan, M.J. (2002). Descending control of pain. *Progress in Neurobiology* 66, 355-474.

Morecraft, R.J. & Van Hoesen, G.W. (1997). Convergence of limbic input to the cingulate motor cortex in the rhesus monkey. *Brain Research Bulletin* 45, 209-232.

Morrison, I., Lloyd, D.M, di Pellegrino, G., & Roberts, N. (2004). Vicarious responses to pain in anterior cingulate cortex: is empathy a multisensory issue? *Cognitive, Affective, and Behavioral Neuroscience* 4, 270-8.

Morrison, I. (in press). Motivational-affective processing and the neural foundations of empathy. In T. Farrow & P. Woodruff, Eds., *Empathy in Mental Illness and Health.* Cambridge: Cambridge University Press.

Morrison, I., Poliakoff, E., Gordon, L., & Downing, P.E. (in press). Response-specific effects of pain observation on motor behavior. *Cognition.*

Nachev, P., Rees, G., Parton, A., Kennard, C., & Husain , M. (2006). Volition and conflict in human medial frontal cortex. *Current Biology* 15, 122-28.

Nichols, T., Brett, M., Andersson, J., Wager, T., Poline, J.B. (2005). Valid conjunction inference with the minimum statistic. *Neuroimage,* 15, 653-60.

Niki, H. & Wantabe, M. (1976). Cingulate unit activity and delayed response. *Brain Research* 110, 381-86.

Nimchinsky, E.A., Vogt, B.A., Morrison ,J.H., & Hof, P.R. (1995). Spindle neurons of the human anterior cingulate cortex. *Journal of Comparative Neurology* 24, 27-37.

Nishitani, N., & Hari, R. (2000). Temporal dynamics of cortical representation for action. *Proceedings of the National Academy of Science USA* 97, 913-8.

Noë, A (2004). *Action in Perception.* Cambridge, MA: MIT Press.

O'Doherty, J., Critchley, H., Deichmann, R., & Dolan, R.J. (2003). Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *Neuroscience* 23, 7931-7939.

Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.

Olsson, A. & Phelps, E.A. (2004). Learned fear of "unseen" faces after Pavlovian, observational, and instructed fear. *Psychological Science* 15, 822-8.

Panksepp, J. (1998). *Affective neuroscience: The Foundations of Human and Animal Emotions.* New York: Oxford University Press.

Panksepp, J. (2005). On the neuro-evolutionary nature of social pain, support, and empathy. In Murat Aydede (Ed.), *Pain: New Essays on Its Nature and the Methodology of Its Study,* 367-387. Cambridge, MA: MIT Press.

Parr, L.A. (2001). Cognitive and physiological markers of emotional awareness in chimpanzees (*Pan troglodytes*). *Animal Cognition* 4, 223–229.

Pastoriza, L.N., Morrow, T.J., & Casey, K.L. (1996). Medial frontal cortex lesions selectively attenuate the hot plate response. *Pain* 64, 11-17.

Paus, T., Petrides, M., Evans, A.C., & Meyer, E. (1993). Role of the anterior cingulate cortex in the control of oculomotor, manual, and speech

responses: a positron emission tomography study. *Journal of Neurophysiology* 70, 453-69.

Paus, T., Otaky, N., Caramanos, Z., MacDonald, D., Zijdenbos, A., D'Avirro, D., Gutmans, D., Holmes, C., Tomaiuolo, F. & Evans, A. C. (1996). In-vivo morphometry of the intrasulcal gray-matter in the human cingulate, paracingulate and superior-rostral sulci: hemispheric asymmetries and gender differences. *Journal of Comparative Neurology* 376, 664-673.

Paus, T. (2002). Primate anterior cingulate cortex: where motor control, drive, and cognition interface. *Nature Reviews Neuroscience* 2, 417-424.

Pavani, F., Spence, C., & Driver, J. (2000). Visual capture of touch: out-of-the-body experiences with rubber gloves. *Psychological Science* 11, 353–359.

Peelen, M.V.& Downing, P.E. Selectivity for the human body in the fusiform gyrus. *Journal of Neurophysiology* 93, 603-8.

Penfield, W. and Rasmussen, T. (1955). *The Cerebral Cortex of Man: A Clinical Study of Localization of Function.* New York: Macmillan Company.

Peyron R., Laurent B., & Garcia-Larrea L. (2000a). Functional imaging of brain responses to pain: a review and meta-analysis. *Clinical Neurophysiology* 30, 263-88.

Peyron, R., Garcia-Larrea, L., Gregoire, M. C., Convers, P., Richard, A., Lavenne, F., Barral, F. G., Mauguiere, F., Michel, D., & Laurent, B. (2000b). Parietal and cingulate processes in central pain. A combined positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) study of an unusual case. *Pain*, 84, 77-87.

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* 2: 389, 495-8.

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 in Biological Sciences* 265, 1809-17.

Phillips, J.C. & Ward, R. (2002). S-R correspondence effects of irrelevant visual affordance: time course and specificity of response activation. *Visual Cognition* 9, 540-58.

Picard, N., & Strick, P.L. (1996). Motor areas of the medial wall: a review of t heir location and functional activation. *Cerebral Cortex* 6, 342-53.

Picard, N., & Strick, P.L. (2001). Imaging the premotor areas. *Current Opinion in Neurobiology* 11, 663-672.

Ploner M., Freund H.J., & Schnitzler A. (1999). Pain affect without pain sensation in a patient with a postcentral lesion. *Pain* 81, 211-14.

Ploner, M., Schmitz, F., Freund, H.J., & Schnitzler, A. (2000). Differential organization of touch and pain in human primary motor cortex. *Journal of Neurophysiology* 83, 1770-1776.

Ploghaus, A., Tracey, I., Gati, J.S., Clare, S., Menon, R.S., Matthews, P.M., & Rawlins, J.N. (1999). Dissociating pain from its anticipation in the human brain. *Science* 284,1979-81.

Ploghaus, A., Becerra, L., Borras, C., & Borsook, D. (2003). Neural circuitry underlying pain modulation: expectation, hypnosis, placebo. *Trends in Cognitive Sciences* 7, 197-200.

Poole, G.D. & Craig, K.D. (1992). Judgments of genuine, suppressed, and faked facial expressions of pain. *Journal of Personality and Social Psychology* 63, 797-805.

Porro, C.A., Cettolo, V., Francescato, M.P., & Baraldi, P. (2003). Functional activity mapping of the mesial hemispheric wall during anticipation of pain. *NeuroImage* 19, 1738-47.

Posner, M.I. & Rothbart, M.K. (1998). Attention, self-regulation and consciousness. *Philosophical Transactions of the Royal Society of London: Biology* 29, 1915-1927.

Powell, T. P. S., & Mountcastle, V. B. (1959). The cytoarchitecture of the postcentral gyrus of the monkey *Macaca mulatta. Bulletin of Johns Hopkins Hospital*, 105, 108-131.

Preston, S. D., & de Waal, F. B. M. (2002). Empathy: Its ultimate and proximate bases. *Behavioral and Brain Science*, 25, 1-20.

Price, D.D. (2000). Psychological and neural mechanisms of the affective dimension of pain. *Science* 288, 1769-72.

Price, D.D., Barrell J.J., & Rainville P. (2002). Integrating experiential-phenomenological methods and neuroscience to study neural mechanisms of pain and consciousness. *Consciousness and Cognition* 11, 593-608.

Prinz, W. (1990). A common coding approach to perception and action. In *Relationships between perception and action: Current approaches,* O. Neumann and W. Prinz, Eds., 167-201. New York: Springer-Verlag.

Prinz, W. (1997). Perception and action planning. *European Journal of Cognitive Psychology.* 9, 129-54.

Prkachin, K.M., Berzins, S. & Mercer, S.R. (1994). Encoding and decoding of pain expressions: a judgement study. *Pain* 58, 253-259.

Prkachin, K.M., Mass, H., & Mercer, S.R. (2004). Effects of exposure on perception of pain expression. *Pain* 111, 8–12.

Raichle, M.E. (1998). The neural correlates of consciousness: an analysis of cognitive skill learning. *Philosophical Transactions of the Royal Society of London, Biology* 353, 1889-1901.

Raij, T.T. Forss, N., Stancak, A., Hari, R. (2004). Modulation of motor cortex oscillatory activity by painful Aδ- and C-fiber stimuli. *NeuroImage* 23, 569-73.

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.

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, 159-71.

Rainville, P. (2002). Brain mechanisms of pain affect and pain modulation. *Current Opinion in Neurobiology* 12, 195-204.

Redican, W.K. (1982). An evolutionary perspective on human facial displays. In *Emotion in the Human Face*, 2nd ed., P. Ekman, Ed. 213-280. Cambridge: Cambridge University Press.

Ridderinkhof, K.R., Ullsperger, M., Crone, E., & Nieuwenhuis, S. (2004a). The role of the medial frontal cortex in cognitive control. *Science* 306, 443-7.

Ridderinkhof, K.R., van den Wildenberg, W.P., Segalowitz, S.J., & Carter, C.S. (2004b). Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain and Cognition* 56, 129-40.

Ringler, R., Greiner, M., Kohlloeffel, L., Handwerker, H. O.,& Forster, C. (2003). BOLD effects in different areas of the cerebral cortex during painful mechanical stimulation. *Pain* 105, 445-453.

Rizzolatti, G., Scandolara, C., Matelli, M., & Gentilucci, M. (1981). Afferent properties of periarcuate neurons in macaque monkeys. II. Visual responses. *Behavioral Brain Research* 2, 147–163.

Rizzolatti, G. & Berti, A. (1990). Neglect as a neural representation deficit. *Reiviews in Neurology* 146, 626–634.

Rizzolatti G., Fadiga L., Gallese V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. *Cognitive Brain Research* 3, 131-41.

Rizzolatti, G., Fogassi, L., & Gallese, V. (1997). Parietal cortex: from sight to action. *Current Opinion in Neurobiology* 7, 562-7.

Rizzolatti, G., Fadiga, L., Fogassi, L., & Gallese, V. (1999). Resonance behaviors and mirror neurons. *Archives Italiennes de Biologie*, 137, 85-100.

Rizzolatti, G. & Luppino, G. (2001). The cortical motor system. *Neuron.* 27, 889-901.

Rizzolatti G., Fogassi, L., & Gallese, V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. *Nature Reviews Neuroscience* 2, 661-70.

Rizzolatti, G., Fogassi,L, & Gallese, V. (2002). Motor and cognitive functions of the ventral premotor cortex. *Current Opionion in Neurobiology* 12, 149-54.

Rizzolatti, G. & Matelli, M. (2003). Two different streams form the dorsal visual system: anatomy and functions. *Experimental Brain Research* 153, 146–157.

Rizzolatti, G. and Craighero, L. (2004). The mirror neuron system. *Annual Review of Neuroscience* 27, 169-192.

Rorden, C., Heutink, J., Greenfield, E., & Robertson, I.H. (1999). When a rubber hand"feels" what the real hand cannot. *Neuroreport* 10, 135–138, 1999.

Rostomily, R.C., Berger, M.S., Ojemann, G.A., & Lettich, E. (1991). Postoperative deficits following removal of tumors in the dominant hemisphere supplementary motor area. *Journal of Neurosurgery* 75, 62-68.

Rozin, P., Haidt J., & McCauley, C.R. (2000). Disgust. In M. Lewis and J.M. Haviland-Jones, Eds., *Handbook of Emotions, 2nd Ed.,* 637-653. New York:Guildford Press.

Ruby, P., & Decety, J. (2004). How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. *Journal of Cognitive Neuroscience,* 16, 988-99.

Rubia, K., Russell, T., Overmeyer, S., Brammer, M.J., Bullmore, E.T., Sharma, T., Simmons, A., Williams, S.C.R., 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.

Ruehle, B.S., Handwerker, H.O., Lennerz, J.K.M., Ringler, R., & Forster, C. (2006). Brain activation during input from mechanoinsensitive versus polymodal C-nociceptors. *Journal of Neuroscience* 26, 5492-99.

Rushworth, G. & Denny-Brown, D. (1959). The two components of the grasp reflex after ablation of frontal cortex in monkeys. *Journal of Neurological and Neurosurgical Psychiatry* 22, 91-98.

Rushworth, M.F.S., Hadland, K.A., Gaffan, D., & Passingham, R.E. (2003). The effect of cingulate cortex lesions on task switching and working memory. *Journal of Cognitive Neuroscience* 15, 338-353.

Rushworth, M.F.S,. Walton, M.E., Kennerley, S.W., & Bannerman, D.M. (2004). Action sets and decisions in the medial frontal cortex. *Trends in Cognitive Sciences* 8, 410-17.

Russo, G.S., Backus, D.A., Ye, S., & Crutcher, M.D. (2002). Neural activity in monkey dorsal and ventral cingulate areas: comparison with the supplementary motor area. *Journal of Neurophysiology* 88, 2612-29.

Saab, C.Y. & Willis, W.D. (2003). The cerebellum: organization, functions and its role in nociception. *Brain Research Review* 42, 85–95.

Saarela, M.V., Hlushchuk, Y., Williams, A.C., Schurmann, M., Kalso, E., & Hari, R. (in press). The compassionate brain: humans detect pain intensity from another's face. *Cerebral Cortex.* Epub ahead of print.

Salanova, V., Andermann, F., Rasmussen, T., Olivier, A., & Quesney, L.F. (1995). Parietal lobe epilepsy. Clinical manifestations and outcome in 82 patients treated surgically between 1929 and 1988. *Brain* 118, 607– 627.

Sathian, K., & Zangaladze, A. (2001). Feeling with the mind's eye: the role of visual imagery in tactile perception. *Optometry and Vision Science* 78, 276-81.

Sathian, K., & Zangaladze, A. (2002). Feeling with the mind's eye: contribution of visual cortex to tactile perception. *Behavioral Brain Research*, 20, 127-32.

Sawamoto, N., Honda, M., Okada, T., Hankawa, T., Kanda, M., Fukuyama, H., & Shibasai, H. (2000). Expectation of pain enchances to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic imaging study. *Journal of Neuroscience* 20, 7438-45.

Schnitzler, A., & Ploner, M. (2000). Neurophysiology and functional

neuroanatomy of pain perception. *Journal of Clinical Neurophysiology*, 17, 592-603.

Schnitzler, A., Seitz, R. J., & Freund, H.-J. (2000). The somatosensory system. In A. W. Toga & J. C. Mazziotta (Eds.), *Brain mapping: The systems* (pp. 291-329). San Diego: Academic Press.

Schulkin, J., & Erikson, K. (2003). Facial expressions of emotion: A cognitive neuroscience perspective. *Brain and Cognition* 52, 52–60.

Sewards T.V. & M.A. Sewards (2002). The medial pain system: neural representations of the motivational aspect of pain. *Brain Research Bulletin* 59, pp 163-80.

Sewards T.V. & M.A. Sewards (2003). Representations of motivational drives in medial cortex, medial thalmus, hypothalamus, and midbrain. *Brain Research Bulletin* 61, pp 25-49.

Shamay-Tsoory, S.G., Lester, H., Chisin, R., Israel, O., Bar-Shalom, R., Peretz, A., Tomer, R., Tsitrinbaum, Z., & Aharon-Peretz, J. (2002). Empathy deficits in Asperger syndrome: a cognitive profile. *Neurocase* 8, 245-252.

Shamay-Tsoory, S.G., Tomer, R., Berger, B.D., Goldsher, D., & Aharon-Peretz, J. (2005). Impaired "affective theory of mind" is associated with right ventromedial prefrontal damage. *Cognitive Behavioral Neurology* 18, 55-67.

Shamay-Tsoory, S.G., Tomer, R., Goldsher, D., Berger, B.D., & Aharon-Peretz, J. (2004). Impairment in cognitive and affective empathy in patients with brain lesions: anatomical and cognitive correlates. *Journal of Clinical Experimental Neuropsychology* 2004 26, 1113-27.

Shamay-Tsoor, S.G., Tomer, R., Berger, B.D., & Aharon-Peretz, J. (2003). Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. *Journal of Cognitive Neuroscience* 15, 324-37.

Sherrington, C.S. (1948). *The Integrative Action of the Nervous System.* Cambridge: Cambridge University Press.

Shidara, M., & Richmond, B.J. (2002). Anterior cingulate: single neuronal signals related to degree of reward expectancy. *Science* 296, 1709–1711.

Shima, K, and Tanji, J. (1998). Role for cingulate motor area cells in voluntary movement selection based on reward. *Science* 282, 1335-1338.

Shipp S, Blanton M, & Zeki S. (1998). A visuo-somatomotor pathway through superior parietal cortex in the macaque monkey: cortical

connections of areas V6 and V6A. *European Journal of Neuroscience* 10, 3171–3193.

Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, & Frith CD. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science* 20, 1157-62.

Singer, T., Seymour, B., O'Doherty, J.P., Stephan, K., Dolan, R.J., & Frith, C. (2006). Empathic neural responses are modulated by the perceived fairness of others. *Nature* 439, 466-9.

Singer, T., & Fehr, E. (2006). The neuroeconomics of mind reading and empathy. *American Economic Review*, 95 (2), 340-345.

Singer, T. & de Vignemont, F. (in press). *Trends in Cognitive Sciences.*

Smith, A. (1759). *The theory of moral sentiments.* D.D. Raphael and A.L. Macfie, Eds. Indianapolis: Liberty Classics, 1982.

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, 17, 143-155.

Smith, S. & Brady, M. (1997). SUSAN - a new approach to low level image processing. *International Journal of Computational Vision* 23, 45–78.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Fritney, D.E., Niazy ,R.K., Saunders, J., Vicreri, J., Zang, Y., De Stefano, M., Brady, J.M., & Matthews, P.M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 23 *Suppl* 1: S208–S219.

Sonnenburg, F.A. Andersen OK, & Arendt-Nielsen L. (2000). Modular organization of excitatory and inhibitory reflex receptive fields elicited by electrical stimulation of the foot sole in man. *Clinical Neurophysiology* 111, 2160-9.

Stancak, A., Raij, T.T., Pohja, M., Forss, N., & Hari, R. (2005). Oscillatory motor cortex-muscle coupling during painful laser and nonpainful tactile stimulation. *Neuroimage* 26, 793-800.

Stein, E. (1917). *On the Problem of Empathy.* tr. Waltraut Stein, 3rd edition. Washington DC: ICS Publications, 1989.

Strick, P.L., Dum, R.P., & Picard, N. (1998). Motor areas on the medial wall of the hemisphere. *Novartis Foundation Symposium* 218, 64-75.

Swick, D. & Jovanovic, J. (2002). Anterior cingulate cortex and the Stroop task: evidence for topographic specificity. *Neuropsychologia* 40, 1240-53.

Sönnby-Borgstrom, M. (2002). Automatic mimicry reactions as related to differences in emotional empathy. *Scandinavian Journal of Psychology* 43, 433-43.

Tanji, J. (1996). New concepts of the supplementary motor area. *Current Opinion in Neurobiology* 6, 782-7.

Tang, J., Ko, S., Ding, H., Qiu, C., Calejesan, A.A., & Zhuo, M. (2005). Pavlovian fear memory induced by activation in the anterior cingulate cortex. *Molecular Pain* 9, 1-6.

Tastevin, J. (1937). En partant de l'experience d'Aristotle. *L 'Encephale* 1, 57–84.

Timmermann, L., Ploner, M., Haucke, K., Schmitz, F., Baltissen, R., & Schnitzler, A. (2001). Differential coding of pain intensity in the human primary and secondary somatosensory cortex. *Journal of Neurophysiology*, 86, 1499-1503.

Titchener, E.B. (1909). *Lectures on the Experimental Psychology of the Thought-Processes.* Macmillan: New York. Reprinted 1973, New York: Arno Press.

Titchener, E. B. (1921). Brentano and Wundt: Empirical and experimental psychology. *American Journal of Psychology*, 32, 108-120.

Toates, F. (2001). *Biological Psychology: An Integrative Approach.* London: Prentice Hall.

Treede, R.D., Kenshalo, D.R., Gracely, R.H., Jones, A.K. (1999). The cortical representation of pain. *Pain* 79, pp 105-11.

Tsakiris, M.& Haggard, P. (2005). The rubber hand illusion revisited: visuotactile integration and self-attribution. *Journal of Experimental Psychology Human Perception and Performance* 31, 80–91.

Tucker, M.,& Ellis, R. (1998). On the relations between seen objects and components of potential actions. *Journal of Experimental Psychology: Human Perception and Performance, 24*, 830–846.

Turken, A.U., & Swick, D. (1999). Response selection in the human anterior cingulate cortex. *Nature Neuroscience* 10, 920-4.

Turnbull, O., Worsey, R., & Bowman, C. (under review). Emotion and intuition: Does *schadenfreude* make interns poor learners?

Tye, M. (2005) "Another look at representationalism about pain." In Murat Aydede (Ed.), *Pain: New Essays on Its Nature and the Methodology of Its Study,* 99-120. Cambridge: MIT Press.

Umiltá, M.A., Kohler, E., Gallese, V., Fogassi, L., Fadiga, L., Keysers, C., & Rizzolatti, G. (2001). I know what you are doing. a neurophysiological study. *Neuron* 19, 155-65.

Urban, P.P. Solinski, M., Best, C., Rolke, R., Hopf, H.C., & Dieterich, M. (2004). Different short-term modulation of cortical motor output to distal and proximal upper-limb muscles during painful sensory nerve stimulation. *Muscle Nerve* 29, 663-9.

Valeriani, M. Restuccia, D., Di Lazzaro, V., Oliviero, A., Le Pera, D., Profice, P., Saturno, E., & Tonali, P. (2001). Inhibition of biceps brachii muscle motor area by painful heat stimulation of the skin. *Experimental Brain Research* 139, 168-72.

van Veen, V., Holroyd, C.B., Cohen, J.D., Stenger, V.A., & Cameron, C.S. (2004). Errors without conflict: implications for performance monitoring theories of anterior cingulate cortex. *Brain and Cognition* 56, 267-76.

Vogt, B.A., Berger, G.R., & Derbyshire, W.G. (2003). Structural and functional dichotomy of human midcingulate cortex. *European Journal of Neuroscience* 18, 3134-3144.

Vogt, B.A. & Sikes, R.W. (2000). The medial pain system, cingulate cortex, and parallel processing of nociceptive information. *Progress in Brain Research* 122, 223-35.

Vogt, B.A., Nimchinsky, E.A., & Hof, P.R. (1995). Human cingulate cortex: Surface features, flat maps, and cytoarchitecture. *Journal of Comparative Neurology* 359, 490-506.

Vogt, B.A., Wiley, R.G., & Jensen, E.L. (1995). Localization of Mu and delta opioid receptors to anterior cingulate afferents and projection neurons and input/output model of Mu regulation. *Experimental Neurology* 135, 83-92.

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., Vogt, L., & Laureys, S. (2006). Cytology and functionally correlated circuits of human posterior cingulate areas. *NeuroImage* 29, 452-66.

Völlm, B.A., Taylor, A.N.W, Richardson, P., Corocoran, R., Stirling, J., McKie, S., Deakin, J.F.W., & Elliott, R. (in press). Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. *NeuroImage,* epub ahead of print.

Wallbott, H.G. (1991). Recognition of emotion from facial expression via imitation? Some indirect evidence for an old theory. *British Journal of Social Psychology* 30, 207-19.

Wall, P. (1999). *Pain: The Science of Suffering.* London: Weidenfeld & Nicolson.

Walton, M.E., Bannerman, D.M., Alterescu, K., & Rushworth M.F. (2003). Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. *Journal of Neuroscience* 23, 6475-6479.

Walton, M.E., Devlin, J.T., & Rushworth, M.F. (2004). Interactions between decision making and performance monitoring within prefrontal cortex. *Nature Neuroscience* 11, 1259-65.

Walton, M. & Spence, C. (2004). Cross-modal congruency and visual capture in a visual elevation-discrimination task. *Experimental Brain Research* 154, 113–120.

Wang, Y., Shima, K., Sawamura, H., & Tanji, J. (2001). Spatial distribution of cingulate cells projecting to the primary, supplementary, and pre-supplementary motor areas: a retrograde multiple labeling study in the macaque monkey. *Neuroscience Research* 39, 39-49.

Wentura, D., Rothermund, K., & Bak, P. (2000). Automatic vigilance: the attention-grabbing power of approach- and avoidance-related social information. *Journal of Personality and Social Psychology* 78, 1024-37.

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, pp 655-664.

Williams, AC. (2002) Facial expression of pain: an evolutionary account. *Behavioral and Brain Sciences* 25, 439-455.

Williams, Z.M., Bush, G., Rauch, S.L., Cosgrove G.R., & Eskandar, E.N. (2004). Human anterior cingulate neurons and the integration of monetary reward with motor responses. *Nature Neuroscience* 7, 1370-75.

Winkielman, P., Berridge, K.C., & Wilbarger, J.L. (2005). Unconscious affective reactions to masked happy versus angry faces influence consumption behavior and judgments of value. *Personality and Social Psychology Bulletin* 31, 121- 35.

Wispé, L. (1987). History of the concept of empathy. In *Empathy and its Development*, Ed. N. Eisenberg & J Strayer. Cambridge: Cambridge University Press.

Wispé, L. (1991). *The Psychology of Sympathy.* New York: Plenum Press.

Wolpert, D.M., Ghahramani, Z., Flanagan, J.R. (2001). Perspectives and problems in motor learning. *Trends in Cognitive Science* 5, 487-494.

Wolpert, D.M., Doya, K., & Kawato, M. (2003). A unifying computational framework for motor control and social interaction. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 358, 593-602.

Woolrich, M.W., Behrens, T.E., Beckmann, C.F., Jenkinson, M., and Smith, S.M. (2004). Multilevel linear modelling for fMRI group analysis using Bayesian inference. *Neuroimage* 21, 1732–1747.

Woolrich, M.W., Ripley, B.D., Brady, M., & Smith, S.M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage* 14, 1370–1386.

Worsley, K.J., Evans, A.C., Marrett, S., & Neelin, P. (1992). A three-dimensional statistical analysis for CBF activation studies in human brain. *J Cerebral Blood Flow and Metabolism* 12, 900–918.

Yamasaki, H., LaBar, K. S., & McCarthy, G. (2002). Dissociable prefrontal brain systems for attention and emotion. *Proceedings of the National Academy of Sciences*, 99, 11447-11451.

Öhman, A., Soares, J.J. (1998). Emotional conditioning to masked stimuli: expectancies for aversive outcomes following nonrecognized fear-relevant stimuli. *Journal of Experimental Psychology: General* 127, 69-82.